Mitochondrial Therapies for Neurodegenerative Diseases: Emerging Approaches and Challenges

Monara Kaélle Sérvulo Cruz Angelim

ABSTRACT

Mitochondrial dysfunction is a defining feature of numerous neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, where it contributes to impaired energy metabolism, oxidative stress, and neuronal loss. Advances in mitochondrial-targeted therapies have paved the way for innovative interventions, such as mitochondrial transplantation, gene editing, antioxidants, and mitophagy enhancers, each offering unique potential to restore mitochondrial function and provide neuroprotection. This review examines these cutting-edge strategies, addressing their mechanisms of action, therapeutic potential, and the challenges associated with clinical translation.

Keywords: Mitochondrial dysfunction, Neurodegenerative diseases, Mitophagy enhancers, Mitochondrial transplantation, Oxidative stress

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Introduction

Mitochondria are dynamic organelles essential for cellular energy production, calcium homeostasis, and regulation of apoptosis, all of which are critical for maintaining metabolic and cellular health. First described by Altmann in 1890 as "bioblasts," mitochondria were later named by Benda in 1898, with their key role in ATP production established through pioneering work on oxidative phosphorylation (OXPHOS).[1] Mitochondrial dysfunction is now recognized as a hallmark of numerous diseases, particularly those affecting the central nervous system (CNS). In the brain, mitochondrial dysfunction is closely linked to cognitive decline, aging, and various neurodegenerative disorders.[2,3] Diseases such as Alzheimer's, Parkinson's, Huntington's, amyotrophic lateral sclerosis (ALS), and epilepsy share a common feature: profound metabolic disturbances involving mitochondrial function (Figure 1).

Alzheimer's disease (AD) is marked by the extracellular accumulation of amyloid-beta (Aβ) peptides and the formation of intracellular neurofibrillary tangles composed of hyperphosphorylated tau. These pathological changes lead to the loss of cholinergic neurons, resulting in brain atrophy and progressive memory and cognitive decline.[4] Intriguing, Aβ binds to mitochondrial enzymes, causing severe alterations in mitochondrial morphology and function, including increased reactive oxygen species (ROS) production, ATP depletion, calcium dysregulation, defective mitophagy, and apoptosis induction.[5,6]

Parkinson's disease (PD) is characterized by the degeneration of dopaminergic neurons in the substantia nigra pars compacta and reduced dopamine levels in the striatum, which together result in motor dysfunction. Hallmarks of PD include Lewy body formation and alpha-synuclein aggregation.[7] Similarly, mitochondrial dysfunction is central to PD pathogenesis, with familial cases often linked to mutations in mitochondrial genes such as PINK1 and Parkin.[8] Both familial and sporadic forms involve oxidative stress, disrupted mitochondrial dynamics, and impaired mitophagy.[9,10]

Huntington's disease (HD) is a genetic neurodegenerative disorder caused by mutations in the huntingtin gene, leading to the loss of GABAergic striatal medium spiny neurons. Patients experience progressive behavioral changes, motor coordination deficits, and cognitive decline until death.[11] The pivotal drivers of HD progression also involve mitochondrial dysfunction, including increased ROS production, impaired OXPHOS, calcium imbalance, and defective mitophagy.[12,13]

ALS is another neurodegenerative disorder, characterized by the progressive loss of motor neurons, leading to muscle atrophy, weakness, and ultimately respiratory failure.[14] While most ALS cases are sporadic, some are linked to mutations in the superoxide dismutase 1 gene, which promotes protein aggregation and neuroinflammation.[15] In the early stages of ALS, mitochondrial dysfunction is also evident, manifesting as ATP depletion, oxidative stress, disrupted mitochondrial dynamics, and impaired mitophagy.[16]

