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Abstract

Alpha-synuclein aggregation is a critical pathological process implicated in neurodegenerative diseases such as Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). This review explores the molecular mechanisms underlying alpha-synuclein aggregation, its role in neurodegeneration, and the clinical implications across various synucleinopathies. By elucidating the complex interplay of protein misfolding, propagation of pathology, and genetic and environmental factors, this review aims to provide insights into current therapeutic strategies and future directions for combating these devastating disorders. Alpha-synuclein, a protein intrinsic to the nervous system, has become a focal point in understanding neurodegenerative diseases, particularly Parkinson's disease (PD). The aggregation of alpha-synuclein is central to the pathophysiology of these conditions, marking a critical intersection between molecular biology and clinical manifestations.

Introduction

e role of alpha-synuclein in neurodegeneration

Alpha-synuclein is predominantly found in presynaptic terminals of neurons, where it plays a role in regulating neurotransmitter release and synaptic function. In its native state, alpha-synuclein is soluble and may have physiological roles in maintaining neuronal health and plasticity. However, under certain conditions, alpha-synuclein can misfold and aggregate into insoluble brils, which are a hallmark of neurodegenerative diseases known as synucleinopathies [1].

Molecular mechanisms of aggregation

e process of alpha-synuclein aggregation involves a complex interplay of molecular events. Misfolded alpha-synuclein proteins adopt beta-sheet-rich conformations that promote self-association and aggregation. ese aggregates can further propagate by seeding the conversion of soluble alpha-synuclein into pathological forms, thereby spreading pathology throughout the brain .

Clinical implications: parkinson's disease and beyond

Parkinson's disease, a progressive neurodegenerative disorder, is characterized by the loss of dopaminergic neurons in the substantia nigra region of the brain. e presence of alpha-synuclein aggregates, known as Lewy bodies and Lewy neurites, in a ected neurons is a pathological hallmark of PD. ese aggregates are thought to contribute to neuronal dysfunction and cell death, leading to the motor and non-motor symptoms observed in patients.

Beyond Parkinson's disease, alpha-synuclein pathology is implicated in other synucleinopathies such as dementia with Lewy bodies and multiple system atrophy. Each of these disorders exhibits distinct clinical features but shares a common underlying mechanism of alpha-synuclein aggregation and neurodegeneration [2].

transform the landscape of neurodegenerative disease management Continued interdisciplinary collaboration and concerted e orts across basic science, clinical research, and pharmaceutical development are essential to achieve meaningful advances in the treatment and prevention of alpha-synuclein-associated disorders, o ering hope to millions a ected worldwide. Understanding alpha-synuclein aggregation bridges molecular biology with clinical phenomena in synucleinopathies, o ering insights into disease mechanisms and therapeutic targets. By advancing our knowledge of protein misfolding, propagation mechanisms, and genetic/environmental in uences, we strive towards transformative treatments that can delay or halt the progression of alpha-synuclein-associated neurodegeneration, ultimately improving outcomes for patients a ected by these devastating disorders.

References

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Alpha-synuclein aggregation represents a pivotal mechanism linking molecular biology to the clinical manifestations of Parkinson's disease and related synucleinopathies. By elucidating the pathways of alpha-synuclein misfolding, understanding genetic and environmental risk factors, and advancing therapeutic strategies, researchers aim to