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Mechanisms of Aggregate Clearance in Protein Misfolding Disorders

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DESCRIPTION

Accumulation of misfolded proteins is a hallmark of many neurodegenerative disorders and the ability of cells to remove these aggregates is critical for neuronal survival. Misfolded proteins can form oligomers, fibrils and larger deposits that interfere with cellular processes, including synaptic communication, energy metabolism and intracellular transport. Cells employ multiple mechanisms to clear these aggregates and failure of these pathways contributes to the progression of disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis. Understanding the cellular strategies for aggregate clearance provides insight into potential therapeutic approaches. One major pathway for clearing misfolded proteins is the ubiquitin-proteasome system. Proteins tagged with ubiquitin are recognized and degraded by the proteasome, a multi-subunit protease complex. This system efficiently removes damaged or misfolded proteins before they accumulate into larger, insoluble aggregates. In neurodegenerative disorders, proteasome activity can be impaired due to the overwhelming presence of misfolded proteins or direct inhibition by aggregates. Reduced proteasomal clearance allows toxic proteins to persist, disrupt cellular function and trigger stress responses, highlighting the importance of maintaining proteasome efficiency.

Autophagy is another critical mechanism for aggregate removal. In this process, misfolded proteins are enclosed in double-membrane vesicles called auto phagosomes, which then fuse with lysosomes for degradation. Autophagy can target both individual misfolded proteins and larger aggregates, providing a flexible mechanism for maintaining protein homeostasis. Defective autophagy is observed in multiple neurodegenerative disorders, leading to accumulation of protein deposits and increased neuronal stress. Enhancing autophagy has emerged as a strategy to reduce aggregate burden and support cell survival. Molecular chaperones play a supportive role in protein clearance. These proteins recognize misfolded conformations, prevent aggregation and facilitate refolding or targeting for degradation. Chaperones interact with the proteasome and autophagy machinery, bridging recognition and clearance pathways. In disorders where chaperone function is impaired, misfolded proteins escape detection, increasing the likelihood of toxic accumulation. Strategies that enhance chaperone activity can therefore improve aggregate removal and reduce cellular stress.

The interaction between misfolded proteins and cellular membranes affects clearance efficiency. Aggregates can disrupt organelle membranes, impair lysosomal function and alter vesicular trafficking. These disruptions limit the cell's ability to direct misfolded proteins toward degradation pathways. For instance, lysosomal dysfunction reduces autophagic clearance, allowing aggregates to persist and accumulate. Maintaining organelle integrity is therefore essential for effective protein quality control. Genetic mutations can influence clearance mechanisms. Variants in genes encoding chaperones, autophagy regulators or proteasomal components can reduce the efficiency of aggregate removal. For example, mutations affecting lysosomal enzymes or autophagy-related proteins impair the degradation of misfolded proteins, leading to early-onset and more severe neurodegenerative disease. These observations highlight the interplay between protein folding, clearance mechanisms and genetic predisposition in shaping disease outcomes.

Inflammatory responses also interact with aggregate clearance. Microglia recognize extracellular aggregates and attempt to remove them through phagocytosis. While this

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process can reduce toxic protein burden, chronic microglial activation may create an inflammatory environment that further impairs neuronal function. Astrocytes support this process by maintaining extracellular homeostasis and providing metabolic support. Dysfunction in glial clearance pathways can exacerbate aggregate accumulation and accelerate disease progression. Metabolic factors influence aggregate removal. Proteasomal degradation, autophagy and chaperone activity require energy and neurons are highly dependent on Adenosine Triphosphate (ATP) to sustain these processes. Impaired mitochondrial function reduces the energy available for clearance pathways, increasing the likelihood of misfolded protein accumulation. The combination of energy deficits, impaired clearance and aggregate toxicity creates a cycle that progressively undermines neuronal function. Therapeutic strategies targeting aggregate clearance focus on enhancing proteasome and autophagy activity, supporting chaperone function and protecting organelle integrity. Small molecules that stabilize chaperone interactions, compounds that activate autophagy and interventions that improve lysosomal function are under investigation. By reducing the burden of misfolded proteins, these strategies aim to preserve neuronal function, delay disease progression and mitigate cognitive and motor deficits.

CONCLUSION

In conclusion, effective clearance of misfolded proteins is essential for maintaining neuronal health. The proteasome, autophagy pathways, molecular chaperones and glial support systems coordinate to remove toxic aggregates and prevent cellular dysfunction. Failures in these systems contribute to the progression of neurodegenerative disorders, highlighting the importance of understanding and enhancing aggregate removal. Targeting clearance mechanisms offers a promising avenue for therapeutic development and emphasizes the need for integrated strategies to maintain protein homeostasis in neurons.

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