

THE ROLE OF KINESINS IN PARKINSON'S DISEASE

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Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra and the accumulation of α -synuclein aggregates in the form of Lewy bodies. While PD has been traditionally associated with mitochondrial dysfunction, oxidative stress, and protein aggregation, emerging evidence suggests that intracellular transport defects play a crucial role in the pathogenesis of the disease. Kinesins, a superfamily of microtubule-associated motor proteins, are responsible for the anterograde transport of vesicles, organelles, and proteins within neurons. Given the highly polarized nature of neurons, efficient kinesin-mediated transport is essential for maintaining cellular homeostasis. This abstract provides an overview of the role of kinesins in PD, focusing on their involvement in mitochondrial trafficking, autophagy regulation, and axonal transport.

Kinesins and Axonal Transport Dysfunction in PD

Neurons rely on an elaborate transport system to maintain the distribution of essential cellular components. Kinesins facilitate this process by moving cargo along microtubules towards the synapse. In PD, mutations in kinesin motor proteins, as well as regulatory defects, have been implicated in impairing axonal transport. Studies have shown that kinesin dysfunction results in the mislocalization of mitochondria, which contributes to synaptic failure and neurodegeneration. The accumulation of misfolded α -synuclein also disrupts kinesin function by interfering with microtubule stability and motor protein dynamics. Consequently, impaired intracellular trafficking exacerbates neuronal stress and accelerates cell death.

Mitochondrial Dysfunction and Kinesin-Mediated Transport

Mitochondria play a pivotal role in neuronal survival by supplying ATP and regulating calcium homeostasis. Kinesins, particularly KIF5A and KIF1B, are responsible for the anterograde transport of mitochondria, ensuring their proper distribution along the axon. In PD, mitochondrial dysfunction is a well-established pathological hallmark, and recent evidence suggests that defective kinesin-mediated transport further exacerbates this issue. Mutations in genes such as PINK1 and PARK2 (which encode Parkin) lead to disrupted mitochondrial quality control, preventing the recruitment of kinesin-associated proteins necessary for mitochondrial transport. The resulting energy deficits and increased oxidative stress contribute to neuronal vulnerability and degeneration in PD.

Kinesins in Autophagy and Clearance of α -Synuclein Aggregates

Autophagy is a critical cellular process for degrading misfolded proteins and damaged organelles. Kinesins play a crucial role in autophagosomal transport, facilitating the clearance of toxic aggregates, including α -synuclein. Dysfunction in kinesin-driven autophagy impairs the degradation of pathological protein inclusions, contributing to PD progression. For instance, the FYCO1 protein, a kinesin-binding adaptor, is essential for directing autophagosomes towards lysosomes. Studies indicate that mutations in kinesin-associated proteins result in defective autophagic flux, allowing α -synuclein aggregates to accumulate and interfere with normal cellular function.

Therapeutic Potential of Targeting Kinesins in PD

Given their significant role in neuronal transport, kinesins represent potential therapeutic targets for PD. Strategies aimed at enhancing kinesin activity or stabilizing microtubules may help restore intracellular trafficking. Small-molecule activators of kinesins are being explored as potential interventions to improve mitochondrial transport and autophagy in PD models. Additionally, gene therapy approaches aimed at correcting mutations in kinesin-related genes could provide a novel avenue for slowing disease progression.

Conclusion

Kinesins are essential for maintaining neuronal function, and their dysfunction is increasingly recognized as a key contributor to PD pathogenesis. By regulating axonal transport, mitochondrial trafficking, and autophagy, kinesins help sustain neuronal health. Understanding their role in PD offers new insights into disease mechanisms and highlights potential therapeutic strategies aimed at restoring intracellular transport. Future research should focus on identifying specific kinesin modulators that could be used as neuroprotective agents in PD therapy.



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