Given the central role of mitochondrial dysfunction in these diseases, targeting this organelle has emerged as a promising strategy to combat neurodegeneration. Enhancing mitophagy—the cellular process responsible for clearing damaged mitochondria—has been shown to restore cellular homeostasis and reduce oxidative stress. Additionally, minimizing mitochondrial ROS production, a key driver of oxidative damage, protects neurons from DNA damage, chronic inflammation, and functional decline. More recently, advances in gene-editing technologies, such as Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR), offer new opportunities to correct mitochondrial DNA (mtDNA) mutations and enhance mitochondrial resilience. Another innovative approach is mitochondrial transplantation, which involves delivering healthy, functional mitochondria to the CNS to restore metabolic balance and slow disease progression. Ultimately, the future neurodegenerative disease treatment lies in integrating mitochondrial-targeted therapies with broader neuroprotective strategies. As our understanding of mitochondrial biology deepens and therapeutic delivery systems advance, novel interventions will continue to emerge, addressing the underlying metabolic challenges of these debilitating conditions.

Mitophagy Enhancers

Mitophagy is a highly specialized cellular process responsible for selectively removing damaged mitochondria, ensuring mitochondrial quality control and cellular homeostasis. Impaired mitophagy leads to the progressive accumulation of defective mitochondria, which can trigger cellular degeneration and contribute to disease pathology. A recent review by Antico et al.[17] provides comprehensive evidence that mitophagy dysfunction is a hallmark of several neurodegenerative diseases, including AD, prion disease, PD, HD, and ALS. In these conditions, the accumulation of damaged mitochondria results in reduced ATP production, excessive ROS generation, protein misfolding, synaptic dysfunction, and cognitive decline.

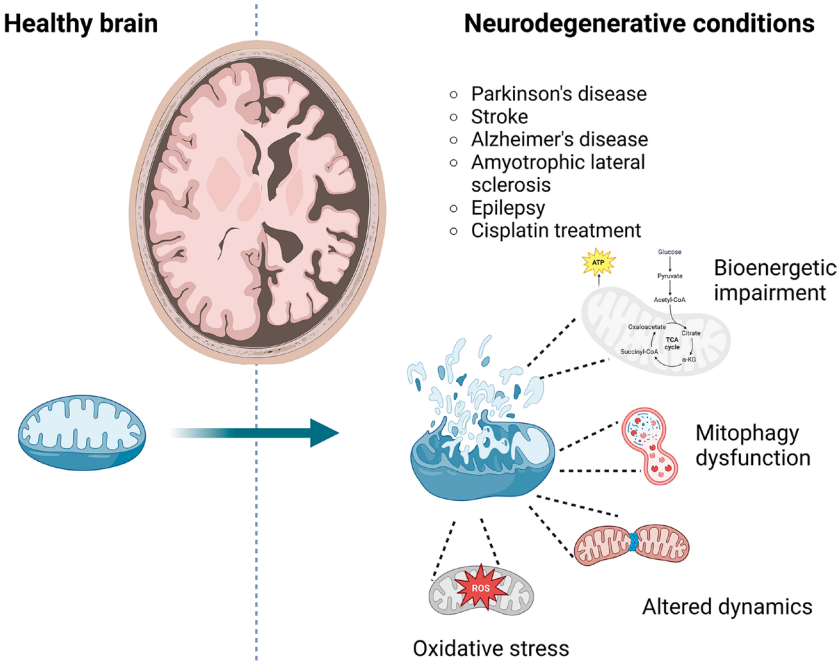

Fig 1 | Mitochondrial dysfunction in neurodegenerative conditions. Mitochondrial impairments are a common feature in numerous neurological conditions, including neurodegenerative disorders and complications arising from anti-cancer therapies.[95] These dysfunctions encompass a broad spectrum of maladaptations in mitochondrial functions within neurons, such as diminished energy metabolism, disrupted mitophagy, imbalanced mitochondrial dynamics (fusion and fission), and elevated oxidative stress. Collectively, these alterations contribute significantly to neuronal loss observed in CNS pathologies

