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Toward Effective Management of Neurodegenerative Diseases: Challenges and Future Directions

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ABSTRACT

Neurodegenerative diseases (NDs), such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), represent a growing global health challenge characterized by progressive neuronal loss and irreversible neurological decline. This review comprehensively explores the pathogenesis of NDs, focusing on the central roles of proteinopathy (e.g., Aβ, tau, and α-synuclein aggregation), mitochondrial dysfunction, and genetic mutations. We systematically evaluate the current landscape of pharmacological management, which primarily offers symptomatic relief through mechanisms such as cholinesterase inhibition, dopamine replacement, and glutamate regulation. Furthermore, we highlight promising advances in novel therapeutic strategies, including monoclonal antibodies (e. g., Lecanemab, Donanemab), gene therapy, and stem cell-based approaches, which aim to modify disease progression by targeting underlying pathological mechanisms. Despite these innovations, significant translational challenges persist, such as the limitations of animal models and the complexity of early diagnosis. This review concludes by discussing future directions, emphasizing the potential of personalized medicine, the gut-brain axis, and emerging targets like USP30 to overcome current hurdles and achieve effective management of these devastating disorders.

KEYWORDS

Neurodegenerative diseases; Alzheimer's disease; Parkinson's disease; Proteinopathy; Mitochondrial dysfunction; Therapeutic strategies; Monoclonal antibodies; Drug development; Review

1 Introduction

Neurodegenerative diseases are irreversible conditions that include the progressive deterioration of neurons, primarily due to the loss of neuronal cells and their protective myelin sheath in the brain and spinal cord. These conditions, which deteriorate over time, ultimately result in structural damage and dysfunction within the nervous system. Neurodegenerative diseases are generally categorized into three types: cognitive disorders, mobility disorders and inflammatory neurodegenerative conditions (Chandrasekaran & Bonchev, 2016). The most prevalent examples include Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS). This condition predominantly affects adults over 65. With the increasing elderly population, neurodegenerative diseases have emerged as leading causes of mortality and disability, not only in China but worldwide.

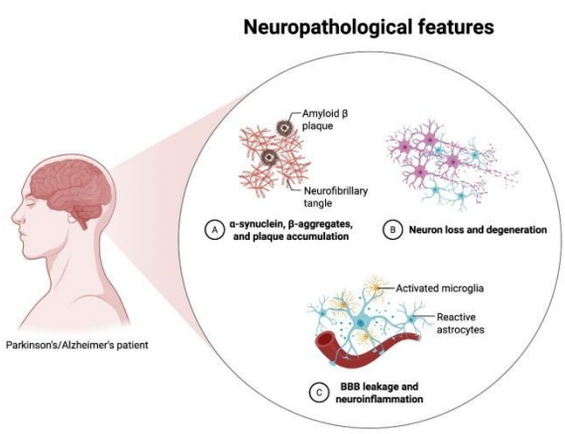

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Figure 1 Neuropathological features observed in Parkinson's/Alzheimer's patients. Panel A shows accumulation of α - synuclein, β - aggregates, and plaques (including amyloid β plaques and neurofibrillary tangles). Panel B illustrates neuron loss and degeneration. Panel C depicts blood - brain barrier (BBB) leakage and neuroinflammation, characterized by activated microglia and reactive astrocytes, all contributing to the neuropathology of these diseases.

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Table 1 Types of neurodegenerative diseases and their key characteristics

Category	Key Diseases	Age of Onset	Primary Pathophysiological Features	Reference
Cognitive Disorders	Alzheimer's Disease (AD)	65+ years	Amyloid plaques, tau tangles, cognitive decline	(Zweig et al., 1993)
	Frontotemporal Dementia(FTD)	45-65 years	Tau/TDP-43 inclusions, Frontal lobe atrophy, Glial activation	(Bang et al., 2015)
	Dementia with Lewy Bodies(DLB)	50-85 years	α-synuclein Lewy bodies, Dopamine/acetylcholine imbalance	(Arnaoutoglou et al., 2019)
Mobility Disorders	Parkinson's Disease (PD)	60+ years	Dopaminergic neuron loss, α-synuclein aggregation, motor symptoms	(Ascherio & Schwarzschild, 2016)
	Multiple System Atrophy(MSA)	40-60 years	α-synuclein oligomers in oligodendrocytes, Striatonigral degeneration	(Zoetmulder et al., 2014)
	Amyotrophic Lateral Sclerosis(ALS)	40-70 years	TDP-43 aggregates, Motor neuron degeneration, Glutamate excitotoxicity	(Feldman et al., 2022)
Inflammatory Disorders	Amyotrophic Lateral Sclerosis (ALS)	50-70 years	Motor neuron degeneration, SOD1 mutations	(Feldman et al., 2022)
	Huntington's Disease(HD)	30-50 years	mHTT aggregates, Striatal neuron loss, Microglia-mediated, neuroinflammation	(Walker, 2007)
	Progressive Supranuclear Palsy(PSP)	60-70 years	Tau filaments in basal ganglia, Neuroinflammatory cytokine release	(Boxer et al., 2017)

