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Alexa Q. Xiang

alexax2027@gmail.com

The Ohio State University <https://orcid.org/0009-0001-9087-0178>

Clare Kingsley

Cerritos High School, Cerritos, California, United States

Nicole Ahad

The University of Kansas, Lawrence, Kansas, United States

Kaleb Rodriguez

Middleton High School, Tampa, Florida, United States

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Nanoparticle-Mediated Modulation of the PINK1/Parkin Mitophagy Pathway in Parkinson's Disease: A Narrative Review

Clare Kingsley^{1,2}, Nicole Ahad^{1,3}, Kaleb Rodriguez^{1,4}, Alexa Q. Xiang^{1,5}

¹ThinkNeuro, LLC, Los Angeles, California, United States

²Cerritos High School, Cerritos, California, United States

³Department of Pharmacology and Toxicology, The University of Kansas, Lawrence, Kansas, United States

⁴Middleton High School, Tampa, Florida, United States

⁵William G. Lowrie Department of Chemical and Biomolecular Engineering, The Ohio State University, Columbus, Ohio, United States

*Correspondence:

Corresponding Author

xiang.431@osu.edu

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Abstract

Mitochondrial dysfunction and impaired mitophagy are key mechanisms underlying neurodegeneration in Parkinson's disease (PD). The PTEN-induced kinase 1 (PINK1)/Parkin signaling pathway is a primary regulator of mitochondrial quality control and a promising target for disease-modifying therapies. However, clinical translation of small molecules and neuroprotective agents targeting this pathway remains limited by poor aqueous solubility and unfavorable pharmacokinetics due to restricted blood-brain barrier (BBB) penetration. Nanoparticle-based drug delivery systems offer a potential strategy to overcome these barriers. This narrative review evaluates the literature investigating nanoparticle-mediated therapeutic modulation of the PINK1/Parkin pathway in PD. In particular, it focuses on a primary study evaluating a dual-stage nanoparticle platform comprising a B6 peptide-functionalized hyaluronic acid/chitosan nanocarrier conjugated with a PINK1 antibody and loaded with USP30 siRNA.

The study reported selective accumulation at depolarized mitochondria through PINK1-dependent targeting, resulting in enhanced mitophagy and reduced neuronal injury. In vivo, treatment was associated with preservation of nigrostriatal dopaminergic neurons and improved motor function in experimental PD models. Despite these promising findings, direct empirical literature combining targeted nanocarriers with canonical PINK1/Parkin signaling remains

exceptionally sparse. Existing evidence also relied predominantly on indirect measures of mitochondrial function instead of quantitative assessments of mitophagic flux. Future studies employing standardized mitophagy assays and human induced pluripotent stem cell-derived neuronal models are needed to establish mechanistic efficacy and support clinical translation.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder worldwide, affecting more than 10 million individuals and representing one of the fastest-growing neurological diseases in terms of prevalence and mortality. Although current pharmacological interventions provide symptomatic relief through dopaminergic replacement strategies, no approved therapy has been shown to halt or reverse the underlying neurodegenerative process (Ge et al., 2020). The cardinal motor manifestations of PD, including bradykinesia, resting tremor, rigidity, and postural instability, arise from the progressive degeneration of dopaminergic neurons within the substantia nigra pars compacta and the consequent disruption of the nigrostriatal pathway. Increasing evidence further suggests that mitochondrial dysfunction and neuroinflammation interact throughout disease progression; PD is a multifactorial disorder instead of being driven by a single pathological mechanism.

Among these pathogenic mechanisms, mitochondrial dysfunction is one of the earliest and most consistently implicated contributors to neuronal degeneration. Dopaminergic neurons are particularly susceptible to mitochondrial damage because of their exceptionally high energetic demands and continuous pacemaking activity, which require sustained oxidative phosphorylation. Consequently, efficient mitochondrial quality control is essential for neuronal survival. Failure to remove damaged mitochondria results in excessive reactive oxygen species production, impaired ATP generation, and activation of apoptotic signaling pathways that ultimately contribute to neuronal loss (Ge et al., 2020; Truban et al., 2017).