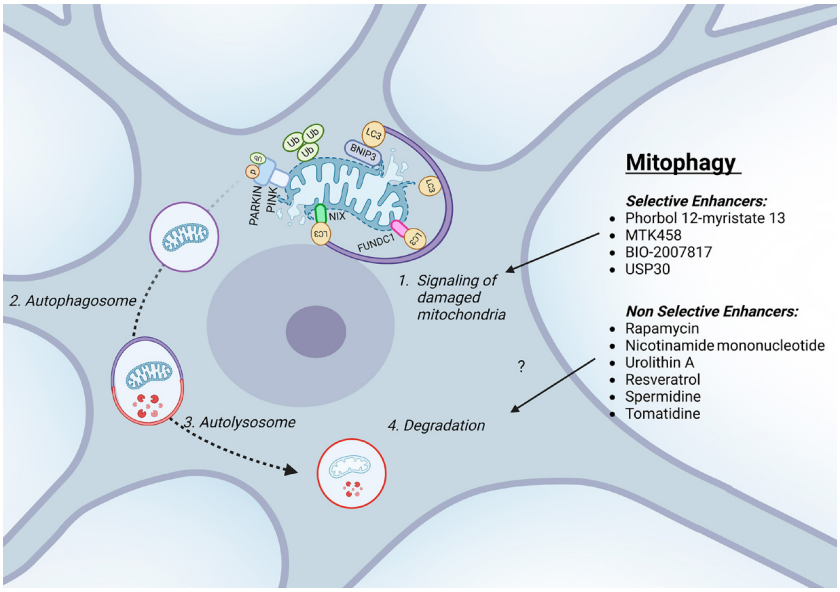

Fig 2 | Pathways of mitochondrial clearance. Schematic representation of the two main mitophagy pathways. In the conventional PINK1/Parkin-dependent pathway, mitochondrial damage leads to PINK1 stabilization on the outer membrane, where it phosphorylates ubiquitin and activates Parkin, amplifying ubiquitination and recruiting autophagy adaptors for mitochondrial degradation. Alternatively, receptor-mediated mitophagy occurs independently of PINK1/Parkin, where BNIP3 and NIX directly interact with LC3 on autophagosomes to facilitate mitochondrial clearance. Both pathways facilitate mitochondrial engulfment by autophagosomes and degradation via lysosomes

In conventional mitophagy (Figure 2), damaged mitochondria are tagged with molecular signals, such as phosphorylation and ubiquitination, marking them for removal by lysosomes. A key player in this process is PTEN-induced putative kinase 1 (PINK1), a protein that accumulates on damaged mitochondria and serves as a molecular distress signal. Upon mitochondrial damage and membrane depolarization, PINK1 accumulates on the outer mitochondrial membrane, where it phosphorylates and ubiquitinates several proteins, including Parkin. Parkin, an E3 ubiquitin ligase, further ubiquitinates a wide range of mitochondrial proteins, amplifying the mitophagy signal. This cascade of phosphorylation and ubiquitination facilitates the recruitment of autophagy receptors, which in turn attract phagophores containing microtubule-associated protein 1A/1B-light chain 3 (LC3). This ultimately leads to lysosomal degradation of dysfunctional mitochondria, completing the PINK1/Parkin-dependent mitophagy process.[18]

One approach to sustaining PINK1 activation under mitochondrial stress is the use of MTK458, a brain-penetrant small molecule that binds to PINK1, stabilizing it and thereby enhancing mitophagy. MTK458 has entered Phase I clinical trials (NCT06414798) to assess its effectiveness in promoting mitophagy. Despite its complexity due to multiple activated domains, Parkin has also been targeted for drug development. Biogen has pioneered Parkin modulators, specifically tetrahydropyrazolo-pyrazines such as BIO-2007817, which enhance Parkin's enzymatic activity under mitochondrial stress.[17]

Further advancing the modulation of ubiquitin-dependent mitophagy, USP30 inhibitors have been developed as another promising strategy. USP30 is the most extensively studied deubiquitylating enzyme known to counteract Parkin-mediated ubiquitination. Inhibition of USP30 has been shown to induce mitophagy and reduce oxidative stress in human Parkin-deficient neurons.[19] Currently, numerous patents have been filed, and both preclinical and clinical studies are underway to evaluate the therapeutic impact of these inhibitors.