Given the current lack of effective treatments for most neurodegenerative diseases and the impossibility of a cure, the financial burden on patients' families is exacerbated, often leading to emotional distress. As the population continues to age, the incidence of these diseases rises, contributing to growing societal financial pressures (Ren et al., 2022). Therefore, identifying effective treatments is imperative, which necessitates a deeper understanding of the potential pathogenesis of neurodegenerative diseases as a foundation for successful prevention and therapeutic strategies.

2 Pathological mechanisms of neurodegenerative diseases

2.1 Proteinopathy: from misfolding to propagation

A hallmark of neurodegenerative diseases is the progressive loss of neurons and their function, with protein misfolding and aggregation playing a central pathogenic role. While various external factors such as infections, toxins, vascular impairments, vitamin B12 deficiency, and neoplasms contribute to cognitive deterioration in NDDs, intracellular protein misprocessing is now recognized as a hallmark of disease pathology.

In AD, the amyloid cascade hypothesis remains a prevailing model, proposing that Dysregulated processing of the amyloid precursor protein (APP) causes a heightened generation and accumulation of amyloid-beta (Aβ) peptides, particularly Aβ40 and Aβ42. With age, reduced efficiency of β- and γ-secretases exacerbates extracellular deposition of Aβ, resulting in senile plaque formation and neurotoxicity. Concurrently, intracellular hyperphosphorylation of tau proteins leads to neurofibrillary tangle (NFT) formation, disrupting microtubule stability and inducing neuronal death .

The amyloid cascade hypothesis conceptually combines the amyloid and tau theories, proposing that Aβ deposition triggers subsequent tau pathology. However, emerging evidence suggests that tau pathology may more directly correlate with disease severity than Aβ accumulation, indicating a more complex interplay between these proteins in AD pathogenesis.

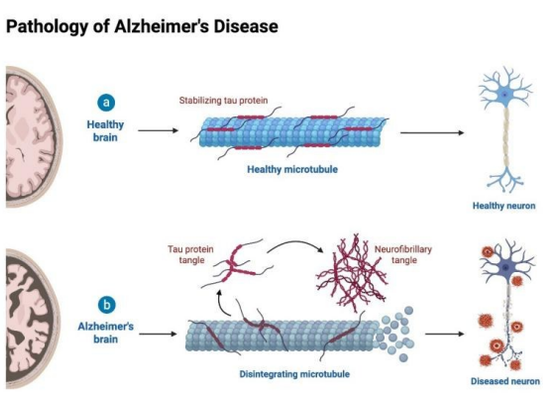

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Figure 2. Pathology of Alzheimer's Disease. In a healthy brain (a), stabilizing tau protein maintains healthy microtubules, supporting normal neuron structure and function. In an Alzheimer's brain (b), tau protein tangles form, leading to disintegrating microtubules. These tangles further aggregate into neurofibrillary tangles, contributing to the degeneration of neurons, as shown by the diseased neuron with pathological changes.

The cardinal pathological signature of Parkinson's disease is the abnormal aggregation of α-synuclein, leading to intracellular inclusions known as Lewy bodies in the vulnerable dopaminergic neurons of the substantia nigra pars compacta. The toxic oligomeric forms of α-synuclein are considered more neurotoxic than mature fibrils, and their formation is strongly influenced by mutations in genes such as SNCA and GBA. Notably, α-synuclein can be detected peripherally in blood, suggesting its potential as a non-invasive biomarker.