Mitophagy, a selective form of macroautophagy responsible for degrading dysfunctional mitochondria, constitutes a central component of this quality-control network (Nguyen et al., 2016). The best-characterized mechanism regulating stress-induced mitophagy is mediated by the PTEN-induced kinase 1 (PINK1)/Parkin signaling cascade. Under physiological conditions, PINK1 is constitutively imported into healthy mitochondria through the TOM/TIM translocase complexes, where it undergoes proteolytic cleavage and rapid degradation, maintaining minimal cytosolic signaling. Loss of mitochondrial membrane potential following cellular stress interrupts mitochondrial protein import, allowing full-length PINK1 to accumulate on the outer mitochondrial membrane. Stabilized PINK1 phosphorylates both ubiquitin and the E3 ubiquitin ligase Parkin at Ser65, initiating a feed-forward amplification mechanism that recruits activated Parkin to damaged mitochondria. Parkin subsequently ubiquitinates numerous outer mitochondrial membrane proteins, generating polyubiquitin chains that recruit selective autophagy receptors such as OPTN and NDP52, thereby promoting autophagosome formation

and lysosomal degradation of dysfunctional mitochondria (Harper et al., 2018; Nguyen et al., 2016; Sekine & Youle, 2018).

Genetic and experimental evidence strongly supports the importance of this pathway in PD pathogenesis (Truban et al., 2017). Loss-of-function mutations in either PINK1 or PRKN (Parkin) are established causes of autosomal recessive early-onset Parkinsonism, while impaired mitochondrial quality control has also been observed in sporadic PD, suggesting that disruption of mitophagy extends beyond hereditary disease. Consequently, pharmacological restoration of PINK1/Parkin signaling has emerged as an attractive disease-modifying strategy aimed at preserving neuronal viability beyond alleviating symptoms (Ge et al., 2020; Truban et al., 2017).

Despite this compelling biological rationale, translation of PINK1/Parkin-targeted therapeutics is limited by fundamental drug delivery challenges. Many candidate neuroprotective compounds, including small molecules, nucleic acid therapeutics, peptides, and natural products, demonstrate poor aqueous solubility and inadequate penetration across the blood–brain barrier (BBB). Because the BBB excludes the overwhelming majority of circulating therapeutics, molecular efficacy demonstrated in vitro frequently fails to translate into meaningful in vivo outcomes. These pharmacokinetic barriers have motivated increasing interest in nanomedicine as a platform capable of improving drug stability, prolonging circulation time, enabling receptor-mediated BBB transport, and facilitating subcellular delivery to neuronal mitochondria (Liu et al., 2025).

Numerous nanoparticle platforms, including lipid nanoparticles, polymeric nanoparticles, dendrimers, extracellular vesicles, and biomimetic nanocarriers, have demonstrated the ability to improve central nervous system drug delivery. However, whether these technologies have specifically been developed to modulate the PINK1/Parkin mitophagy pathway has not been systematically characterized. To our knowledge, no previous narrative review has synthesized the empirical literature on the combination of nanoparticle-mediated drug delivery and PINK1/Parkin-directed mitophagy in Parkinson's disease.

Accordingly, this narrative review evaluates the foundational principles regarding nanoparticle-based therapeutic strategies engineered to modulate the PINK1/Parkin pathway in PD, critiques the mechanical design of existing nanocarriers, and identifies methodological and translational gaps that must be addressed to guide future preclinical investigation.

Methods

Literature for this narrative review was identified through structured searches of PubMed, Web of Science, and Google Scholar from database inception through February 2026. Search terms included combinations of keywords surrounding "PINK1," "Parkin," "mitophagy," "nanoparticles," "nanomedicine," and "Parkinson's disease."

Following initial literature exploration conducted with operational support from ThinkNeuro, LLC research intern cohorts, candidate studies were reviewed based on their focus on engineered nanoparticle platforms targeted toward the PINK1/Parkin signaling cascade in preclinical or translational models of Parkinson's disease, with all core authors participating in the evaluation and narrative synthesis.