While PINK1/Parkin-dependent mitophagy plays a key role in mitochondrial quality control, other compounds can stimulate mitophagy through broader cellular pathways. Alternatively, mitophagy can also occur through outer mitochondrial membrane proteins that directly interact with LC3 motifs. Among these,

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BNIP3 (B cell lymphoma2/adenovirus E1B19 interacting protein 3) and NIX (BNIP3L) play critical roles. Both proteins can be activated by hypoxia-inducible factor transcription factors to sustain efficient mitophagy under stress conditions.[20] NIX has been linked to mitophagy by isolating mitochondria into autophagosomes, compensating for deficits in PINK1/Parkin-mediated mitophagy.[21] Supporting its role in neurodegenerative diseases, Koentjoro and collaborators demonstrate that phorbol 12-myristate 13-acetate-induced Nix expression restored mitophagy in Parkinson's disease models.[22]

In addition to selective mitophagy enhancers, certain naturally occurring compounds can stimulate mitophagy through indirect mechanisms. These molecules have gained interest for their potential neuroprotective effects, including rapamycin, the NAD+ precursor nicotinamide mononucleotide, urolithin A, resveratrol, spermidine, and tomatidine.[23,24] Nicotinamide mononucleotide has been shown to enhance autophagy by activating sirtuin 1 (SIRT1), which deacetylates autophagy-related proteins involved in autophagosome formation.[25,26] As a result, NAD^+ supplementation has shown promise in treating CNS disorders and is currently being evaluated in clinical trials for PD.[27–29]

Urolithin A, a metabolite produced by gut bacteria such as *Gordonibacter urolithinfaciens*, has been shown to improve mitochondrial health in elderly individuals and enhance mitophagy in preclinical studies.[30,31] While the exact mechanism underlying its mitophagy-promoting effects remains unclear, rodent studies have demonstrated that methylated urolithin A administration increases the levels of ubiquitinated mitochondrial proteins, supporting its role in mitophagy enhancement.[32] This molecule holds promise for neurodegenerative disease treatment, as evidenced by its beneficial effects in AD models, where urolithin A treatment reduced disease pathology and improved cognitive function.[33] However, further research is needed to elucidate the precise mechanisms and therapeutic potential of urolithin A in humans.

In addition to these compounds, other bioactive molecules have been implicated in mitophagy regulation, like resveratrol, a polyphenol abundant in red grape skins that also activates SIRT1, thereby influencing mitophagy.[34] Similarly, spermidine, a polyamine found in foods like wheat germ, soybeans, and broccoli, promotes mitophagy by inhibiting EP300, an acetyltransferase that suppresses autophagosome formation.[35] Studies have shown that spermidine-induced autophagy modulates inflammatory processes in AD.[36]

Although these compounds show promise in preclinical models, further research is needed to determine their safety, optimal dosing, and long-term effects in humans. Understanding how mitophagy interacts with other cellular pathways, such as inflammation and metabolism, will be crucial for developing effective therapies for neurogenerative diseases.

Antioxidants

The brain is highly vulnerable to oxidative damage because it consumes large amounts of oxygen, contains easily oxidized fatty acids in neuronal membranes, and has a weaker antioxidant defense system compared to other organs. While ROS play essential roles in cell signaling and neuronal development, excessive ROS can overwhelm the cell's defense systems, leading to oxidative stress and neuronal damage. ROS-induced DNA, protein oxidation, and lipid peroxidation[39–41] contribute to neurotransmission defects,[42] neuronal dysfunction, and, ultimately, neuronal death.[43] Oxidative stress is also implicated in the aggregation of neurotoxic proteins such as α-synuclein in PD,[44] mutant huntingtin protein in HD,[45,46] and β-amyloid in AD.[47,48]

Because mitochondria generate most of the ROS in neurons, they are particularly vulnerable to oxidative damage. This has driven research into developing antioxidants that specifically target mitochondrial ROS, like mitoquinone (MitoQ), CoQ10, SkQ1, and Mito-TEMPO.