Misfolded proteins like tau and α-synuclein exhibit prion-like properties, capable of cell-to-cell transmission. Experimental models have demonstrated that pathological tau can propagate through synaptic pathways when brain extracts from AD patients are injected into healthy murine brains. These aberrant proteins may serve as templates that induce misfolding of native proteins in recipient cells. However, the extent to which the intracellular environment modulates this transmission remains under investigation, with individual variability complicating mechanistic interpretation (Hardy & Higgins, 1992).

Mitochondrial dysfunction is another critical contributor to neurodegeneration. In AD, Aβ peptides localize to the mitochondrial membrane, impairing enzymatic activity and membrane potential, which leads to excessive reactive oxygen species (ROS) production and apoptosis . Similarly, disruption of the endoplasmic reticulum (ER)—a key site for protein folding and post-translational modification—triggers cellular stress. Perturbations in calcium homeostasis can exacerbate ER dysfunction, further promoting protein misfolding, cellular toxicity, and neuronal loss.

In PD, early degeneration of dopaminergic neurons in the nigrostriatal pathway leads to decreased striatal dopamine levels, manifesting as motor symptoms. Contributing factors include oxidative stress, inflammation, and impaired proteostasis. Genetic mutations—such as PINK1 (linked to mitochondrial quality control), LRRK2 (involved in cytoskeletal regulation), and PARK2 (which encodes an E3 ubiquitin ligase)—have been causally linked to familial PD. The pathogenic variants in these genes are known to moderate neuronal survival and cellular morphology.

Amyotrophic lateral sclerosis (ALS) likewise demonstrates strong links to aberrant protein aggregation and underlying genetic mutations. Globally, the number of new ALS diagnoses each year falls within a range of 1 to 2.6 per 100,000 individuals, typically with disease onset around 58 – 60 years of age and a median survival of 3 – 4 years. Key gene mutations include C9ORF72, SOD1, FUS, and TARDBP, which affect RNA metabolism and protein homeostasis.

2.2 Mitochondrial dynamics in neurodegeneration

Mitochondrial dynamic—encompassing fission, fusion, mitophagy, and transport—are critically involved in regulating cellular metabolism, energy supply, and apoptotic signaling.The pathological process of neurodegeneration often begins years before clinical symptoms of neurodegenerative diseases become apparent, and mitochondrial dynamic changes such as ATP production, the generation of reactive oxygen species (ROS) via oxidative phosphorylation (OXPHOS), along with the precise regulation of calcium homeostasis, are critical for sustain normal interneuronal signaling and metabolic function. Recent studies have shown that gene mutation disorders related to mitochondrial function can be a key factor causing NDs.

For example, FIS1, DRP1, NFN1, NFN2 and other proteins can be located on the mitochondrial membrane and play related roles. In addition, ensuring the stable operation of mitochondrial phagocytosis and the ubiquitin-proteasome system (UPS) also helps to maintain mitochondrial dynamic homeostasis. Mitochondria-lysosome contacts (MLC) regulates mitophagy and calcium transport through the contact between lysosomes and mitochondria through the Rab7-GTP protein site. The dynamic imbalance of these organelles forms A vicious cycle with the accumulation of erroneous proteins, such as Aβ, exacerbating the condition

2.3 Genetic mutations and risk factors

Genetic predisposition plays a pivotal role in the onset and progression of neurodegenerative disorders. In Parkinson's disease, for instance, mutations in the LRRK2 gene represent the most commonly identified genetic alteration in both familial and sporadic cases. Variants in this gene are associated with increased kinase activity, which is believed to disrupt neuronal integrity through altered intracellular signaling and cytoskeletal dynamics.

Beyond single-gene mutations, the interaction of multiple genetic and environmental risk factors contributes to disease susceptibility, phenotype variability, and response to treatment. As genomic technologies advance, polygenic risk scores and whole-genome sequencing are increasingly employed to uncover disease-associated variants and better understand the heritability of these complex conditions.

