International Journal of Nanomedicine

Dovepress
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REVIEW

Exosome-Mediated Mitochondrial Regulation: A Promising Therapeutic Tool for Alzheimer's Disease and Parkinson's Disease

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Abstract: Alzheimer's disease (AD) and Parkinson's disease (PD) are representative neurodegenerative diseases with abnormal energy metabolism and altered distribution and deformation of mitochondria within neurons, particularly in brain regions such as the hippocampus and substantia nigra. Neurons have high energy demands; thus, maintaining a healthy mitochondrial population is important for their biological function. Recently, exosomes have been reported to have mitochondrial regulatory potential and antineurodegenerative properties. This review presents the mitochondrial abnormalities in brain cells associated with AD and PD and the potential of exosomes to treat these diseases. Specifically, it recapitulates research on the molecular mechanisms whereby exosomes regulate mitochondrial biogenesis, fusion/fission dynamics, mitochondrial transport, and mitophagy. Furthermore, this review discusses exosome-triggered signaling pathways that regulate nuclear factor (erythroid-derived 2)-like 2-dependent mitochondrial antioxidation and hypoxia inducible factor 1α-dependent metabolic reprogramming. In summary, this review aims to provide a profound understanding of the regulatory effect of exosomes on mitochondrial function in neurons and to propose exosome-mediated mitochondrial regulation as a promising strategy for AD and PD.

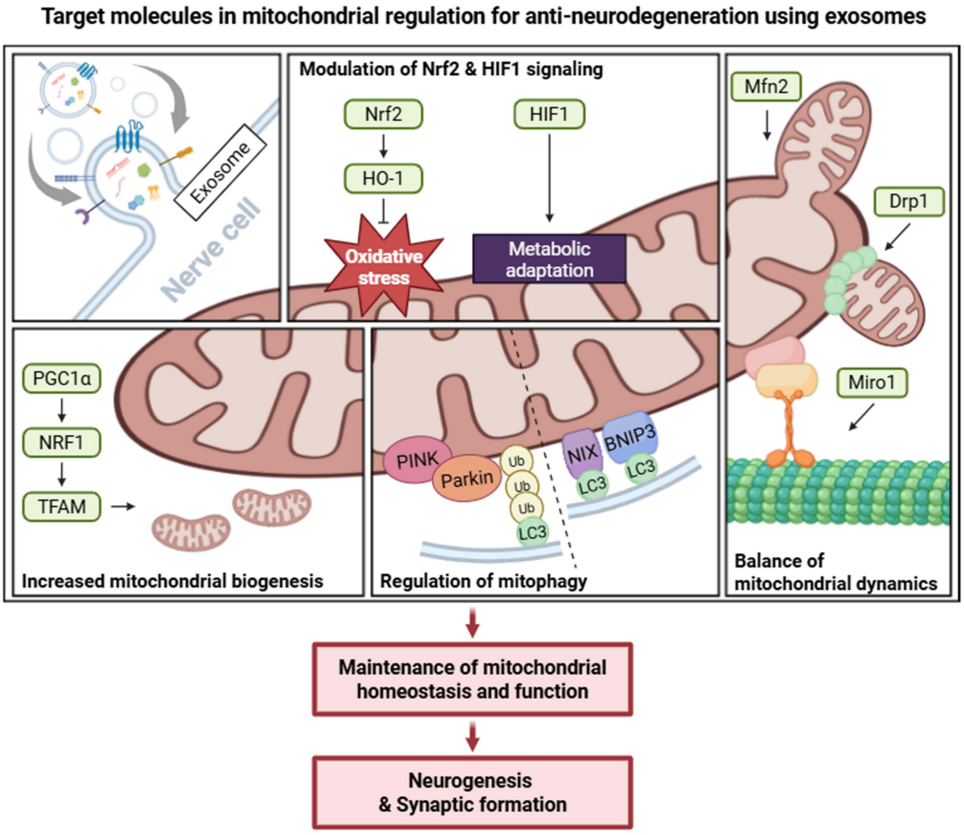
Keywords: neurodegenerative disease, Alzheimer's disease, Parkinson's disease, exosome, mitochondria

Introduction

Neurodegenerative diseases (NDs), including Alzheimer's (AD) and Parkinson's disease (PD), are characterized by progressive neuron degeneration, primarily within the central nervous system (CNS).[1] These debilitating NDs are a major global health challenge because they are growing at epidemic proportions, and have only a few treatment options.[2] AD and PD are associated with different pathological characteristics in their clinical manifestations. AD is the most common ND and is characterized by progressive cognitive impairment. Such impairment is associated with the accumulation of amyloid-beta peptide (Aβ) plaques and neurofibrillary tangles formed by hyperphosphorylated tau protein in the hippocampus and cerebral cortex, which results in neuronal death and brain atrophy.[3] The amyloid cascade hypothesis suggests that Aβ accumulation causes tau pathology, neuroinflammation and oxidative stress.[4] By contrast, PD is characterized by motor symptoms such as bradykinesia, rigidity, tremor, and postural instability, which occur when α-synuclein forms Lewy bodies in dopaminergic neurons in the substantia nigra.[5] These distinctive pathologies are closely associated with the signs of mitochondrial dysfunction, such as increased oxidative stress and impaired energy metabolism, which are the main drivers of NDs and result in severe disability and reduced quality of life.[6] The number of patients affected by dementia is estimated to increase to 130 million by 2050.[7] Further, the global economic cost

Received: 5 January 2025
Accepted: 7 April 2025
Published: 17 April 2025

Graphical Abstract



of AD-associated dementia and PD is estimated to reach US$2 trillion by 2030 and US$79 billion by 2037, respectively.[8,9] However, despite extensive research and clinical efforts, developing effective therapeutic strategies to reverse the pathogenesis of AD and PD remains challenging.