MitoQ is a mitochondrial-targeted antioxidant designed to neutralize harmful ROS, such as superoxide, peroxyl, and peroxynitrite.[50] By reducing oxidative stress, it helps restore mitochondrial function in models of PD,[51] AD,[52] ALS,[53] and HD.[54] Similarly, SkQ1 targets mitochondrial superoxide and has shown efficacy in ameliorating symptoms in mouse models of PD[55] and AD.[56] MitoTEMPO functions as a SOD mimetic, mitigating oxidative damage in AD,[57] ALS,[58] and PD models.[59] Another promising molecule is MitoVitE, a mitochondria-targeted form of vitamin E that is rapidly absorbed by mitochondria.[60] While it has demonstrated potential in preventing cell death under various conditions, its role in neurodegenerative diseases remains underexplored.

Despite the promising preclinical results, mitochondrial antioxidants have struggled in clinical trials. Challenges include difficulty crossing the blood-brain barrier (BBB), low bioavailability in the brain, difficulty determining the right dosage, potential toxicity, and the body's natural compensatory mechanisms that can reduce their effectiveness over time.

To overcome the challenge of the BBB and enhance mitochondrial targeting, various strategies have been explored. One approach involves conjugating antioxidants to lipophilic cations, which allows them to accumulate in mitochondria by exploiting the organelle's natural membrane potential. Examples of such molecules include triphenylphosphonium (TPP+), rhodamine 123, MKT-077, and anthracyclins.[61,62] Among these, MitoQ, a TPP+-conjugated antioxidant, is the most extensively studied for mitochondrial targeting both *in vitro* and *in vivo*.[63] Additionally, liposomes and nanoparticles have been developed to encapsulate antioxidants, improving drug stability, solubility, and BBB penetration and potential fusion with the mitochondrial membrane.[64] Peptide-based delivery systems, such as cell-penetrating peptides and mitochondrial-targeting sequences, offer another target approach.[65] More recently, tannic acid and melanin-modified nanomedicine have been explored for ROS neutralization, particularly in conditions of BBB disruption.[66] Although promising strategies exist for

targeting mitochondrial antioxidants to the brain, further research is needed to optimize drug formulations, improve brain penetration, and ensure safety in long-term treatments. Future studies should also explore how these therapies interact with other cellular pathways involved in neurodegeneration.

Mitochondrial Gene Editing

Gene editing is a revolutionary technique that uses recombinant DNA technology to correct or replace faulty genes, potentially reversing disease progression. In the context of mitochondrial disorders, caused by mutations in mtDNA that disrupt energy production and contribute to neurodegeneration, gene therapy provides a targeted solution. By directly correcting these genetic defects, this approach restores mitochondrial function and enhances neuroprotection. Its primary advantage lies in its ability to modify or induce gene expression at the source of dysfunction, offering a direct path to cellular homeostasis. Moreover, gene therapy can be tailored to disease pathogenesis, stage, and spatial context, making it a promising strategy for treating mitochondrial-related neurodegenerative diseases.

To deliver therapeutic genes into cells, researchers have explored various vectors, with adeno-associated viruses (AAVs) emerging as the gold standard for targeting CNS disorders.[67,68] These vectors have been used to increase the expression of key neurotransmitters like gamma-aminobutyric acid-GABA[69] and dopamine[70] and neuroprotective proteins (Parkin and PINK1, glial cell line-derived neurotrophic factor-GDNF, nerve growth factor-NGF).[71,72] PINK1 and Parkin regulate mitochondrial quality control by promoting mitophagy. Mutations in these genes impair mitochondrial biogenesis by disrupting proliferator-activated receptor gamma coactivator-1α (PGC-1α), a key regulator of energy metabolism. In a PD mouse model, delivering lentivirus-PGC-1α into the striatum restored mitochondrial function,[47] highlighting its therapeutic potential.