Table 2 Genetic mutations associated with Parkinson's Disease

Gene	Mutation Type	Impact on Neuronal Function	Prevalence in Familial PD	References
LRRK2	G2019S(kinase domain)	enhanced kinase activity, lysosomal dysfunction neuroinflammation	5-6％(Global), 30-40％(North Africa)	(Tolosa et al., 2020)
SNCA	Missense(A53T, A30P, E46K)	α-synuclein misfolding, synaptic dysfunction, mitochondrial impairment	1-2%	(Fernández-Santiago et al., 2019)
GBA	N370S, L444P(loss-of-function)	Lysosomal-autophagy defects, ER stress, α -synuclein accumulation	5-10%(Global)	(Fernández-Santiago et al., 2019)
PRKN	Exonic deletions/duplications	Impaired mitophagy, proteasomal dysfunction, mitochondrial QC failure	10-15%(Early-onset)	(Clausen et al., 2024)
PINK1	Truncating mutations	Mitophagy pathway disruption, oxidative stress susceptibility	1-9%(Early-onset)	(Matheoud et al., 2016)

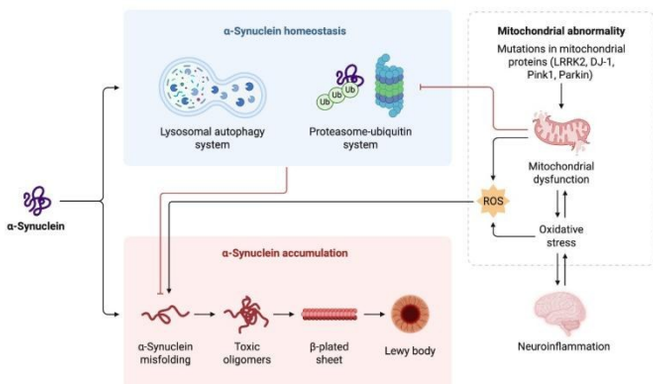

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Figure 3. Schematic illustration of α - Synuclein - related pathways in neurodegeneration. This illustration demonstrates how α-Synuclein homeostasis is regulated through the coordinate actions of the lysosomal autophagy pathway and the ubiquitin-proteasome system. Disruptions, such as mitochondrial abnormalities (via mutations in proteins like LRRK2, DJ - 1, Pink1, Parkin resulting in dysfunction, oxidative stress, and ROS production), can lead to α - Synuclein accumulation. The pathogenic cascade is characterized by protein misfolding, progressive assembly into toxic oligomers and β-sheet-rich fibrils, and eventual aggregation into Lewy bodies, which collectively propagate neuroinflammatory pathways and synaptic dysfunction.

3 Current status of drug therapy

Different neurodegenerative diseases require distinct therapeutic approaches. However, current treatments remain focused on preventing disease progression and alleviating symptoms rather than offering a cure.

3.1 Drug treatment for AD

3.1.1 Cholinesterase inhibitors

First- line pharmacological treatment for Alzheimer's disease includes acetylcholinesterase inhibitors such as donepezil, rivastigmine, and galantamine, which are employed to mitigate clinical symptoms. Research indicates that AD is associated with reduced acetylcholine levels. These medications enhance cognitive function by inhibiting cholinesterase activity, thereby increasing acetylcholine in the brain.

3.1.2 Glutamate receptor antagonists

Memantine, a noncompetitive antagonist, targets the N-methyl-D-aspartate (NMDA) receptor to regulate glutamatergic neurotransmission. By binding to NMDA receptors, memantine reduces glutamate-induced overstimulation of postsynaptic neurons, thereby preventing neuronal damage. Importantly, it does not completely block glutamate binding, allowing normal neural signals transmission. Memantine is often administered alongside cholinesterase inhibitors for enhanced therapeutic effect.

3.2 Drug treatment for PD

3.2.1 Dopamine replacement therapy

Levodopa, the precursor to dopamine, is used to increase dopamine levels in the brain's substantia nigra, thereby compensating for the deficiency and improving motor symptoms in PD patients.

3.2.2 Dopamine receptor agonists

Dopamine receptor agonists exert their therapeutic effects by directly binding to and activating postsynaptic dopamine receptors, thereby mimicking the endogenous neurotransmitter and enhacing dopaminergic signaling in neural circuits and are often used in combination with levodopa. While these drugs are effective, their mechanism are not fully understood, and individual responses to treatment may vary.

