Opinion

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Protein-Protein Interaction Networks in Neurodegenerative Disease Progression

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Introduction

Protein-Protein Interaction (PPI) networks play a central role in maintaining cellular homeostasis, regulating processes such as signal transduction, synaptic plasticity, mitochondrial dynamics, and intracellular transport. In neurodegenerative diseases including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and Amyotrophic Lateral Sclerosis (ALS) these interactions become dysregulated, leading to the accumulation of misfolded proteins, impaired cellular communication, and progressive neuronal dysfunction. Understanding how PPI networks change during disease progression provides valuable insights into the molecular mechanisms underlying neurodegeneration and enables the identification of potential biomarkers or therapeutic targets. As technological advancements in computational biology, structural proteomics, and systems biology continue to expand, mapping disease-specific PPI alterations has become essential for elucidating both early-stage defects and late-stage pathological cascades in the nervous system [1].

Description

PPI networks in neurodegeneration are often centered around disease-specific pathogenic proteins that undergo conformational alterations, leading to aberrant interactions. For example, in Alzheimer's disease, amyloid-β (Aβ) peptides and hyperphosphorylated tau proteins disrupt synaptic PPI networks responsible for memory formation and neuronal stability. Aβ oligomers interact abnormally with receptor complexes such as NMDA receptors, impairing calcium signaling and triggering excitotoxicity. Similarly, tau aggregates destabilize microtubule-associated PPIs, hindering axonal transport and mitochondrial distribution. In Parkinson's disease, mutant or misfolded α-synuclein interacts with a wide range of synaptic and vesicular trafficking proteins, resulting in synaptic dysfunction and dopamine neuron loss. These disruptions highlight how a single misfolded protein can propagate widespread failures across entire interaction networks [2].

Another major determinant of neurodegenerative progression is mitochondrial dysfunction, which is closely intertwined with PPI network dysregulation. Mitochondrial proteins involved in fission and fusion, such as DRP1, MFN1/2, and OPA1, exhibit altered interactions in several neurodegenerative disorders, leading to impaired energy metabolism, oxidative stress, and apoptotic signaling. For instance, PINK1-Parkin–mediated mitophagy, a key PPI-regulated process, is compromised in Parkinson's disease, resulting in the accumulation of damaged mitochondria. Similarly, SOD1 and TDP-43 aggregates in ALS interfere with PPIs essential for RNA metabolism and stress granule dynamics, accelerating neuronal degeneration [3].

These examples underscore how PPI networks coordinate multiple cellular systems and how their disruption contributes to disease complexity. Recent advances in high-throughput proteomics and computational modeling have enabled large-scale mapping of neurodegenerative PPI networks, revealing previously unidentified interactions and potential intervention points. Techniques such as yeast two-hybrid screening, affinity purification–mass spectrometry, and cryo-electron microscopy allow researchers to visualize interaction changes at molecular resolution [4,5].

Conclusion

Protein-protein interaction networks provide a comprehensive framework for understanding the molecular basis of neurodegenerative diseases. Disruptions in these networks propagate through interconnected cellular pathways, contributing to synaptic failure, mitochondrial impairment, and neuronal death. Advances in proteomics, structural biology, and computational modeling are enhancing our ability to map these complex networks and identify therapeutic targets. By integrating multi-omics data with network-based analyses, researchers can develop more precise and effective strategies for early detection and intervention, ultimately paving the way toward improved treatments for neurodegenerative disorders.

Acknowledgement

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Conflict of Interest

None

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