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Neurodegenerative Diseases: Mechanism, Limitations, and Emerging Treatments

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Abstract. Neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotropic lateral sclerosis (ALS), are characterized by gradual neural damage, leading to cognitive and behavioral impairments. Their prevalence increased along the aging population, bringing significant medical, social, and economic problems worldwide. Thorough and abundant research on these diseases have been conducted since their discovery, including aspects such as their characteristics, mechanisms, causes, and stages of development. However, despite this extensive research, effective therapies still remain undiscovered, largely due to complicatedness and multifactoriality of their pathogenesis. In recent years, advances in molecular biology, technologies, and models are starting to provide possible approaches such as targeted protein clearance, anti-inflammatory strategies, gene therapy, and metabolic modulation to address these gaps. This review summarizes shared and distinct features across major neurodegenerative diseases, the core pathogenic mechanisms, progress in disease modeling and biomarker development, and emerging therapeutic strategies. By integrating current mechanistic insights with innovative research tools, this work presents the importance of early diagnosis and precision medicine interventions, aiming to inform future research directions and improve patient outcomes.

Keywords: neurodegenerative diseases, proteostasis, Neuroinflammation, RNA Metabolism, Mitochondrial Dysfunction

1. Introduction

Neurodegenerative diseases, Well known examples include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotropic lateral sclerosis (ALS). These diseases are characterized by gradual damage of parts the pateint's nervous system, and lead to two core categories of symptoms: cognitive and behavioral (motor) symptoms. Cognitive symptoms are primary symptoms of diseases like Alzheimer's disease and other dementias. Examples include memory loss, disorientation, language problems (Aphasia) and difficulty with concentrating, understanding, remembering, following instructions, and solving problems. The other category, motor symptoms are primary symptoms of diseases like Parkinson's disease, Huntington's disease, and ALS (Amyotrophic Lateral Sclerosis). Examples include tremors, muscle rigidity (stiffness), postural instability, ataxia, and atrophy (muscle weakening). Although primary focus on some types

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might be only on one category of symptom (resting tremors (especially in the hands) of the parkinson's [motor], memory loss of the Alzheimer's [cognitive], etc.), most neurodegenerative diseases actually present both cognitive and motor symptoms, only that some are more significant than others.

With the aging population, prevalence of these neurodegenerative diseases across the globe increased remarkably, bringing serious medical, social, and economic problems worldwide. According to a major study released by The Lancet Neurology, in 2021, more than 3 billion people worldwide were living with a neurological condition [1]. Neurological disorders have become the world's leading source of disability and illness. Since 1990, the global burden of these conditions—measured in disability-adjusted life years (DALYs)—has risen by 18%. Additionally, over 80% of neurological deaths and health loss occur in low- and middle-income countries, and access to treatment varies widely: high-income countries have up to 70 times more neurological professionals per 100000 people than low and middle-income countries. Statistics are clearly stating the fact that neurodegenerative diseases are a major source of global crisis, and urgent preventions are needed as number of patients soars worldwide [2].

Thorough and abundant research on these diseases have been conducted since their discovery, including aspects such as their characteristics, mechanisms, causes, and stages of development. Despite this extensive research, effective therapies still remain undiscovered, largely due to complicatedness and multifactoriality of their pathogenesis. However, in recent years, advances in molecular biology, technologies, and models are starting to provide possible approaches such as targeted protein clearance, anti-inflammatory strategies, gene therapy, and metabolic modulation to address these gaps. This review summarizes shared and distinct features across major neurodegenerative diseases, the core pathogenic mechanisms, progress in disease modeling and biomarker development, and emerging therapeutic strategies. By integrating current mechanistic insights with innovative research tools, this work presents the importance of early diagnosis and precision medicine interventions, aiming to inform future research directions and improve patient outcomes.

2. Core pathological mechanism

2.1. Loss of proteostasis

The first pathological mechanism this research is going to discuss about is the disruption of protein homeostasis (proteostasis). First, it leads to abnormal protein aggregation, which is seen across most neurodegenerative diseases. In Alzheimer's disease (AD), important features include extracellular deposits of β-amyloid (Aβ) plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein. Parkinson's disease (PD) is characterized by the accumulation of misfolded α-synuclein in Lewy bodies, while Huntington's disease (HD) involves aggregates of mutant huntingtin protein (mHTT). In amyotrophic lateral sclerosis (ALS), pathological inclusions of TDP-43 protein is presented. These aggregates are believed to exert toxicity through mechanisms described in the "toxic oligomer" hypothesis. This hypothesis suggests that the brain damage leading to neurodegenerative diseases are caused by small, soluble oligomers. Compounding these issues, cellular protein clearance systems—including the ubiquitin–proteasome system (UPS) and the autophagy–lysosome pathway—become impaired, reducing the ability of neurons to eliminate misfolded proteins.