3.3 Drug treatment for ALS

Currently, the only approved medications for ALS are riluzole and edaravone. Riluzole inhibits glutamatergic neurotransmission, preventing excitotoxic neuronal damage by reducing excessive glutamate activity. It also modulates sodium and calcium channels to decrease ion influx, thereby mitigating neuronal damage. Edaravone, on the other hand, functions as a scavenger of reactive oxygen species (ROS) like hydroxyl radicals , to protect nerve cells from oxidative stress.

3.4 Nonpharmacologic therapies for neurodegenerative diseases

Nonpharmacologic interventions, such as cognitive training (including memory and attention exercises), physical and occupational therapy, and maintain proper nutrition, are essential for supporting cognitive function, muscle strength, and overall health in patients with neurodegenerative diseases.

4 Research progress of new drugs

4.1 Alzheimer's disease

Lecanemab is a humanized monoclonal antibody engineered to selectively target soluble amyloid-β protofibrils with high binding affinity, thereby promoting their clearance from the brain via phagocytic mechanisms and reducing parenchymal amyloid plaque burden. In clinical studies, it has shown significant improvements in early-stage AD symptoms. However, it also has notable side effects—approximately 12.5% of patients in the treatment group experienced cerebral edema or hydrocephalus. Additional side effects may include cerebral microbleeds, intracerebral hemorrhage, and headaches, and the drug is still undergoing clinical trials. Recently, some researchers have proposed that certain pathogens are not fully cleared after infection, leading to persistent formation of amyloid-β peptides and amyloid plaques, thereby accelerating neurodegenerative processes. Recent studies have confirmed the pathogenic role of herpesvirus family viruses in AD (Readhead et al., 2018), offering a new perspective on treatment approaches. Future therapies may involve inhibiting the expression of related genes, developing vaccines, or using antiviral drugs to slow or prevent disease progression.

4.2 Parkinson's disease

The pathogenesis of Parkinson's disease is fundamentally driven by the aberrant aggregation of α-synuclein protein, which evolves from soluble monomers into insoluble fibrillary assemblies that disrupt proteostatic balance and propagate neuronal toxicity. New therapeutic strategies are being developed to either inhibit α-synuclein aggregation or promote its clearance. On the genetic front, Denali Therapeutics has obtained an exclusive global license from Genentech to develop and commercialize LRRK2 inhibitors. Mutations in the LRRK2 gene have been identified as the most frequent genetic cause of hereditary PD, and the gene is believed to play a crucial role in the disease's development. Additionally, a research team from the Center of Excellence in Brain Science and Intelligence Technology at the Chinese Academy of Sciences utilized gene editing technology to convert astrocytes into dopamine neurons. In a Parkinson's disease mouse model, this technique successfully restored motor function to near-normal levels, but further research is necessary before this approach can be applied to humans.

4.3 Amyotrophic lateral sclerosis

In April 2023, the FDA approved an antisense oligonucleotide therapy for ALS patients with SOD1 mutations. This drug, delivered intrathecally, targets SOD1 mRNA, reducing protein synthesis and subsequently lowering the levels of neurofilament light chains in cerebrospinal fluid, thereby slowing the progression of the disease. However, common side effects include pain, fatigue, and an increase in white blood cells in the cerebrospinal fluid.

Table 3 Current drug therapies for neurodegenerative diseases

Disease	Drug Class	Drug(s)	Mechanism of Action	Reference
AD	Cholinesterase Inhibitors	Donepezil, Rivastigmine, Galantamine	Inhibit acetylcholinesterase, increasing acetylcholine availability	(Moodie et al., 2019)
AD	NMDA Receptor Antagonists	Memantine	Regulates glutamatergic neurotransmission to prevent excitotoxicity	(Song et al., 2018)
PD	Dopamine Precursors	Levodopa	Converts to dopamine to replenish brain's dopamine levels	(Zupnick et al., 1990)
PD	Dopamine Receptor Agonists	Pramipexole, Ropinirole	Stimulates dopamine receptors to alleviate motor symptoms	(Ziaei et al., 2022)
PD	MAO-B Inhibitors	Selegiline, Rasagiline	Reduce dopamine breakdown	(Tripathi & Ayyannan, 2019)
ALS	Glutamate Inhibitors	Riluzole	Reduces glutamate excitotoxicity, protecting motor neurons	(Gajewski & Barger, 2023)
ALS	Antioxidants	Edaravone	Scavenges reactive oxygen species, reducing oxidative stress	(Kabir et al., 2022)