Beyond gene replacement strategies, RNA interference has been employed to silence pathogenic proteins, such as polyglutamine huntingtin in HD.[73,74] More recently, CRISPR/Cas9 gene editing has gained interest for its ability to directly modify disease-related genes, as seen in experimental treatments for AD.[75] In the context of mitochondrial disorders, gene therapy offers a promising approach for targeting mutations within mtDNA, which have been implicated in several neurodegenerative diseases, including ND3 mutations in PD, C9orf72 and TARDBP mutations in ALS, and ATP6 mutations in AD.[72,76,77] By delivering healthy mtDNA, gene therapy could bypass defective mitochondrial genes, potentially restoring mitochondrial function and slowing disease progression.

Despite its promise, mitochondrial gene therapy faces significant challenges, particularly in the development and optimization of delivery vectors. Although AAVs are the most commonly used vectors, their clinical application faces challenges, including the risk of immune system activation, which can reduce effectiveness and cause adverse effects, especially when injected directly into the CNS. The immune system can recognize AAVs, triggering responses that not only reduce therapeutic efficacy but also increase the risk of adverse effects. To overcome these limitations and enable repeated administration, researchers have developed non-viral delivery systems, such as nanoparticles and liposomes.[78] These carriers can encapsulate gene-editing tools, protecting them from degradation and improving their ability to cross the BBB. However, challenges remain, including potential toxicity at high doses.

One approach to bypassing the BBB and facilitating transcytosis involves encapsulating plasmids in immunoliposomes-liposomes conjugated with antibodies that enhance brain uptake of nanoparticle-based therapeutics.[79,80] Additionally, gold nanoparticles and cell-penetrating peptides have gained interest due to their biocompatibility, small size, and surface charges, making them promising candidates for CNS-targeted delivery.[81–83] Once within the brain parenchyma, delivery vectors must effectively diffuse throughout the brain to reach their target cells. Among the most promising candidates is poly(β-amino ester), a biodegradable polymer shown to efficiently diffuse through the extracellular matrix and internalize into cells, bypassing the cell membrane.[84] This approach can be further optimized using focused ultrasound to transiently open the BBB, allowing increased poly(β-amino ester) accumulation in targeted brain regions.[85]

An additional challenge is ensuring that gene therapy reaches the correct neuronal populations. One strategy is receptor-mediated targeting, which uses molecules that bind to specific cell surface receptors to enhance precision, such as neurotensin, NGF, transferrin receptors, and ten-eleven translocation-1.[86,87]

While mitochondrial gene therapy has made significant progress, future research must focus on refining microinjection techniques, improving gene delivery precision, and addressing immune-related challenges. Continued innovation in gene editing and targeted delivery could pave the way for more effective, personalized treatments for neurodegenerative diseases.

Mitochondrial Transplantation

Mitochondrial transplantation, or mitotherapy, is a novel therapeutic strategy designed to replace dysfunctional mitochondria with healthy, respiratory-competent organelles. This process involves isolating mitochondria from a donor and delivering them directly to the target site to restore mitochondrial activity (Figure 3). Common donor sources for mitochondria include stem cells, with the primary mechanisms of transfer being endocytosis and membrane fusion.[88] Before transferring, mitochondria can be preconditioned to improve their function in energy production or protecting them from stress. The integration of exogenous mitochondria into the recipient cell's mitochondrial network remains an area of ongoing investigation. Nevertheless, preclinical studies have demonstrated