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2.2. Mitochondrial dysfunction and oxidative stress

Mitochondrial dysfunction and oxidative stress have been present in the pathological mechanisms of most neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. Oxidative stress, which is the imbalance between free radicals (reactive oxygen species, ROS) and the antioxidants, is potential of causing mitochondrial gene mutations leading to mitochondrial dysfunction, resulting in insufficiency of ATP. More results of mitochondrial DNA mutation include damage of mitochondrial membrane, mitochondrial respiratory system (electron transport chains), and mitochondrial defense systems, which all act as triggers or amplifiers of neurodegeneration, playing a significant role in the development of neurodegenerative diseases. Additionally, the excessive concentration of free radicals (the production of free radicals exceeds the cell's antioxidant capacity) causes oxidative damage to cellular such as lipids (specifically plasma membranes [lipid bilayers] of cells), proteins, and DNA [3]. Damage of these macromolecules contributes significantly to the progression of neurodegenerative diseases. Moreover, oxidative stress also disrupts the calcium (Ca^{2+}) homeostasis of neurons, and excess calcium influx into the neurons from extracellular environment, reaching mitochondrion and the nuclei as concentration of calcium increase further. As calcium is a neurotoxin when its concentration is too high, calcium influxes causes abnormal neuronal calcium signaling that leads to cell death. In mitochondrion, for example, calcium influx accelerates metabolic reactions, leading to eventual cell death. Similarly, in the nuclei, calcium influx modulates gene transcription in charge of cell apoptosis (suicide). Calcium's effect on both cellular components are lethal to the neurons inside human brains, causing significant decrease in neuron numbers, resulting in neural degeneration [4].

2.3. Neuroinflammation

Neuroinflammation, defined as inflammation located in the brain or spinal cord, is believed to be a major factor that leads of neural cell death in the neurodegenerative diseases mentioned above, especially Parkinson's disease and Alzheimer's disease. Often, this inflammatory response is due to the aggregation of proteins that act as "danger signals". For example, extracellular β-amyloid (Aβ) plaques in Alzheimer's and misfolded α-synuclein in Parkinson's. Their presence activates microglia, primary immune cells in the CNS (central nervous system), through pattern recognition receptors (PRRs) [5]. Normally, activation of these cells repair injuries and provide maintenance of neural networks (clear debris, misfolded protein, and pathogens). However, when overactivated, it triggers the NLRP 3 inflammasome, a multi-protein complex inside microglia that acts like a "molecular alarm system", which then activates caspase-1. This inflammasome influences two types of inflammatory cytokines: IL-1β and TNF-α. IL-1β is produced when caspase-1, a result of operation of NLRP3 inflammasomes) matures its inactive form, pro-IL-1β. This inactive form's concentration increases when NF-κB is operating. The other inflammatory cytokine TNF-α, unlike IL-1β, does not require the inflammasome for activation. Instead, it is produced as an active cytokine via secondary NF-κB signaling (caused by the increased IL-1β concentration, the downstream procedure of NF-κB signaling that quicken pro-IL-1β formation. Together, IL-1β and TNF-α create a chronic inflammatory environment in the brain [6,7].

It is important to note that overactivation of microglia does not only trigger release of IL-1β and TNF-α, but also other toxic mediators such as ROS (mentioned above) and nitric oxide (neurotoxic when excessive). These molecules contribute to oxidative stress, which damages lipids

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(membranes), proteins, and DNA, trigger the release of more danger signals, further activating microglia, and maintains this cycle, leading to ultimate neuronal apoptosis or necrosis.

2.4. RNA metabolism disorders / dysregulation

Neurons are highly specialized, hence requires on precise gene expression. This precision largely depends on instructions for protein synthesis and regulation (which, when, and where) from RNAs, including mRNAs, non-coding RNAs, microRNAs, and long non-coding RNAs. As it controls protein synthesis, dysregulation of RNA leads to abnormal protein expression, aggregation, and toxicity, which are central features of many neurodegenerative diseases.