5 Drug development based on pathological mechanisms

5.1 Beta-amyloid scavengers

The accumulation of beta-amyloid (Aβ) is a hallmark pathological characteristic in Alzheimer's disease (AD) study. Inovative Aβ scavengers aim to mitigate this condition by promoting the removal of Aβ from the brain. Certain drugs achieve this by binding to Aβ, thereby enhancing its clearance by the immune system or directly breaking down the protein. For example, monoclonal antibody therapies are capable of specifically targeting Aβ, triggering immune activation to eliminate these protein aggregates. Current research highlights the crucial role of microglia in the clearance of Aβ. However, prolonged exposure to high Aβ concentrations can impair microglial function. Therefore, treatment aimed at enhancing microglia healthy can help preserve their functionality and promote Aβ clearance.

5.2 Tau protein modulators

The hyperphosphorylation of tau protein, leading to neurofibrillary tangle formation, is another critical pathological hallmark of AD. Tau modulators aim to block abnormal phosphorylation or promote the disassembly of pathological tau aggregates. Additionally, compromised autophagy, which disrupts the elimination of misfolded proteins and cytoplasmic oligomers, is a common feature in various neurodegenerative conditions. Enhancing autophagic processes offers a promising approach to prevent tau aggregation and may serve as a valuable therapeutic approach for AD management.

Table 4 Emerging drugs targeting Tau and Aβ Proteins

Drug	Target	Action	Disease Focus	Clinical Status	Reference
Lecanemab	Aβ (Amyloid-beta)	Monoclonal antibody clearing Aβ plaques	Alzheimer's Disease (AD)	Ongoing clinical trials	(van Dyck et al., 2023)
BMS-986168	Tau	Tau aggregation inhibitor	Alzheimer's Disease (AD)	Phase 2 clinical trial	(Vaz & Silvestre, 2020)
TRx0237 (LMTM)	Tau	Tau aggregation inhibitor/microglial modulator	Alzheimer's Disease(AD), Frontotemporal Dementia (FTD)	Phase 3 clinical trial	(Kondak et al., 2023)
PRX002	α-synuclein	Monoclonal antibody targeting α -synuclein	Parkinson's Disease (PD)	Phase 1 clinical trial	(Jankovic et al., 2018)
Semorinemab	Extracellular tau	Monoclonal antibody binding pathological tsu	Alzheimer's Disease(AD), Frontotemporal Dementia (FTD)	Phase 2 clinical trial	(Vaz & Silvestre, 2020)
Donanemab	Pyroglutamate Aβ(N3pG)	mAb clearing established amyloid plaques	Early Alzheimer's	FDA approval pending	(Mintun et al., 2021)
ALN-APP	APP mRNA	siRNA reducing Aβ/APP production(CNS-delivered)	Early Alzheimer's	Phase 1 clinical trial	
Anle138b	α-synuclein oligomers	Small molecule preventing toxic aggregation	Parkinson's Disease(PD)	Phase 2 clinical trial	(Lemos et al., 2020)
Prasinezumab	α-synuclein oligomers	mAb blocking cell-to-cell propagation	Parkinson's	Phase 2 clinical trial	(Lemos et al., 2020)

5.3 Neuroprotection and neuronutrition

In treating neurodegenerative conditions like ALS, neuroprotective strategies are crucial. Riluzole, an FDA-approved drug for ALS, functions by inhibiting glutamate release, thereby reducing excitotoxic neuronal damage and slowing disease progression. However, its therapeutic efficacy is limited, necessitating further exploration of optimized drug delivery systems or combination therapies. Brain-derived neurotrophic factor (BDNF) is important for neuronal health, yet its instability and poor blood-brain barrier permeability limit its direct use. BDNF mimetics, designed to replicate BDNF activity, can support neuronal survival and repair, showing potential in treating conditions such as PD. Despite their promise, challenges like low bioavailability and safety concerns must be addressed.