Roles of Mitochondrial Dysfunction in AD and PD

Mitochondria are central organelles that play a key role in the cellular metabolism of all mammalian cells, including neurons.[10] As neurons are particularly high energy demanding cells, which they need for synaptic formation and functional homeostasis, mitochondrial dysfunction is closely associated with energy depletion, oxidative stress and Ca^{2+} overload, leading to neurodegeneration.[11,12] Further, imbalanced mitochondrial dynamics and dysfunction are significantly related to loss of neuron function in AD and PD.[13] In AD, mitochondrial dysfunction and reactive oxygen species (ROS) overproduction are key in the processing of the amyloid precursor peptide (APP), Aβ accumulation, and formation of tau neurofibrillary tangles.[14] A previous report in AD cybrids showed that mitochondrial ROS reduction reversed upregulated AD markers such as Aβ levels, apoptosis, and mitochondrial fission.[15] In addition, inhibition of mitochondrial energetics results in neuron loss in the substantia nigra and striatum with tau hyperphosphorylation and aggregation.[16,17] Moreover, age-related mitophagy dysregulation impairs lysosomal maturation and clearance of defective mitochondria.[18] This failure in mitochondrial quality control (MQC) results in abnormal mitochondrial trafficking in neurons, leading to synaptic dysfunction.[18] In PD, nigral neurons with high density of mitochondria are susceptible to mitochondrial dysfunction, eventually resulting in extensive neuronal degeneration.[19] In addition, pesticides that stimulate mitochondrial fragmentation by inhibiting the ubiquitin protease system induced a PD-like phenotype in SH-SY5Y neuron cell models.[20] Competitive inhibition of the interaction between nuclear factor (erythroid-derived 2)-like 2 (Nrf2)

and Kelch-like ECH-associated protein 1 (Keap1) by 6-hydroxydopamine (6-OHDA), a structural analog of dopamine, is important for mitochondrial ROS-dependent neuronal apoptosis.[21] Severe mitochondrial DNA damage has been observed in postmortem brain samples from PD patients.[22] Further, previous studies demonstrated that sporadic PD is closely linked to a deficiency of mitochondrial complex I, with decreased ATP levels and excessive ROS generation.[23–25] Mutations in mitophagy-regulating molecules such as Parkin and PTEN-induced kinase 1 (PINK1) are considered key players in familial PD pathogenesis.[13] In fact, Parkin or PINK1 mutation in various in vivo models impairs mitochondrial complex I and III-mediated respiration, leading to significant loss of dopaminergic neurons.[26–28]

Exosomes

Given the crucial involvement of mitochondrial dysfunction in NDs, elucidating intercellular communication that can govern mitochondrial function is essential.[13] Exosomes are a type of extracellular vesicle typically 40–100 nm in diameter.[29] Exosomes are formed through inward budding of the plasma membrane within multivesicular bodies and subsequently released into the extracellular space by exocytosis.[30,31] Exosomes are found in nearly all biological fluids, including blood, urine, saliva, cerebrospinal fluid, and breast milk,[29,32] and play a crucial role in intercellular communication by delivering exogenous substances such as proteins, mRNAs, microRNAs, and lipids.[29] Importantly, exosomes can transfer mitochondrial DNA, proteins, and metabolites which are able to alter mitochondrial function in the recipient cells and may rescue mitochondrial abnormalities found in NDs.[33] In the CNS, the exosomes have attracted attention due to their therapeutic potential in NDs such as AD, PD, traumatic brain injury and brain stroke, as well as in intercellular communication.[34] Brain-derived exosomes (BDEs) are a crucial mediator of intercellular communications and waste control between CNS cells, including neurons, glial cells, and connective tissues.[34] Therefore, these findings suggest that BDE-regulated neurogenic niches including the hippocampus, are important for neurogenesis and cognitive improvement in NDs.[35] Exosomes are able to regulate MQC pathways such as mitophagy and biogenesis, which could be exploited as a therapeutic strategy for the mitochondrial dysfunction seen in AD and PD pathology.[36] In addition, exosomes can be used as non-invasive diagnostic biomarkers for AD and PD.[37,38] Exosomes have potential as a drug delivery system because of their easily engineered membrane and high permeability to tissue and the blood-brain barrier (BBB).[39,40] As natural nanoparticles with low immunogenicity, exosomes have a lower risk of causing an immune response when crossing the BBB. Further, they can be selectively targeted through surface modification, for instance, by attaching ligands that bind to BBB-associated receptors.[30,41] This review will introduce the regulatory effects of exosomes on mitochondrial biogenesis, dynamics, mitophagy, antioxidant systems, and metabolic reprogramming, and highlight the potential of exosome-based therapeutics targeting mitochondria in AD and PD.

Therapeutic Effect of Exosomes on AD and PD

The therapeutic effects of different kinds of exosomes from various cell origins, including mesenchymal stem cells (MSCs), neural cells, and immune cells, have been reported in AD and PD.[34] In AD, MSC-derived exosomes are emerging as a promising therapeutic strategy for amyloidogenesis and neurodegeneration. MSC-derived exosomes increased α-secretase expression but decreased beta-secretase 1 (BACE1) expression, suppressing Aβ accumulation and microglia-regulated neuroinflammation.[42,43] Exosomes derived from hypoxia-preconditioned MSCs improved synaptic dysfunction and anti-inflammation through anti- and pro-inflammatory cytokine regulation in APP/presenilin 1 (PS1) AD mice.[44] In addition, exosome injection into the lateral ventricle of AD mice increased BDNF expression, a key factor in synapse formation and neurogenesis.[45] Previous studies using animal behavioral tests, including the Morris water maze, open field, and novel object recognition tests, supported the neuronal recovery and cognitive improvement produced by MSC-derived exosomes.[43,45,46] In addition, exosomes from curcumin-pretreated MSCs could inactivate the protein kinase B (Akt)/GSK3β pathway and ameliorate cognitive dysfunction by inhibiting tau hyper-phosphorylation.[47] Intravenous administration of MSC exosomes modified with CNS-specific rabies virus glycoprotein for brain targeting significantly reduced Aβ accumulation and inactivated astrocytes.[48] In addition, those modified exosomes improved cognitive function in APP/PS1 mice better than control exosomes.[48] Emerging data indicate that exosomes are involved in AD pathology through regulation of Aβ neurotoxicity and tau hyperphosphorylation. In 6-OHDA-induced PD rats, intranasal administration of exosomes derived from human dental stem cells normalized