Results

Narrative Synthesis

Literature exploration identified a core proof-of-concept study directly investigating nanoparticle-mediated regulation of the canonical PINK1/Parkin mitophagy axis in Parkinson's disease models (Chen et al., 2022). This baseline study utilizes an advanced, multi-targeted dual nanoparticle platform designed to respond dynamically to varying severities of mitochondrial stress. Under mild cellular injury, hyaluronic acid nanoparticles (HA-NPs) function as a protective baseline to restore mitochondrial bioenergetics. For severe cellular injury, a sophisticated B6-peptide-HA-PINK1 antibody-chitosan-TPP framework was deployed to deliver USP30 siRNA directly to damaged organelles. This system utilizes targeted mitophagy to facilitate clearance of damaged mitochondria through the accumulation of PINK1 on the outer mitochondrial membrane, promoting silencing of the USP30 gene, with comprehensive evidence reported in **Table 1**.

Parameter Grouping	Empirical Specifications
Primary Study Aims	To develop a dual-stage, targeted nanoparticle delivery framework capable of differentiating between mild and severe mitochondrial damage to regulate mitochondrial quality control in PD models.
Nanoparticle Composition and Size Metrics	Hyaluronic acid nanoparticles (HA-NPs) for mild injury; B6-peptide-HA-PINK1 antibody-chitosan-TPP (CS-TPP) core-shell nanoparticles loaded with USP30 siRNA for severe injury.
Targeting Mechanisms	Blood-Brain Barrier (BBB) B6 peptide functionalization; subcellular targeting with PINK1 antibody conjugation to selectively cross-link with

	PINK1 accumulating on the outer mitochondrial membrane of damaged organelles.
Experimental Models Evaluated	<i>In vitro</i> SH-SY5Y cells, mouse embryonic fibroblasts (MEF) wildtype, and PINK1 knockout PINK1 ^{-/-} cells. <i>In vivo</i> MPTP-induced Parkinsonian mouse models.
Sample Sizes and Dosing Regimens	Cohort-based sampling of cell cultures and experimental arms was utilized for preclinical assessments. Dosing was standardized using nanoparticles of targeted siRNA, adjusted according to media volume and corresponding body weight equivalents.
Mitophagy and Mitochondrial Readouts	Mitochondrial membrane potential ($\Delta\Psi_m$), mitochondrial morphological structures, USP30 protein knockdown efficiency, ATP and bioenergetic production rates, and indirect markers of mitochondrial clearance.
Key Therapeutic Outcomes	Successful specific clearance of severely damaged mitochondria without destroying healthy organelles; recovery of baseline cellular bioenergetics; structural preservation of striatal dopaminergic neurons; and reversal of objective motor deficits <i>in vivo</i> .
Geographical Origin	International research origin (Chen et al., 2022).
Methodological Limitations	Heavy reliance on indirect functional proxies of mitochondrial clearance rather than direct, real-time mitophagy flux assays; exclusive use of preclinical animal and immortalized cell lines rather than humanized iPSC-derived neurons.

Table 1. *Comprehensive evidence synthesis of Chen et al. (2022)**Methodological Quality and Confounding Considerations*

The empirical findings from Chen et al. (2022) demonstrate strong experimental validity, supported by instrument-driven assays that minimize observer-related measurement bias. For instance, mitochondrial respiratory function was assessed via Seahorse XFe24 extracellular flux analysis, mitochondrial membrane potential was assessed fluorometrically using rhodamine 123, and USP30 gene silencing was confirmed through quantitative real-time PCR. Automated data collection across these analytical platforms substantially mitigates investigator bias.

However, several methodological factors and environmental variables inherent to preclinical study designs warrant consideration. These include the use of multiple cell line variants (SH-SY5Y neuroblastoma, MEF+/+, and MEF PINK1-/-) without explicit baseline comparative justifications, the testing of four hyaluronic acid molecular weights without documented prior rationale, and the restriction of in vivo experimentation to male C57BL/6 mice aged eight weeks. This demographic limitation precludes immediate generalization across sex, age, and species differences known to influence Parkinson's disease pathophysiology. Additionally, variability in H₂ O₂ concentrations across experimental conditions introduces potential bioenergetic confounders. Collectively, these factors are characteristic of early cell- and rodent-based preclinical research; while they do not compromise the primary findings, they highlight uncertainties regarding the broader translational scope.