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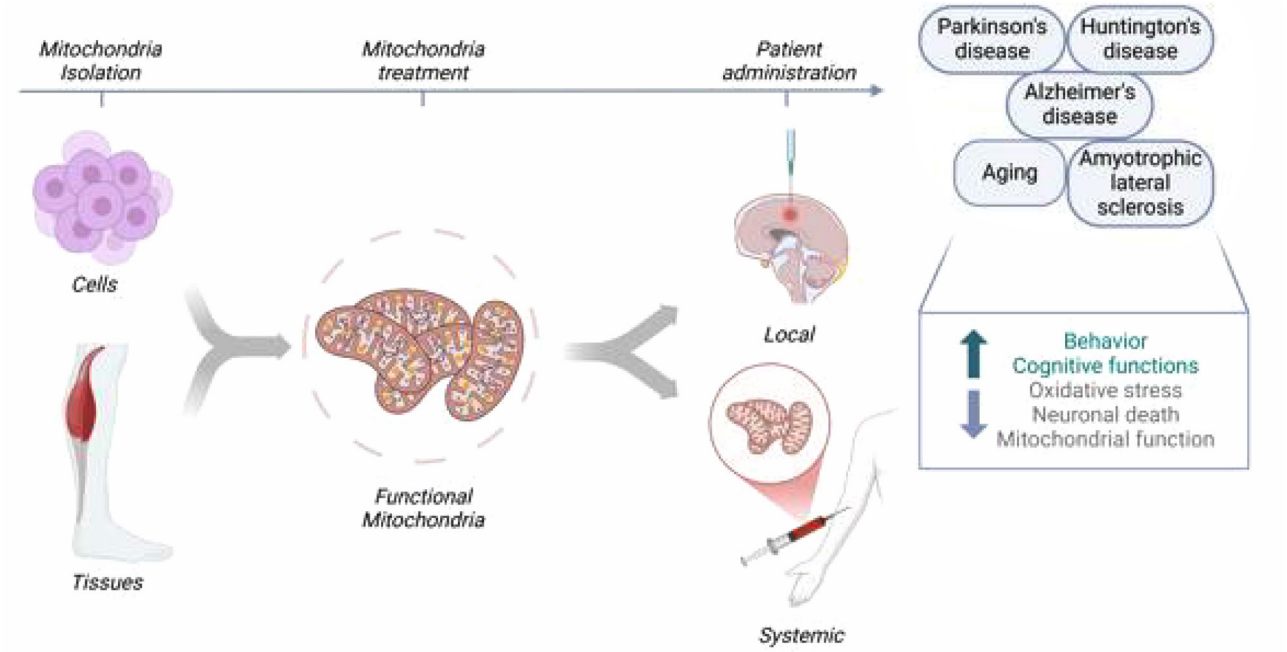

Fig 3 | Mitochondrial transplantation (mitotherapy) for treating neurodegenerative diseases. Mitotherapy is a novel strategy to restore mitochondrial function by delivering healthy, respiratory-competent mitochondria from donor cells, often stem cells or from healthy tissues, like muscles. These mitochondria can be administered systemically or directly at the target site and be uptaken by cells with impaired mitochondria for the treatment of neurodegenerative diseases

the potential of mitotherapy in a variety of diseases, including neurodegenerative disorders such as PD,[85,86] AD,[89,90] and conditions associated with aging.[91]

In PD models, mitochondrial transplantation has shown significant promise. Studies report improvements in rotational and locomotor behaviors, reduced oxidative stress, and attenuation of dopaminergic neuron degeneration when mitochondria were administered locally or intranasally. Importantly, intranasal administration demonstrated the ability of exogenous mitochondria to cross the BBB, further underscoring the feasibility of this approach.[92] Similarly, in AD models, mitochondrial transplantation via localized delivery improved cognitive functions, mitigated neuronal death, and ameliorated mitochondrial function both in the brain and peripheral organs.[89] Mitochondrial transplantation has also been explored as a strategy to combat age-related mitochondrial dysfunction. In rodent studies, the transfer of mitochondria from young, healthy donors into aged animals resulted in improved mitochondrial function, cognitive and motor performance, and alleviation of depression-like behaviors, all without signs of toxicity.[91] As of now, there are no clinical trials specifically investigating mitochondrial transplantation for the treatment of neurodegenerative diseases.

For human applications, the safest method is using a patient's own mitochondria (autologous transplantation) to reduce the risk of immune rejection. However, this approach can be challenging because mitochondrial disorders may affect a significant proportion of mitochondria across different tissues in the body. To address this, researchers are investigating techniques like gene editing to repair damaged mitochondria before they are transplanted, the delivery methods, and integration mechanisms. Mitochondrial transplantation offers a unique therapeutic avenue for conditions characterized by mitochondrial dysfunction, with the potential to restore cellular energy production and improve overall tissue health. As preclinical and clinical research advances, this innovative approach may become a cornerstone in the treatment of mitochondrial and neurodegenerative diseases.