tyrosine hydroxylase levels in the substantia nigra and striatum, and it improved spatial recognition and memory.[49] Microglial exosomes have been shown to play a critical role in α-synuclein transmission and its pathology in PD.[50] In fact, exosomes from microglia containing α-synuclein preformed fibrils stimulated protein aggregation in recipient neurons, suppressing autophagic flux and resulting in lysosome-associated membrane protein 2 (LAMP2) degradation.[50]

Exosomes and Mitochondrial Regulation in AD and PD

Mitochondrial dysfunction results in lower energy production and increased ROS, which contributes to oxidative stress, leading to metabolic dysregulation. This is marked by a reduction in glucose uptake and the tricarboxylic acid cycle, impairments in oxidative phosphorylation, and a reduction in the energetic support provided to neurons by astrocytes and oligodendrocytes.[51,52] Exosomes have emerged as critical regulators of mitochondrial function, offering new insights into the pathogenesis and potential treatment of NDs. These exosomes influence various aspects of mitochondrial function and dynamics.[53,54] By delivering specific cargo molecules, exosomes modulate the expression of genes and proteins crucial for mitochondrial homeostasis and their proper function. This review describes the intricate relationship between exosomes and mitochondrial regulation in diverse pathologic aspects of AD and PD.

Regulatory Effect of Exosomes on Mitochondrial Biogenesis

Recent studies have revealed a close relationship between mitochondrial dysfunction and NDs such as AD and PD, leading to increased interest in therapeutic approaches targeting mitochondrial biogenesis,[55] a process in which exosomes play a crucial role. Extensive research on mitochondrial biogenesis and the Peroxisome proliferator-activated receptor gamma coactivator 1α (PGC1α), nuclear respiratory factor 1 (NRF1), and mitochondrial transcription factor A (TFAM) pathways has shown that PGC1α activation in the cell nucleus which is triggered by stimuli such as AMP-activated protein kinase (AMPK), sirtuin (SIRT), P38 mitogen activated protein kinase (P38 MAPK), and Akt, initiates transcription of *NRF1* and *TFAM*, driving mitochondrial biogenesis.[56,57] In a PD mouse model, a significant loss of dopamine neurons was observed in mice harboring a conditional knockout of PGC1α in the ventral midbrain.[58] Accordingly, researchers are currently investigating how exosomes from different cell types can influence mitochondrial biogenesis by transferring these regulatory factors. For example, Feng et al reported that STIM-activating enhancer (STIMATE)-positive type II alveolar epithelial cell-derived exosomes enhanced mitochondrial biogenesis by activating the PGC1α pathway in conditional knockout mice lacking STIMATE, which helped reduce lung damage.[59] Further, exosomes derived from stem cells from human exfoliated deciduous teeth could deliver *TFAM* mRNA to dental pulp stem cells, boosting mitochondrial biogenesis and enhancing bone regeneration.[60] Moreover, transfer of circRNA from oxaliplatin-resistant cells via exosomes could revert the *miR-30e-5p*-mediated inhibition of PGC1α activity, increasing mitochondrial biogenesis and reprogramming the cells to favor oxidative phosphorylation.[61] Similarly, a rat model for investigating potential treatments for liver ischemia-reperfusion injury received exosomes from adipose tissue-derived MSCs, increasing expression levels of PGC1α, NRF1, and TFAM, all related to mitochondrial biogenesis, along with improved liver function.[62] Considering the depletion of factors related to mitochondrial biogenesis in NDs, using exosomes to supplement them can have therapeutic benefits. In fact, in a neural system-specific *Sirt1* conditional knockout APP/PS1 mouse model of AD, neural stem cell-derived exosomes significantly increased SIRT1-dependent PGC1α signaling and improved mitochondrial biogenesis by increasing NRF1 and cytochrome c oxidase subunit 4 (COXIV) synthesis.[63] These findings suggest that certain exosomes can enhance mitochondrial biogenesis in neurons, potentially offering a treatment for AD (Figure 1).

Regulatory Effect of Exosomes on Mitochondrial Dynamics

Mitochondria are dynamic intracellular organelles that continuously change their number and morphology. Here, mitochondrial dynamics will be categorized into fusion, fission, and transport. Mitochondrial dynamics is critical for maintaining mitochondrial homeostasis and regulates several cellular processes such as cell cycle progression, apoptosis, cell migration, mitophagy, and mitochondrial ROS production.[64,65] Closely related to mitochondrial biogenesis, mitochondrial dynamics plays a crucial role in the pathogenesis and progression of NDs. The imbalance in mitochondrial