Discussion*General Interpretation*

This review reveals a major gap in the current literature surrounding nanoparticle-mediated regulation of the PINK1/Parkin mitophagy pathway in Parkinson's disease. Although mitochondrial nanomedicine has been widely discussed as a therapeutic strategy, very little empirical research has directly connected PINK1/Parkin mitophagy regulation to engineered nanoparticle delivery systems (Milane et al., 2021). Across the synthesized literature, only one primary experimental study directly targeted this mechanistic intersection. This finding is important, because it shows that this specific therapeutic intersection is still in a very early stage of development despite its potential.

Chen et al. (2022) provides the only direct baseline evidence for this area. The study tested a dual nanoparticle strategy which attempted to address different degrees of mitochondrial damage. For mild or reversible mitochondrial injury, HA-NPs were used to improve mitochondrial function and support cellular bioenergetics. For irreversible mitochondrial damage, the authors used a B6-peptide-HA-PINK1 antibody-CS-TPP nanoparticle system loaded with USP30 siRNA. This design was intended to target damaged mitochondria more selectively while promoting mitophagy through USP30 knockdown, a useful proof of concept for how nanomedicine may be used to regulate mitochondrial quality in PD models.

The nanoparticle mechanics are especially relevant, because they attempt to solve several major barriers at once. The B6 peptide was used to improve delivery, while HA provided a mitochondrial protective component. The PINK1 antibody gave the system a way to recognize damaged mitochondria, since PINK1 accumulates on the outer mitochondrial membrane during mitochondrial injury. The addition of USP30 siRNA then allows the nanoparticles to promote removal of damaged mitochondria by reducing USP30 activity. Broad activation of mitophagy can potentially clear healthy mitochondria; by targeting PINK1-positive damaged mitochondria, this system attempts to increase the specificity of mitochondrial clearance.

Categorization of Current Literature and Related Frameworks

An examination of the broader literature highlights three main categories of research surrounding Parkinson's disease nanomedicine. The first category comprises comprehensive conceptual reviews. While these works provide valuable theoretical frameworks regarding the neuroprotective potential of biomimetic nano-scaffolds, their high volume relative to original empirical investigations highlights a significant translational bottleneck. The scientific community is heavily engaged in detailing what precision nanomedicine could achieve (Denyer & Douglas, 2012; Jung et al., 2025; Majumdar & Badwaik, 2024; Milane et al., 2021; Owais & Siddique, 2023; Wang et al., 2023), while very few primary studies have experimentally evaluated these specific designs.

The second category includes studies evaluating neuroprotective nanocarriers that lack specific PINK1/Parkin mitophagy markers. An analysis of these near-miss investigations demonstrates that current neuroprotective nanotechnology remains anchored to broad, non-specific physiological endpoints. Many of these projects successfully engineered advanced delivery platforms to cross the blood-brain barrier and clear reactive oxygen species (ROS) in dopaminergic zones (Hu et al., 2017; Sánchez-Giraldo et al., 2020; Srivastav et al., 2020). However, they stopped short of verifying organelle-specific clearance pathways or downstream autophagic recruitment mechanisms (Yealland et al., 2016).

The third category involves adjacent projects that track secretory profiles or autophagic endpoints using natural biological vectors instead of engineered synthetic nanoparticle matrices (Carbajal et al., 2025; Howard et al., 2022; Song et al., 2016). This includes approaches that

utilize biological extracellular vesicles or natural macrophage transfection models (Zhao et al., 2019; Zhao et al., 2022). Examining these adjacent fields alongside conceptual reviews highlights the boundaries of the current field: outside of the pioneering framework established by Chen et al. (2022), the targeted combination of synthetic nanotechnology and canonical mitophagy signaling remains fundamentally limited.

Geographical Distribution and Research Implications

A clear imbalance exists in where this literature originates. Across the evaluated literature, authorship remains tightly grouped within just a few nations. Chinese institutions led the dataset in total volume, followed by contributing groups in India, the United States, and the United Kingdom. This geographic clustering points directly to a deeper structural issue in global research. It shows that only a handful of regions possess the massive funding streams, specialized nanotechnology labs, and preclinical regulatory setups required to execute these studies.