5.4 Anti-inflammatory and immunomodulatory therapies

In autoimmune neurological diseases, such as MS, the immune system targets the myelin sheath, causing significant damage. Immunosuppressive therapies help mitigate this by suppressing autoreactive immune cells and reducing inflammation. However, the risk of immunodeficiency from new immunosuppressants highlights the need to balance efficacy and safety. Emerging anti-inflammatory therapies focus on inhibiting the overactivation of microglia and suppressing the release of inflammatory mediators. These approaches show potential for managing neurodegenerative diseases and brain injury. However, optimal treatment regimens, including dosage, timing, duration, remain to be established.

5.5 Gene therapy and RNA therapy

Gene editing technologies like CRISPR/Cas9 offer hope for treating hereditary neurodegenerative diseases. For instance, CRISPR/Cas9 has been explored for editing pathogenic genes in Huntington's disease. Despite its potential, challenges such as off-target effects and immune responses need to be addressed to ensure safety and efficacy in human applications. For neurodegenerative diseases arising from gene deletions or loss-of-function mutations, gene replacement therapies utilize viral vectors to introduce functional genes, compensating for the missing proteins . However, the immunogenicity of viral vectors poses significant challenges. RNA interference technology reduces the synthesis of pathogenic proteins by degrading their mRNA. It has demonstrated effectiveness in certain neurological diseases. Nevertheless, issues such as in vivo delivery efficiency, stability, and off-target effects remain significant barriers.

5.6 Cell therapy

Stem cell therapy offers novel avenues for treating neurodegenerative diseases like PD, characterized by neuronal loss. Stem cells can differentiate into neurons, potentially alleviating symptoms. Yet, challenges such as cell sourcing, differentiation efficiency, immune rejection and tumorigenicity persist. Neural precursor cells, capable of differentiating into neurons and glial cells, show promise for promoting neural repair through transplantation. Key challenges include controlling differentiation pathways, improving cell survival rates, and addressing issues related to cell preparation and outcome evaluation.

6 Clinical challenges and recent advances

The early detection of neurodegenerative diseases remains a critical challenge, as current technologies often fail to diagnose patients in the early stages of these conditions. Imaging techniques show promise as diagnostic tools for early Parkinson's disease detection . Cerebrospinal fluid (CSF) is considered the most reliable biological sample for diagnosis; however, its extraction is invasive and not easily applied on a broad scale. For clinical use, enzyme-linked immunosorbent assay (ELISA) and electrochemiluminescence represent practical methods for detection. Identifying disease subtypes is another pressing issue, as the mechanisms underlying different subtypes vary significantly. The necessitates personalized treatment strategies, which are still under investigation. Genetic analysis is emerging as a promising tool for predicting neurodegenerative diseases, particularly in individuals who develop symptoms before age 40, where genetic factors and racial differences may play a role in disease risk. However, distinguishing between different neurodegenerative disease types at the genetic level remains a significant challenge, hindering effective detection and prevention strategies. Moreover, the high specificity of this disease, combined with considerable interindividual variability in clinical symptoms, often makes clinical signs a more sensitive markers for early diagnosis than standardized diagnostic tests

Recent studies have highlighted the connection between gut microbiota composition and neurodegenerative diseases, suggesting that modifying the gut microbiome could be a viable therapeutic approach. Dietary adjustments aimed at altering microbiota composition may serve as a preventive strategy for neurodegenerative diseases. In addition,

research into the mitochondria-related function of USP30, a deubiquitinating enzymes, offers a new perspective on neurodegenerative disease treatment . By regulating mitochondrial fusion and fission, USP30 can help mitigate the accumulation of damaged mitochondria, potentially providing therapeutic benefits. USP30 inhibitors are currently being explored as a treatment for PD (Bingol et al., 2014).