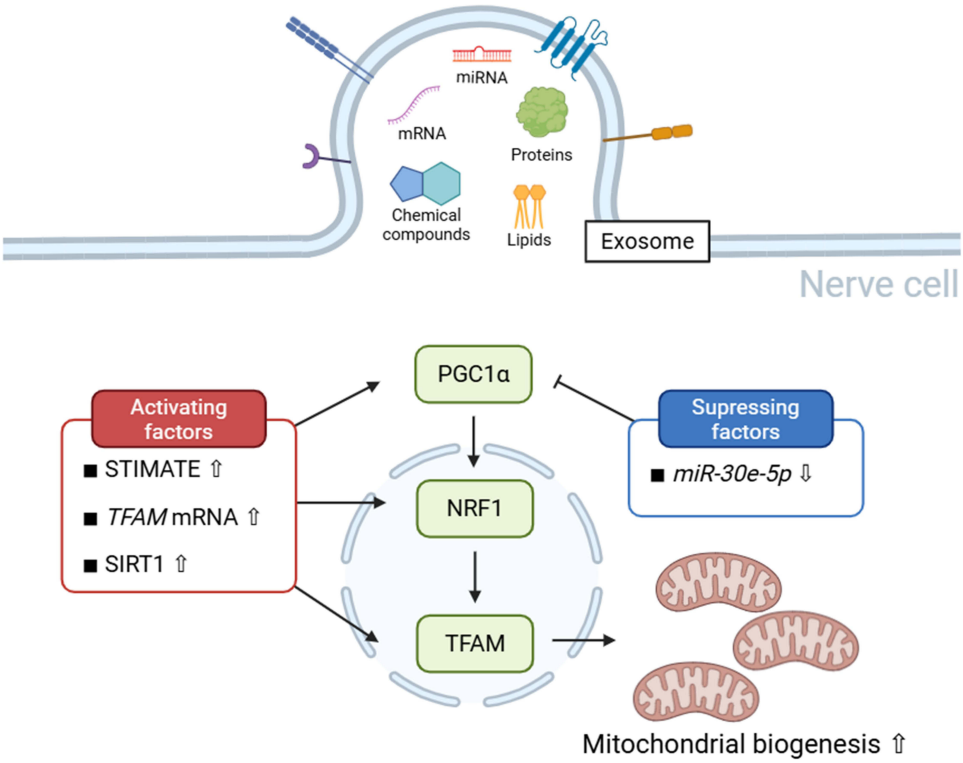


Figure 1 Illustration showing the effect of molecules delivered by exosomes on mitochondrial biosynthesis in neurons. STIMATE, *TFAM* mRNA, SIRT1, and various factors delivered via exosomes upregulate PGC1α/NRF1/TFAM signaling. Exosomes also transfer other factors that downregulate *miR-30e-5p*, which inhibits PGC1α signaling.

dynamics is evident in AD and PD.[66,67] For example, in vulnerable neurons in AD, this imbalance causes excessive oxidative stress and creates an environment likely to lead to energy depletion.[68]

Mitochondrial Fusion

Mitochondrial fusion involves the connection of inner and outer membranes between two mitochondria, facilitating the exchange of genetic material and metabolites.[69] This process increases the oxidative phosphorylation capacity and allows redistribution of mitochondrial DNA between damaged and healthy mitochondria.[70] Mitochondrial fusion comprises two main steps: outer mitochondrial membrane (OMM) fusion and inner mitochondrial membrane (IMM) fusion. OMM fusion is primarily mediated by mitofusin 1 and 2 (Mfn1 and Mfn2), which are transmembrane GTPases, while IMM fusion is facilitated by optic atrophy-1 (OPA1), a dynamin-related protein in the IMM.[71] In AD, Aβ accumulation impairs mitochondrial function, reducing membrane potential and ATP production in hippocampal neurons and astrocytes.[72,73] In mouse hippocampal neurons, inhibition of *miR-195*, a negative regulator of mitochondrial dynamics which targets *Mfn2 gene*, enhanced memory by ameliorating mitochondrial structural damage and reducing synaptic degradation.[74] Regarding PD, α-synuclein overexpression inhibits mitochondrial fusion by reducing the expression of Mfn1, Mfn2, and OPA1.[75] A recent study demonstrated the potential of exosome-mediated mitochondrial fusion regulator delivery which stimulates mitochondrial fusion. For example, trophoblast stem cell-derived exosomes were found to ameliorate doxorubicin-induced cardiotoxicity by increasing Mfn2 expression in mouse cardiomyocytes, thereby enhancing mitochondrial fusion.[76] These findings highlight the therapeutic potential of targeting mitochondrial fusion proteins in AD and PD and that exosomes could be effective delivery vehicles for such interventions (Figure 2). Despite the limited studies focusing on engineering exosomes to improve mitochondrial dynamics for treating AD and PD, the potential applications of exosomes in these NDs require further research.