Several mechanisms under RNA dysregulation have been discovered. This research will mainly discuss two of them: RNA-binding proteins (RBPs) malfunction and non-coding RNA dysregulation. The first mechanism, RNA-binding proteins malfunction, focuses on RNA-binding proteins (RBPs), which are essential proteins that regulate splicing, transport, stability, and translation of RNAs. Hence, mutation or mislocalization of RBPs can lead to RNA misprocessing, with TDP-43, FUS (seen in ALS and FTD) as an example. Another mechanism, non-coding RNA dysregulation, occurs in several non-coding RNAs, including microRNA (miRNA) and long non-coding RNA (lncRNA). miRNAs normally degrade or repress translation of target mRNAs to keep the concentration of specific proteins under an appropriate level. Hence, dysfunction of miRNA leads to excess protein production, as target mRNAs are no longer suppressed when needed, and is seen in most neurodegenerative diseases. The other type of RNA, lncRNA, act as guides to regulate chromatin structure, transcription, splicing, and RNA stability, ensuring fine-tune gene expression at multiple levels. Consequently, dysfunction of lncRNAs leads to deregulated transcription or RNA splicing. For example, loss of certain lncRNAs damages synaptic plasticity and memory [8].

3. Current research models and challenges

Although extensive research have been conducted in the area of neurodegenerative diseases, there are still limitations in each. This section will discuss the process and limitations of animal models, both in vivo and in vitro. In vivo and in vitro animal models are essential when it comes to neurodegenerative diseases' drug discovery. Each helps researchers mimic aspects of diseases like Alzheimer's, Parkinson's, Huntington's, and Amyotrophic Lateral Sclerosis. The in vivo model is a whole-animal system. The most common example is the transgenic mouse model, where genetically modified mouse, which scientists introduce, delete, or alter specific genes in its genome, used to study disease mechanisms and test drugs. However, limitations are obvious: the biological systems of animals, even species that are closely related to humans or have similar anatomies, can be significantly different from humans systems. For example, the most commonly used mouse don't fully recapitulate human brain complexity or pathology. Hence drug responses in animals may not translate to humans, also a major reason for clinical trial failures. The fact that in vivo methods normally cause unavoidable pain or distress in the animals involved also drives ethical concerns. Intended address these issues, researchers came up with the in vitro model, which are research conducted outside of a living organism, typically in a controlled laboratory environment such as test tubes, culture dishes, or flasks. This eliminates ethical problems, but also triggers other shortcomings. First, systems are simplified, as it is impossible to create full brain microenvironment, immune system, and vascular components artificially in labs. This results in less relevant outcomes compared to in vivo models. Additionally, 2D cell cultures don't capture 3D cell–cell and cell–

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matrix interactions, which also reduces the result's reliability. Although most drug research usually integrates both, still, significant limitations are inevitable [9].

4. Therapeutic strategies and future directions

Although past models present significant limitations, most recent research have provided us with insight to future therapies and research strategies that display strong potential in the future. However, it is important to note that there are still no promising cures to neurodegenerative diseases, only possible drugs under research or strategies to slow down the degenerative process.

4.1. Targeted protein degradation via monoclonal antibodies

The first strategy focuses on removing target proteins (sources of toxin) out of the brain. In Alzheimer's disease, monoclonal antibodies (proteins made in laboratories that act like antibodies) such as Lecanemab are designed to target and remove amyloid-β (Aβ) plaques, which are proteins linked to memory loss and cognitive decline. In Parkinson's disease, vaccines against α-synuclein are invented to reduce harmful protein buildup and protect neurons. By removing target proteins, these therapies specifically focuses on abnormal protein aggregation, which is an important characteristic shared by neurodegenerative diseases [10,11].

4.2. Anti-inflammatory therapy

Another possible strategy is to reduce neuroinflammation, a core pathological mechanism of neurodegeneration. As neuroinflammation is caused by overactivation of microglia's downstream effects, drugs are designed to inhibit microglia activation or the cellular components involved in the specific step that leads to the inflammatory responses.. For example, drugs such as MCC950, which blocks the NLRP3 inflammasome, show potential in reducing inflammatory responses inside the brain. Another example, the CSF1R antagonist, regulate microglial activity [12].

4.3. Gene therapy

Gene therapy is also an emerging option. Antisense oligonucleotides (ASOs) are short strands of DNA or RNA that bind to specific messenger RNAs to reduce the production of harmful proteins. Clinical trials are currently testing ASOs in Huntington's disease and amyotrophic lateral sclerosis (ALS). For example, therapies that lower mutant huntingtin protein or toxic RNA species from C9orf72 have shown early signs of safety and effectiveness [13].