Future Directions

Future therapeutic interventions targeting mitochondria for neurodegenerative disorders could also focus on modulating mitochondrial dynamics, enhancing mitochondrial quality control through transmitophagy, and improving targeted drug delivery. Mitochondrial function is tightly regulated by dynamic processes, where fragmented mitochondria are often associated with dysfunction, while fused and more interconnected mitochondria support OXPHOS and ATP production. Pharmacological approaches promoting mitochondrial fusion have shown promise in treating intracerebral diseases and could be explored for mitigating neuronal degeneration. Fusion activators, such as hydrazone M1, or fission inhibitors, like Mdivi-1, may help preserve mitochondrial integrity and counteract excessive fragmentation observed in neurodegenerative diseases.

Additionally, mild mitochondrial uncouplers such as FCCP and CCCP can mitigate oxidative stress by decreasing mitochondrial ROS production through uncoupling proteins, thereby protecting neurons from oxidative damage. Notably, neuronal overexpression of

uncoupling protein 2 has been linked to reduced dopaminergic cell loss via ROS reduction.[93]

Another promising approach involves enhancing neuroglial transmitophagy—the process by which neurons transfer damaged mitochondria to astrocytes for degradation—thus alleviating mitochondrial stress and promoting neuronal survival.[94]

Among the innovative strategies, mitochondrial transplantation represents a groundbreaking advancement in mitochondrial therapy. This approach has demonstrated promising results in preclinical studies, highlighting its potential to replace damaged mitochondria and restore cellular function. However, numerous questions remain unanswered. Key concerns include the risks of immune responses to exogenous mitochondria, ethical considerations surrounding donor mitochondria, mechanisms governing mitochondrial endocytosis and lysosomal escape, and the ability of transplanted mitochondria to traverse the blood-brain barrier and integrate effectively into neuronal networks. Personalized medicine will likely play a pivotal role in determining the most suitable mitochondrial therapy for individual patients. Genetic and metabolic profiling can guide the selection of therapies tailored to address specific mitochondrial defects and disease pathologies. Additionally, a combination of therapeutic approaches—such as pharmacological interventions, gene editing, and mitochondrial transplantation—may provide synergistic benefits to enhance patient outcomes. Furthermore, the development of quantum dot-based nanocarriers presents an innovative strategy for delivering mitochondrial-targeted therapeutics with high precision, improving drug bioavailability and specificity while minimizing off-target effects. Due to their small size (2–20 nm), quantum dots can cross the BBB, and the emergence of non-metallic variants with antioxidant properties enhances their therapeutic potential. Additionally, their administration via nasal or cerebrospinal routes offers a non-invasive approach to alleviate mitochondrial dysfunction and neuronal loss. Integrating these emerging strategies with existing mitochondrial-targeting approaches could pave the way for more effective neuroprotective interventions.

Conclusion

Mitochondria have emerged as a central hallmark of many aging-related diseases, particularly those involving neuronal loss and compromised functions. As the powerhouse of the cell, mitochondria play a pivotal role in energy metabolism, oxidative stress management, and apoptosis regulation, all of which are critical in maintaining neural integrity. Therapeutic interventions targeting mitochondrial dysfunction are actively being explored in clinical trials, though significant challenges remain. These include the heterogeneity of mitochondrial disorders among patients, potential side effects of pharmacological agents, the difficulty of crossing the BBB, peripheral effects, and determining optimal administration routes.

Realizing the full potential of mitochondrial therapies will require multidisciplinary collaboration across fields such as molecular biology, pharmacology, bioengineering, and clinical medicine. Continued innovation in delivery systems, biomaterial engineering, and gene therapy techniques will be critical to overcoming existing challenges. Furthermore, rigorous preclinical and clinical studies will be essential to ensure the safety and efficacy of these interventions. As research progresses, mitochondrial therapies hold immense promise for transforming the treatment landscape of neurodegenerative and mitochondrial disorders, offering hope for improved quality of life and functional recovery in patients suffering from these debilitating conditions.

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