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The Role of Protein Misfolding in Neurodegenerative Diseases

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DESCRIPTION

Proteins are fundamental to virtually every biological process and their function depends on precise three-dimensional structures. When proteins fail to fold correctly, they may aggregate and form abnormal deposits that disrupt cellular processes. Protein misfolding is a central feature in a variety of neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis. These disorders are characterized by progressive neuronal dysfunction, loss of cognitive or motor abilities and the accumulation of specific misfolded proteins. Investigating how protein misfolding impacts neural tissue provides insights into the mechanisms driving disease progression and identifies potential approaches to preserve neuronal function. In normal conditions, protein folding is facilitated by molecular chaperones, which guide proteins into their correct configuration and prevent aggregation. These chaperones recognize unfolded or partially folded proteins and assist in achieving stable conformations. Under conditions of cellular stress, however, these quality control mechanisms can become overwhelmed. Proteins that fail to fold properly accumulate and may form oligomers or larger aggregates, which interfere with intracellular processes, including transport along axons, energy production and synaptic communication. Over time, these disruptions contribute to the functional decline of affected neurons.

Alzheimer's disease provides a clear example of the consequences of protein misfolding. Amyloid-Beta Peptides Misfold and accumulate into extracellular plaques, while tau proteins adopt abnormal conformations that form neurofibrillary tangles inside neurons. Both types of misfolded proteins disrupt intracellular transport, impair synaptic signaling and interfere with energy metabolism. The combined effects of these aggregates compromise neuronal networks and lead to memory loss, impaired reasoning and other cognitive deficits commonly associated with the disease. Research has demonstrated that synaptic dysfunction often appears before noticeable neuron loss, highlighting the early impact of misfolded proteins on network efficiency. Parkinson's disease illustrates how misfolded proteins affect motor systems. Alpha-synuclein, a protein that normally regulates synaptic vesicle dynamics, misfolds and aggregates into Lewy bodies within neurons. These deposits disrupt neurotransmitter release, interfere with axonal transport and trigger local inflammatory responses. The accumulation of alpha-synuclein in the substantia nigra leads to the characteristic motor symptoms of Parkinson's disease, including tremors, rigidity and impaired movement coordination. Misfolded protein aggregates thus serve not only as a hallmark of disease but also as a driving factor in neuronal dysfunction.

The consequences of protein misfolding extend beyond neurons. Glial cells, including microglia and astrocytes, respond to misfolded proteins with immune signaling aimed at clearing harmful aggregates. While initially protective, sustained immune activation contributes to chronic inflammation and increased cellular stress. Energy resources are diverted toward immune responses, reducing support for synaptic maintenance and exacerbating neuronal dysfunction. Persistent immune activity further amplifies the toxic effects of protein aggregates, creating a feedback loop that accelerates disease progression. Metabolic stress is another key factor in the impact of misfolded proteins. Aggregates interfere with mitochondrial function, reducing energy production and increasing oxidative stress. Neurons, which have high energy demands to maintain synaptic signaling and action potential propagation, are particularly vulnerable. Energy deficits combined with misfolded protein accumulation reduce cellular resilience, increasing

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susceptibility to further damage and functional impairment. Genetic factors also influence protein misfolding disorders. Mutations in genes such as presenilin, tau and alpha-synuclein produce proteins that are inherently unstable or prone to aggregation. Individuals with these mutations often experience earlier onset and more severe symptoms.

Therapeutic approaches focus on reducing protein aggregation, enhancing clearance and protecting neurons from the downstream effects of misfolded proteins. Strategies under investigation include molecular chaperones that stabilize protein conformation, small molecules that prevent aggregation and immunotherapies that target misfolded proteins for removal. While fully reversing the effects of accumulated proteins remains challenging, interventions that slow aggregation or support cellular maintenance can preserve neural function and delay symptom progression. Understanding protein misfolding is central to understanding neurodegenerative diseases. Misfolded proteins disrupt synaptic function, impair intracellular transport and increase cellular stress, ultimately compromising neuronal communication and cognitive performance. Research aimed at elucidating how neurons respond to misfolded proteins and how aggregates accumulate offers the potential to identify interventions that maintain protein quality control and reduce the impact of these disorders.

CONCLUSION

Understanding protein miscoding is central to understanding neurodegenerative diseases. Misfolded proteins disrupt synaptic function, impair intracellular transport and increase cellular stress, ultimately compromising neuronal communication and cognitive performance. Research aimed at elucidating how neurons respond to misfolded proteins and how aggregates accumulate offers the potential to identify interventions that maintain protein quality control and reduce the impact of these disorders. By focusing on the mechanisms of protein misfolding, scientists gain insight into both the development and progression of neurodegenerative conditions and the cellular processes that determine neuronal resilience.