4.4. Overview

It is important to note that researchers emphasize that no single treatment will be sufficient on its own. Since neurodegenerative diseases involve overlapping mechanisms—protein aggregation, neuroinflammation, and mitochondrial dysfunction—multi-target and combination therapies are likely necessary. The outcome for the combination of different treatments that act on different pathways may be the most effective in slowing disease progression and improving patient condition.

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5. Conclusion

Neurodegenerative diseases, including Alzheimer's, Parkinson's, Huntington's, and amyotrophic lateral sclerosis (ALS), exhibit several overlapping pathological features. Common mechanisms such as abnormal protein aggregation, mitochondrial impairment, oxidative stress, chronic neuroinflammation, and RNA dysregulation contribute synergistically to a self-sustaining cycle of neuronal injury and loss. These interconnected processes drive the progressive degeneration of neurons, leading to worsening clinical symptoms and functional decline in patients.

Despite the current lack of disease-modifying treatments, recent advances in molecular biology, imaging technologies, and biomarker discovery have significantly enhanced our understanding of these complex disorders. Emerging therapeutic strategies—such as antisense oligonucleotides, immunotherapies targeting pathological protein aggregates, and mitochondrial protectants—offer new avenues for intervention. It is increasingly evident that monotherapies are unlikely to alter disease trajectories substantially. Instead, combination therapies that simultaneously target multiple pathogenic pathways—for example, reducing protein aggregation while dampening neuroinflammation and enhancing mitochondrial function—hold greater potential for slowing disease progression and improving quality of life.

Furthermore, given that neuropathological changes often begin years or even decades before clinical symptoms emerge, early diagnosis and personalized medicine approaches are crucial. Advances in fluid biomarkers and neuroimaging now allow for earlier and more accurate detection, creating a window for intervention before significant neuronal loss occurs. Until truly curative treatments are developed, a multifaceted strategy that combines early detection with multimodal therapy represents the most promising path forward in the management of neurodegenerative diseases.

References

[1] GBD 2021 Nervous System Disorders Collaborators (2024). Global, regional, and national burden of disorders affecting the nervous system, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. The Lancet. Neurology, 23(4), 344–381.
[2] World Health Organization. (n.d.). Over 1 in 3 people affected by neurological conditions, the leading cause of illness and disability worldwide.
[3] Professional, C. C. medical. (2025, August 7). What is oxidative stress?. Cleveland Clinic.
[4] Cenini, G., Lloret, A., & Cascella, R. (2020). Oxidative Stress and Mitochondrial Damage in Neurodegenerative Diseases: From Molecular Mechanisms to Targeted Therapies. Oxidative medicine and cellular longevity, 2020, 1270256.
[5] Nicolson, G. L., Ferreira, G., Settineri, R., Ellithorpe, R. R., Breeding, P., & Ash, M. E. (2018). Mitochondrial dysfunction and chronic disease: Treatment with membrane lipid replacement and other natural supplements. Mitochondrial Biology and Experimental Therapeutics, 499–522.
[6] DiSabato, D. J., Quan, N., & Godbout, J. P. (2016). Neuroinflammation: The devil is in the details. Journal of Neurochemistry, 139(S2), 136–153.
[7] Thameem Dheen, S., Kaur, C., & Ling, E.-A. (2007). Microglial activation and its implications in the brain diseases. Current Medicinal Chemistry, 14(11), 1189–1197.
[8] Li, Y., & Sun, S. (2025). RNA dysregulation in Neurodegenerative Diseases. The EMBO Journal, 44(3), 613–638.
[9] National Research Council (US) Committee on Methods of Producing Monoclonal Antibodies. (1999, January 1). Summary of advantages and disadvantages of in vitro and in vivo methods. Monoclonal Antibody Production.
[10] Reisa, S., David, L., Shobha, D., Steven, H., Larisa, R., Michael, I., Rob, M., Michael, W., & Lynn, K. (2024). Lecanemab in early Alzheimer's disease: Extended efficacy results from the clarity ad study. Lecanemab in Early Alzheimer's Disease: Extended Efficacy Results from the CLARITY AD Study.
[11] Brundin, P., Dave, K.D., & Kordower, J. H. (2017). Therapeutic approaches to target alpha-synuclein pathology. Experimental Neurology, 298, 225–235.

DOI: 10.54254/2753-8818/2025.AU27273

[12] Finneran, D. J., & Nash, K. R. (2019). Neuroinflammation and Fractalkine signaling in Alzheimer's disease. Journal of Neuroinflammation, 16(1).
[13] Targeting Huntingtin expression in patients with Huntington's disease. (2019). New England Journal of Medicine, 381(14), 1398–1398.