Consequently, this lack of diversity threatens to bottleneck the development of new Parkinson's disease treatments. When a field depends on a few distinct hubs, it naturally inherits localized biases in its methodology. The global literature can easily become oversaturated with a single nanoparticle style or specific protocol simply because a regional funding body prefers it. Furthermore, limiting the data to these regions restricts our understanding of how environmental differences or distinct animal models alter therapeutic outcomes. Building standardized, universally reliable nanomedicine protocols will ultimately require the field to actively diversify its authorship and expand cross-border collaborations.

Limitations

Because only one eligible study was identified, the current evidence is not strong enough to make broad conclusions about clinical effectiveness. The included study used preclinical models, including SH-SY5Y cells, wildtype MEFs, and PINK1^{-/-} knockout cells, and MPTP-treated mice. Although these models are useful for studying early mechanisms, they do not fully represent the complex, progressive nature of PD in human patients. As a result, the study establishes an important starting point, but does not yet showcase whether this approach can be translated clinically.

There are also limitations in the mitophagy evaluation. The included study measured mitochondrial function and membrane potential, USP30 knockdown, mitochondrial morphology, and behavioral outcomes. While these measurements are useful, they are indirect representations of mitophagy. More direct mitophagy flux assays and pathway-specific markers would be necessary to confirm the PINK1/Parkin pathway is being consistently and specifically regulated. The clinical and practical implications of this gap are significant; if nanoparticle-based regulation of mitophagy is going to become a meaningful disease-modifying strategy for PD, the field

demands more primary experimental research. However, the identification of only one eligible primary study does not mean that nanoparticle-mediated PINK1/Parkin regulation lacks therapeutic potential; the field is currently operating from a very limited foundation.

Conclusion

This review aimed to lay out the verifiable context of nanoparticle-mediated modulation of the PINK1/Parkin mitophagy pathway in Parkinson's disease. Despite the well-established importance of the PINK1/Parkin pathway in Parkinson's disease, it remains extremely limited in direct empirical evaluation within nanoparticle-mediated systems targeting this pathway.

While preclinical proof-of-concept data demonstrates the potential of antibody-functionalized nanomedicine to selectively clear damaged organelles, the empirical foundation of this field remains fundamentally limited. To advance towards clinical relevance, several vital translational gaps must be addressed by future investigations.

First, researchers must shift away from indirect functional proxies, including mitochondrial membrane potential measurements and OCR-based bioenergetic readouts, towards validated real-time mitophagy flux assays. Validation of markers such as LC3-II/I ratios, p62/SQSTM1 clearance, as well as direct Parkin translocational confirmation is needed to mechanistically confirm pathway-specific claims.

Second, the exclusive reliance on immortalized cell lines and acute toxin-induced rodent models demonstrates a substantial translational gap. Future studies should make use of human iPSC-derived dopaminergic neurons carrying PD-relevant PINK1/Parkin mutations, since they most accurately recapitulate the bioenergetic vulnerabilities, mitochondrial network dynamics, and genetic architecture.

Lastly, the nanoparticle platforms themselves require longitudinal safety profilings, including chronic immunogenicity assessments, pharmacokinetic characterizations beyond the 3-hour biodistribution window, and dose-response optimization in progressive rather than acute PD models. The convergence of antibody functionalized nano scaffolds and brain-targeted delivery chemistry positions PINK1/Parkin-directed nanomedicine as a promising yet critically underdeveloped disease-modifying strategy. Expanding the empirical foundation with rigorous, detailed, flux-confirmed, and humanized experimental models would be valuably essential to determine if the molecular specificity established by Chen et al. (2022) can be successfully translated into a durable clinical intervention for Parkinson's disease.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current review.

Conflicts of Interest

There was no financial support during the creation of this review; however, the review authors received general guidance from ThinkNeuro, LLC's spring bibliometrics research internship program that provided mentorship and general suggestions on data collection methodology and abstract drafting. The review authors do not have any competing interests.

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