https://doi.org/10.2147/IJN.S513816

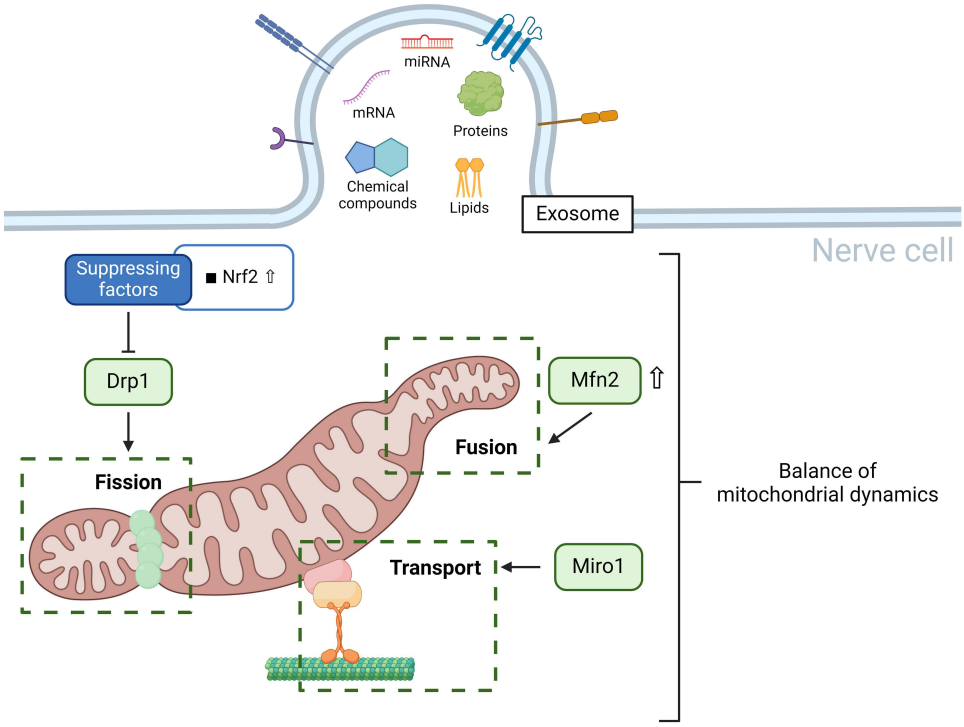


Figure 2 Illustration showing the way molecules delivered by exosomes regulate mitochondrial dynamics in neurons. In neurons, the balance between mitochondrial fusion and fission is important for MQC. Nrf2 delivered via exosomes inactivates Drp1, thereby reducing excessive mitochondrial fission. In addition, delivery of factors regulating the expression or transfer of Miro1 via exosomes are expected to transport healthy mitochondria to deteriorated neurons.

Mitochondrial Fission

Mitochondrial fission occurs when mitochondria divide into two separate organelles. It happens during an increase in mitochondrial population or when damaged mitochondria are removed by mitophagy.[77] Fission begins with ER tubules adhering to the site of impending mitochondrial division. Subsequently, dynamin-related protein 1 (Drp1) accumulates at this location, forming a ring-like structure. Proteins such as mitochondrial fission 1 (Fis1), Mff, MiD49, and MiD51, which are located in the OMM, interact with Drp1. Then, the ring structure formed by Drp1, and mediated by DNM2, cleaves mitochondria.[78,79] Impaired mitochondrial fission has been reported in NDs, resulting in an increased number of elongated mitochondria due to relatively higher fusion rates.[77,80] In AD, Aβ and tau interact with Drp1, causing excessive mitochondrial fragmentation, which leads to synaptic dysfunction, neuronal damage, and cognitive decline.[81] Furthermore, Fis1 aggregation has been reported in AD and is associated with disease progression.[82] In the striatum of PD brain, mitochondrial fragmentation and abnormal mitochondrial localization are observed as well.[83,84] Several studies aimed at improving mitochondrial dynamics using exosomes. For example, injection of CAP-Nrf2-exoS, an exosome produced using an *Nrf2* overexpression vector, into mice inhibited Drp1 phosphorylation in cells. This prevents excessive mitochondrial modification and migration, thereby inhibiting mitochondrial division and dysfunction.[85] PD-related proteins such as α-synuclein, leucine-rich repeat kinase-2, PINK1, and Parkin are known to regulate Drp1 function. Further, some therapeutic approaches aim to partially inhibit Drp1 function in purpose of reducing neuron death in PD. These approaches include *DNM1L* (gene encoding Drp1) silencing using siRNA and Drp1 inhibition using compounds such as mdivi1, which have potential neuroprotective effects by reducing mitophagy impairment and protein aggregation caused by α-synuclein.[86,87] These findings highlight the potential of targeting mitochondrial fission, particularly through exosome-mediated approaches, in the treatment of AD and PD (Figure 2).

Mitochondrial Transport

Mitochondrial transport is intracellularly and intercellularly crucial in neurons, where mitochondria migrate to specific areas such as the axon to meet localized energy demands.[88] Moreover, mitochondria can traverse cell boundaries,

facilitating the exchange of intracellular substances and contributing to recovery in response to CNS stimuli.[89] A key protein involved in mitochondrial transport and anchoring is mitochondrial Rho GTPase 1 (Miro1). This OMM-bound protein typically functions in intracellular axonal transport of mitochondria. Miro1 binds to the OMM, interacts with TRAK1/2, and in turn binds to motor proteins such as dynein or kinesin, forming a motor complex. This complex adheres to microtubules, enabling intracellular movement.[90] Impaired Miro1-dependent mitochondrial transport and associated astrocyte dysfunction play a role in the pathogenesis of both AD and PD.[91–93] A previous study using iPSCs to model the characteristics of PD revealed that Miro1 defects are significantly more common in PD patients than in the healthy population.[94] Further, Miro1 loss is associated with mitophagy dysfunction and mitochondrial hyperactivation in response to stress, potentially contributing to the development of PD in affected cells.[95] In *Miro1* knockout mouse models, there is significant mitochondrial absence, particularly in distal neuronal dendrites.[96] Given the importance of proper mitochondrial distribution for meeting local energy demands and Ca^{2+} buffering, Miro1-mediated mitochondrial transport is a crucial mechanism in neurodegeneration.[96] In addition, *Miro1* overexpression could be useful for improving mitochondrial function. When *Miro1*-overexpressing MSCs were delivered to mice with ischemic damage, cell-to-cell communication was enhanced by transferring healthy mitochondria to damaged astrocytes, resulting in significantly reduced neurological deficits and bioenergetic restoration of astrocytes.[97] Moreover, recent studies have demonstrated that exosomes can alter Miro1 levels in neurons.[98,99] Mitochondria are transferred by exosomes to rescue neurons with mitochondrial dysfunction caused by NDs, but the role of exosome-mediated mitochondrial transport in ND pathogenesis is still understudied.[98,99] Despite the limited studies on exosome-mediated regulation of Miro1 in NDs, the potential of exosomes to deliver or modulate proteins involved in mitochondrial transport offers an intriguing area for future research (Figure 2).

