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Neurodegenerative Disorders and Protein Aggregation: Unraveling the Molecular Tangles

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INTRODUCTION

Neurodegenerative disorders, characterized by the progressive loss of neuronal structure and function, are among the most debilitating conditions affecting the aging population. A common hallmark of many of these disorders is protein aggregation, where misfolded proteins accumulate and form insoluble fibrils within neurons. This article explores the role of protein aggregation in neurodegenerative disorders, examining the mechanisms behind it, the diseases it impacts, and current research and therapeutic approaches. Proteins are essential molecules that perform a wide array of functions within cells. To function properly, they must fold into specific three-dimensional structures. Misfolded proteins can aggregate into insoluble fibrils, forming structures known as amyloid plaques or neurofibrillary tangles, which are toxic to neurons. Under normal conditions, molecular chaperones assist in proper protein folding and prevent misfolding. When these mechanisms fail, proteins misfold and expose hydrophobic regions that promote aggregation.

DESCRIPTION

Aβ is produced from the amyloid precursor protein through enzymatic cleavage. Misfolded Aβ aggregates into extracellular plaques that disrupt cell-to-cell communication and activate immune responses, leading to inflammation and neuronal death. Tau is a microtubule-associated protein that stabilizes microtubules in neurons. In AD, tau becomes hyper phosphorylated and aggregates into intracellular neurofibrillary tangles, disrupting the cytoskeleton and impairing axonal transport. Parkinson's disease is characterized by motor symptoms such as tremors, rigidity, and bradykinesia, along with non-motor symptoms like cognitive impairment. The primary protein aggregate in PD is alpha-synuclein, which forms Lewy bodies. Alpha-synuclein is a presynaptic protein involved in synaptic vesicle trafficking. In PD, misfolded alpha-synuclein aggregates into Lewy bodies, disrupting synaptic function and contributing to neuronal death in the substantia nigra, a brain region crucial for motor control. TDP-43 is a DNA/RNA-binding protein involved in gene expression regulation. In ALS, TDP-43 mislocalizes and aggregates in the cytoplasm, disrupting RNA processing and cellular homeostasis. Mutations in the SOD1 gene lead to misfolded SOD1 protein, which forms toxic aggregates in motor neurons, contributing to their degeneration. Huntington's disease is an inherited disorder characterized by motor dysfunction, cognitive decline, and psychiatric symptoms. Pharmacological chaperones and small molecules that stabilize protein folding are being investigated. Immunotherapy aims to clear protein aggregates through the immune system. Monoclonal antibodies targeting aggregated proteins, such as aducanumab for Aβ in AD, are designed to facilitate their removal and reduce toxicity. Gene therapy approaches aim to correct genetic mutations that lead to protein aggregation.

CONCLUSION

Protein aggregation plays a central role in the pathology of neurodegenerative disorders, leading to neuronal dysfunction and cell death. Understanding the mechanisms behind protein misfolding and aggregation is crucial for developing effective therapies. Advances in molecular biology, genetics, and pharmacology are driving the discovery of novel treatments aimed at preventing or reversing protein aggregation. As research progresses, the hope for better management and potential cures for neurodegenerative disorders grows, offering new avenues for improving the quality of life for affected individuals.

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CONFLICT OF INTEREST

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