7 Translational challenges: from beach to bedside

The clinical translation of research on NDs faces substantial obstacles. A significant limitation arises from the anatomical and physiological differences between rodent models and the human brain. While the rodent models are widely used due to their accessibility and cost effectiveness, their neuroanatomy differs markedly from that of humans, limiting their translational validity. Although non-human primates offer closer biological similarity, their use is constrained by ethical concerns and high costs. Furthermore, replicating the full spectrum of clinical symptoms observed in human patients, particularly across different disease stages, is often unachievable in animal models. For example, intracerebral injection of okadaic acid (OKA) in rats can induce tau hyperphosphorylation, neuronal apoptosis, and Aβ deposition, partially mimicking D pathology. However, it fails to recapitulate neurotoxic symptoms or the progressive cognitive decline characteristic of AD (Arendt et al., 1998). Similarly, although induced pluripotent stem cell (iPSC)-derived neurons retain patient specific genetic background, they lack the ability to faithfully model the gradual neuronal aging process in vitro. These limitations highlight the inadequacy of current models in capturing the complexity of human neuropathological processes. Moreover, the biomarkers currently employed in clinical diagnosis represent only a fraction of those identified in the brain, restricting the diagnostic accuracy and early detection capabilities. Two primary factors contribute to this gap: the incomplete understanding of disease mechanisms, which hampers effective biomarker discovery, and the lack of standardized detection platforms and instrumentation across laboratories and clinical setting.

Despite these barriers, clinical trial design can be improved. One approach involves stratifying participants based on shared genetic profiles or known biomarker levels, such as Aβ42 or phosphorylated tau, to ensure more consistent pathological phenotypes among subjects. Additionally, incorporating early-stage trials focused on subtle cognitive and behavioral changes could enhance early diagnosis efforts. By emphasizing prodromal symptoms and refining clinical endpoints, researchers can better capture the nuanced progression of neurodegenerative disorders and improve therapeutic evaluation.

References

[1] Bingol B., Tea J. S., Phu L., Reichelt M., Bakalarski C. E., Song Q., Foreman O., Kirkpatrick D. S., & Sheng M. (2014). The mitochondrial deubiquitinase USP30 opposes parkin-mediated mitophagy. Nature, 510(7505), 370-375.

[2] Chandrasekaran S., & Bonchev D. (2016). Network Topology Analysis of Post-Mortem Brain Microarrays Identifies More Alzheimer's Related Genes and MicroRNAs and Points to Novel Routes for Fighting with the Disease. PLoS One, 11(1), e0144052.

[3] Feldman E. L., Goutman S. A., Petri S., Mazzini L., Savelieff M. G., Shaw P. J., & Sobue G. (2022). Amyotrophic lateral sclerosis. Lancet, 400(10360), 1363-1380.

[4] Hardy J. A., & Higgins G. A. (1992). Alzheimer's disease: the amyloid cascade hypothesis. Science, 256(5054), 184-185.

[5] Jankovic J., Goodman I., Safirstein B., Marmon T. K., Schenk D. B., Koller M., Zago W., Ness D. K., Griffith S. G., Grundman M., Soto J., Ostrowitzki S., Boess F. G., Martin-Facklam M., Quinn J. F., Isaacson S. H., Omidvar O., Ellenbogen A., & Kinney G. G. (2018). Safety and Tolerability of Multiple Ascending Doses of PRX002/RG7935, an Anti-α-Synuclein Monoclonal Antibody, in Patients With Parkinson Disease: A Randomized Clinical Trial. JAMA Neurol, 75(10), 1206-1214.

[6] Matheoud D., Sugiura A., Bellemare-Pelletier A., Laplante A., Rondeau C., Chemali M., Fazel A., Bergeron J. J., Trudeau L. E., Burelle Y., Gagnon E., McBride H. M., & Desjardins M. (2016). Parkinson's Disease-Related Proteins PINK1 and Parkin Repress Mitochondrial Antigen Presentation. Cell, 166(2), 314-327.

[7] Ren R., Qi J., Lin S., Liu X., Yin P., Wang Z., Tang R., Wang J., Huang Q., Li J., Xie X., Hu Y., Cui S., Zhu Y., Yu X., Wang P., Zhu Y., Wang Y., Huang Y., Wang G. (2022). The China Alzheimer Report 2022. Gen Psychiatr, 35(1), e100751.

[8] Tolosa E., Vila M., Klein C., & Rascol O. (2020). LRRK2 in Parkinson disease: challenges of clinical trials. Nat Rev Neurol, 16(2), 97-107.

[9] van Dyck C. H., Swanson C. J., Aisen P., Bateman R. J., Chen C., Gee M., Kanekiyo M., Li D., Reyderman L., Cohen S., Froelich L., Katayama S., Sabbagh M., Vellas B., Watson D., Dhadda S., Irizarry M., Kramer L. D., & Iwatsubo T. (2023). Lecanemab in Early Alzheimer's Disease. N Engl J Med, 388(1), 9-21.