Mitophagy

Mitophagy is a subtype of autophagy that selectively degrades dysfunctional and impaired mitochondria.[100] This process is crucial for maintaining mitochondrial quality and homeostasis.[101] However, both excessive and insufficient mitophagy occur under abnormal conditions, potentially leading to cell death and neurodegeneration.[102–104] Several mechanisms are responsible for mitophagy, each dependent on proteins such as PINK1, BCL2 interacting protein 3 (BNIP3), BNIP3-like (NIX) and FUNDC1.[105] PINK1 is imported into the IMM and degraded by MG132-sensitive proteases. However, when mitochondria are damaged, proteasomal stress from MG132 causes proteasome dysfunction and PINK1 accumulation.[106] Then, accumulated PINK1s are embedded into the OMM and recruit Parkin, which then activates the ubiquitin-proteasome system and starts the universal ubiquitylation and degradation of OMM proteins, eventually leading to mitophagy.[107] Regulation of mitophagy by exosomal miRNAs and proteins is an effective strategy for MQC.[108,109] Exosomes derived from astrocytes under oxygen-glucose deprivation/re-oxygenation conditions transfer *miR-138-5p*, which downregulates DNA methyltransferase 3A (DNMT3A), leading to decreased methylation of the promoter of Ras homolog enriched in brain like 1 (Rhebl1), ultimately increasing mitophagy in neurons.[108] Other than regulating the DNMT3A/Rhebl1 axis, *miR-138-5p* also affect PINK1/Parkin signaling further enhancing mitophagy and reducing reperfusion injuries in middle cerebral artery occlusion.[108] In addition, insulin-like growth factor 1 regulates mitophagy in astrocytes through exosomal *miR-let-7e* enhancing mitophagy with increased PINK1 and NIX expression in traumatic brain injury.[110] In PD, dysregulated PINK1/parkin-mediated mitophagy reportedly contributes to the accumulation of damaged mitochondria and neuron dysfunction.[111] In dopaminergic neurons of patients with PD, exosomes mediate the disposal of damaged mitochondria and mitochondrial-derived vesicles through the PINK1/Parkin pathway.[112] In PD rodent models, the condition significantly improved after treatment with MSC-derived exosomes, which increased Parkin and DJ-1 levels in the brain compared to rats treated with rotenone.[113] Similarly, M2 microglia-derived exosomes can regulate mitophagy in neurons via the PINK1/Parkin pathway, providing neuroprotection by restoring mitochondrial function and reducing ROS in AD.[114] In most ND cases, exosomes are utilized to increase mitophagy and remove defective mitochondria. However, exosomes can also be used to reduce excessive mitophagy in NDs. Rotenone, a mitochondrial complex I inhibitor, induces excessive mitophagy, leading to neuron apoptosis in PD, but epicatechin gallate-loaded exosomes reverse this effect by suppressing PINK1 and Parkin expression.[115] Taken together, exosome-mediated mitophagy facilitates the clearance of damaged mitochondria thus improving MQC in AD and PD (Figure 3).

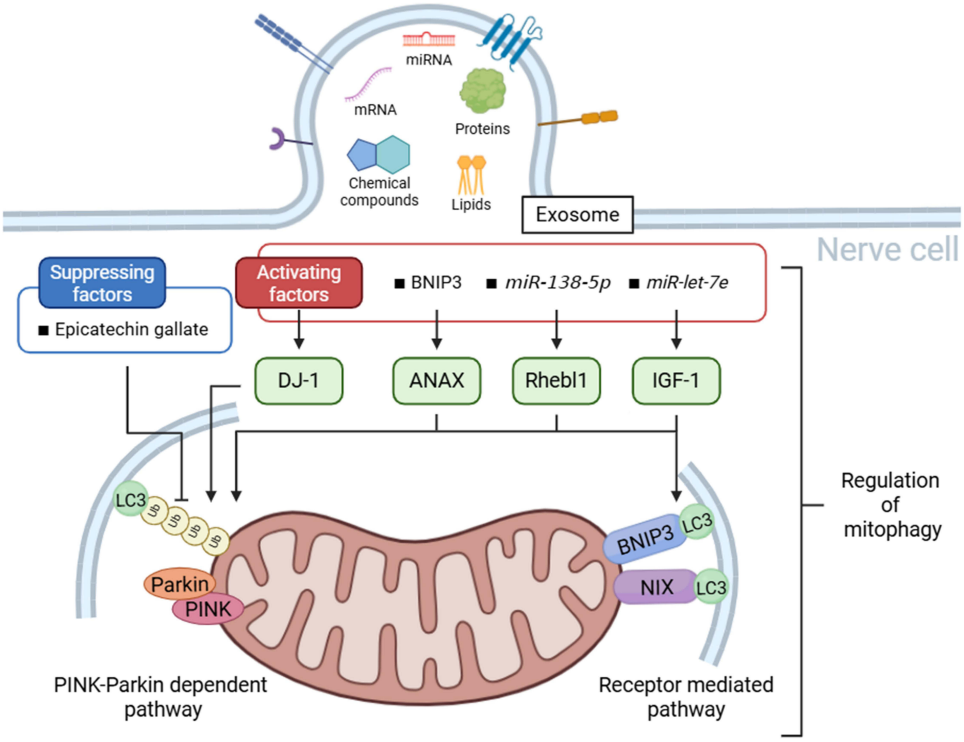


Figure 3 Illustration showing that molecules delivered by exosomes regulate mitophagy in neurons. Numerous activators delivered by exosomes, such as BNIP3, *miR-138-5p*, and *miR-let-7e*, each send signals that ultimately increase mitophagy. However, epicatechin gallate delivered via exosomes alleviated the excessive apoptosis observed in neurodegenerative diseases.

While enhanced mitophagy can be beneficial in clearing damaged mitochondria, excessive mitophagy can be detrimental. Thus, future research should focus on developing exosome-based therapies that fine-tune mitophagy to optimal levels in damaged neurons.

Exosome-Mediated Modulation of Nrf2 and Hypoxia Inducible Factor 1 (HIF1) Pathways

Exosomes are critical mediators in the therapeutic landscape of AD and PD due to their ability to modulate essential cellular pathways. Specifically, Nrf2 and HIF1 pathways are pivotal in modulating mitochondrial antioxidative defenses and metabolic reprogramming, respectively. By influencing these pathways, exosomes protect neurons from mitochondrial oxidative stress, promoting metabolic adaptations. This section discusses how exosome-mediated modulation of these pathways is a promising strategy for the treatment of AD and PD (Table 1).

