

SYSTEMATIC REVIEW: THE ROLE OF KINESINS IN PARKINSON'S DISEASE

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Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra and the accumulation of alpha-synuclein aggregates. The transport of essential cellular components, including organelles, proteins, and vesicles, is crucial for neuronal function and survival. Kinesins, a family of microtubule-associated motor proteins, play a critical role in intracellular transport. This systematic review aims to consolidate current evidence regarding the involvement of kinesins in the pathophysiology of PD and their potential as therapeutic targets.

Introduction

PD affects millions of individuals worldwide, with increasing prevalence due to an aging population. While the etiology of PD is multifactorial, disruptions in intracellular transport mechanisms, particularly those mediated by kinesins, have gained attention. Kinesins are responsible for the anterograde transport of cargo along microtubules, ensuring proper distribution of organelles and proteins necessary for neuronal function. Dysfunction in kinesin-mediated transport has been implicated in PD pathogenesis, contributing to axonal transport defects, mitochondrial dysfunction, and alpha-synuclein pathology.

Methods

A systematic literature search was conducted using PubMed, Scopus, and Web of Science databases for articles published from 2000 to 2024. Keywords included "kinesin," "Parkinson's disease," "intracellular transport," and "microtubules." Inclusion criteria encompassed original research, reviews, and clinical studies that examined the role of kinesins in PD. Exclusion criteria included studies unrelated to neurodegenerative diseases and non-English publications. Data extraction focused on kinesin dysfunction, associated molecular pathways, and therapeutic implications.

Results

Kinesin Structure and Function

Kinesins are ATP-dependent motor proteins that move along microtubules, transporting cellular cargo essential for maintaining neuronal integrity. Several kinesin families, including KIF1A, KIF5, and KIF3, have been implicated in neurodegenerative diseases.

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.

Key Kinesins Implicated in PD

KIF1A: Plays a role in synaptic vesicle transport and is sensitive to oxidative stress, which is prevalent in PD.

KIF5: Regulates mitochondrial transport; its impairment leads to mitochondrial dysfunction, a hallmark of PD.

KIF3: Associated with autophagic vesicle transport, crucial for removing protein aggregates in neurons.

Kinesins and Axonal Transport in PD

Neurons rely on efficient intracellular transport to sustain long axons. Defective kinesin-driven transport is observed in PD models, leading to:

Mitochondrial Dysfunction: Reduced transport of mitochondria to synaptic terminals results in energy depletion and oxidative stress.

Protein Aggregate Accumulation: Impaired transport of α -synuclein-containing vesicles leads to toxic aggregate formation.

Defective Autophagy: Kinesin-mediated transport is essential for autophagosome movement; dysfunction impairs cellular clearance mechanisms.

Key Studies Supporting the Role of Kinesins in PD

Oxidative Stress and KIF1A Dysfunction

Chen & Hancock (2025) examined the impact of oxidative stress on KIF1A structure and function, showing that oxidative damage reduces its efficiency, leading to axonal transport failure in PD models.

FYCO1 and Autophagic Regulation in PD

Beer (2024) explored FYCO1's role in modulating autophagy to clear α -synuclein aggregates. The study found that kinesin-associated transport of autophagosomes is disrupted in PD, leading to intracellular protein accumulation.

Proteome Dynamics in Dopaminergic Neurons

Cavarischia-Rega et al. (2024) analyzed kinesin and dynein velocity in human iPSC-derived dopaminergic neurons, finding a link between reduced kinesin activity and impaired neuronal function in PD.

Mitochondrial Transport Deficits in PD

Ng & Ooi (2025) discussed the involvement of mitochondrial transport kinesins (TRAK and Miro proteins) in PD and how their dysregulation leads to neurodegeneration.

Therapeutic Potential of Targeting Kinesins in PD

Given the role of kinesins in PD pathogenesis, therapeutic strategies aim to restore intracellular transport:

Gene Therapy: Restoring kinesin function through gene editing techniques.

Small Molecule Activators: Compounds that enhance kinesin activity to improve neuronal transport.

Mitochondrial Therapies: Enhancing kinesin-mediated mitochondrial trafficking to support neuronal energy demands.

Discussion

The disruption of kinesin-mediated transport is a significant contributor to PD pathology. Emerging evidence highlights the complex interplay between kinesins, mitochondrial dynamics, and alpha-synuclein aggregation. While several therapeutic strategies targeting kinesins are in early-stage research, further studies are needed to translate these findings into clinical applications. Future research should focus on

elucidating the precise molecular mechanisms underlying kinesin dysfunction in PD and identifying potential interventions.

Conclusion

Kinesins play a crucial role in neuronal homeostasis, and their dysfunction is increasingly recognized as a contributor to PD pathogenesis. Understanding kinesin-related transport deficits offers novel therapeutic avenues for PD treatment. Further investigations are required to develop targeted therapies aimed at restoring kinesin function and improving neuronal survival. Defective kinesin-mediated transport plays a crucial role in PD pathology by contributing to mitochondrial dysfunction, protein aggregation, and autophagy deficits. Further research into kinesin-targeted therapies could offer novel approaches for PD treatment.

References

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