Table 1 Modulation of Nrf2 and HIF1 Signaling in Neurodegenerative Disease Using Exosomes Derived From Different Cells

Origin	Cargo Molecules	Related Pathway	Effects	References
Mouse bone marrow derived mesenchymal stem cells	Non-specific	Nrf2/GCH1/BH4 axis	Suppression of ferroptosis in spinal cord injury	[116]
Rat muscle derived stem cells	Non-specific	Keap1/Nrf2/HO-1 axis	Suppression of ferroptosis in sciatic nerve injury	[117]

(*Continued*)

Table 1 (Continued).

Origin	Cargo Molecules	Related Pathway	Effects	References
Engineered human embryonic kidney cells that produce LAMP2B tagging with CAP	Nrf2	Nrf2/Drp1 axis	Suppression of mitochondrial fragmentation and dysfunction in cartilaginous endplate degeneration	[85]
Mouse Bone marrow derived mesenchymal stem cells	SIRT1	SIRT1/Nrf2/HO-1 axis	Restoration of mitochondrial function in diabetic peripheral neuropathy	[118]
Mouse bone marrow derived mesenchymal stem cells	Non-specific	SIRT1/Nrf2/HO-1 axis	Suppression of ferroptosis in hippocampal neuron	[119]
Rat astrocyte	*miR-17-5p*	Inhibition of BNIP2	Suppression of apoptosis in hypoxic ischemic encephalopathy	[120]
Hypoxic preconditioned mouse adipose derived stem cell	circ-Epc1	*miR-770-3p* /TREM2 axis	Transition of hippocampal microglia polarization from M1 to M2.	[121]

Exosome-Regulated Nrf2-Dependent Mitochondrial Antioxidant System

The transcriptional factor Nrf2 is involved in the control of neuronal antioxidation and protection against cellular damage in NDs, including AD and PD.[122,123] Nrf2 regulates the expression of cytoprotective genes related to cellular antioxidant enzymes, glutathione synthesis, recycling enzymes, and iron sequestration proteins including superoxide dismutase 2, heme oxygenase 1 (HO-1), NAD(P)H quinone oxidoreductase 1, glutathione S-transferases, glutamate-cysteine ligase and glutathione reductase.[124] The interactions between exosomes and Nrf2 not only facilitate the production of protective enzymes but also modulate mitochondrial dynamics. Recent research highlights the potential of exosomes as delivery vehicles for Nrf2 activators, which enhance the therapeutic efficacy of natural compounds and RNA-based treatments for AD.[125] In recipient neurons, exosomes with Nrf2 activators alter Nrf2 signaling through direct transfer of Nrf2 protein or mRNA and transport of Keap1 inhibitors.[125] The delivery of complementary sequences that inhibit *NFE2L2* (gene encoding Nrf2) targeting-miRNAs increases Nrf2 expression.[125] Accordingly, the therapeutic potential of exosome-regulated Nrf2 pathway for NDs has been investigated.[126] MSC-derived exosomes have shown promise in mitigating ferroptosis during acute spinal cord injury, by activating the Nrf2/GTP cyclohydrolase I (GCH1)/5,6,7,8-tetrahydrobiopterin (BH4) axis.[116] In addition, muscle-derived stem cell exosomes offer a potential therapeutic strategy for peripheral nerve injuries by suppressing ferroptosis in the sciatic nerve and dorsal root ganglion through activation of the Nrf2/HO-1 pathway, leading to improved post-injury recovery with enhanced nerve function and reduced muscle atrophy.[117] Exosomes engineered to express chondrocyte affinity peptide carrying *miR-140* and Nrf2 have demonstrated efficacy in the treatment of intervertebral disc degeneration.[85,127] In addition, *SIRT1*-overexpressing exosomes derived from bone marrow MSCs improved diabetic peripheral neuropathy through Nrf2/HO-1-dependent antioxidation.[118] Further, MSC-derived exosomes ameliorated cognitive impairment after exploratory laparotomy by inhibiting hippocampus ferroptosis in old mice with delayed neurocognitive recovery.[119] Despite challenges in ensuring specific delivery into damaged neurons in NDs, it is possible to slow down ND progression through Nrf2-dependent mitochondrial antioxidation. Continued exploration of exosome-Nrf2 interactions holds great promise for advancing our understanding of disease pathogenesis and developing novel therapeutic strategies for AD and PD.

Exosome-Regulated HIF1-Dependent Metabolic Reprogramming

Like the Nrf2 pathway, HIF1-dependent metabolic reprogramming plays a crucial role in cellular stress adaptation responses in NDs such as AD and PD.[128] HIF1 is a heterodimeric transcription factor composed of α (HIF1α) and β subunits (HIF1β). Under normoxic conditions, HIF1α is degraded through the ubiquitin-proteasome pathway.[129] Prolyl hydroxylases hydroxylate proline residues in HIF1α, being recognized by the von Hippel-Lindau E3 ubiquitin ligase

complex.[130] Under hypoxic conditions, HIF-prolyl hydroxylases are inhibited leading to HIF1α stabilization. The stabilized HIF1α then translocates to the nucleus, where it dimerizes with HIF1β and binds to hypoxia-response elements.[129] HIF1-dependent metabolic reprogramming under hypoxia affects glucose metabolism, mitochondrial function, antioxidant capacity, and neuron survival.[131] HIF1 plays a critical role in facilitating cellular adaptation to stress, particularly in NDs. In addition to glucose metabolism and mitochondrial function, lipid and amino acid metabolism are modulated in a HIF1-dependent manner.[132–134] HIF1α has neuroprotective properties by counteracting the detrimental effects of Aβ and preventing excessive tau phosphorylation, which highlights the potential of HIF1α as a therapeutic target for AD.[135] The complex interplay between HIF1 signaling and exosome-mediated communication is identified as a pivotal factor in ND progression. Delivering HIF1 and other molecules specifically to the brain, exosomes can be used as a new therapeutic strategy for AD and PD.[136] A previous study showed that astrocyte-derived exosomes protect neonatal rats from hypoxic-ischemic brain damage by inhibiting BNIP2 expression.[120] This finding indicated that exosomes control HIF1-dependent metabolic pathways by delivering regulatory components such as mRNAs, proteins, and miRNAs. These components exert either a direct or indirect influence on HIF1 stability and functionality. A previous study showed that exosomes from adipose tissue-derived MSCs that underwent hypoxic preconditioning improved cognitive function in AD by delivering circ-Epc1.[121] Then, circ-Epc1 regulated microglial polarization through *miR-770-3p*/TREM2 signaling, associated with shifting microglia from M1 to M2.[121] Taken together, these findings suggest that exosome-regulated HIF1 signaling can be a promising therapeutic strategy for the treatment of AD and PD by controlling metabolic reprogramming and MQC.

Conclusion

In conclusion, this review emphasizes the role of exosomes in regulating mitochondrial function and their therapeutic potential for AD and PD. Exosomes modulate key aspects of mitochondrial biogenesis, fusion/fission balance, mitochondrial transport, and mitophagy, all crucial for neuron survival and function. Moreover, they play a key role in the regulation of Nrf2-dependent mitochondrial antioxidant responses and HIF1-dependent metabolic reprogramming, essential for MQC in neurons. Importantly, in the context of AD, exosomes have been investigated as a therapeutic tool for alleviating Aβ-induced mitochondrial toxicity and tau phosphorylation. Through exosome-mediated transfer of functional mitochondria or regulation of mitochondrial function in recipient neurons, exosomes hold significant potential in maintaining mitochondrial homeostasis. Consistently, in PD, exosomes prevent α-synuclein aggregation and mitochondrial dysfunction, further underscoring their role in disease progression. Despite these findings, detailed mechanisms underlying the interaction between exosomes and mitochondrial regulatory pathways, as well as their impact on AD and PD progression, remain unclear. To advance exosome-based therapeutic strategies for AD and PD, further research is needed to fully elucidate these mechanisms and enhance the engineering of exosome which targets mitochondrial dysfunction-induced NDs. Future studies should focus on optimizing exosome design to enhance mitochondrial function and associated regulatory pathways, ensuring precise delivery to affected brain regions and minimizing potential side effects.

Abbreviations

6-OHDA, 6-hydroxydopamine; AD, Alzheimer's disease; Akt, Protein kinase B; Aβ, Amyloid beta; AMPK, AMP-activated protein kinase; APP, Amyloid precursor peptide; BACE1, beta-secretase 1; BBB, Blood-brain barrier; BDEs, Brain-derived exosomes; BDNF, Brain-derived neurotrophic factor; BH4, 5,6,7,8-tetrahydrobiopterin; BNIP3, Bcl2 interacting protein 3; CAP, Chondrocyte-affinity peptide; CNS, Central nervous system; COXIV, Cytochrome c oxidase subunit 4; DNMT3A, DNA methyltransferase 3A; Drp1, Dynamin-related protein 1; Fis1, Mitochondrial fission 1; FUNDC1, Fun14 domain containing 1; GCH1, GTP cyclohydrolase I; GSK3β, Glycogen synthase kinase 3β; HIF1, Hypoxia inducible factor 1; HIF1α, Hypoxia inducible factor 1 subunit α; HIF1β, Hypoxia inducible factor 1 subunit β; HO-1, Heme oxygenase 1; IMM, Inner mitochondrial membrane; iPSCs, Induced pluripotent stem cells; Keap1, Kelch-like ECH-associated protein 1; LAMP2, Lysosome-associated membrane protein 2; M1, Classical phenotype microglia; M2, Alternative phenotype microglia; Mff, Mitochondrial fission factor; Mfn1, Mitofusin 1; Mfn2, Mitofusin 2; MG-132, Carbobenzoxy-l-leucyl-l-leucyl-l-leucinal; MiD49, Mitochondrial dynamics proteins of 49kda; MiD51, Mitochondrial dynamics proteins of 51kda; Miro1, Mitochondrial rho GTPase 1; MQC, Mitochondrial quality

control; MSCs, Mesenchymal stem cells; NAD(P)H, Nicotinamide adenine dinucleotide (phosphate) hydrogen; NDs, Neurodegenerative diseases; NIX, Bcl2 interacting protein 3-like; NRF1, Nuclear respiratory factor 1; Nrf2, Nuclear factor (erythroid-derived 2)-like 2; OMM, Outer mitochondrial membrane; OPA1, Optic atrophy 1; P38 MAPK, P38 mitogen activated protein kinase; PD, Parkinson's disease; PGC1α, Proliferator-activated receptor gamma coactivator 1α; PINK1, PS1, presenilin 1; PTEN-induced kinase 1; Rhebl1, Ras homolog enriched in brain like 1; ROS, Reactive oxygen species; SIRT, Sirtuin; STIM, Stromal interaction molecule; STIMATE, Stim-activating enhancer; TFAM, Mitochondrial transcription factor A; TRAK1, Trafficking kinesin protein 1; TRAK2, Trafficking kinesin protein 2; TREM2, Triggering receptor expressed on myeloid cells 2.

Acknowledgments

The authors would like to thank Enago (www.enago.com) for the English language review. This research was supported by National R&D Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (NRF-2021R1C1C1009595); Korea government (MSIT, No. RS-2023-00219563); Regional Innovation Strategy (RIS) through the NRF funded by the Ministry of Education (MOE, 2021RIS-001). This work was supported by the Soonchunhyang University Research Fund.

Disclosure

The authors report no conflicts of interest in this work.

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