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Mitochondrial transplantation in brain disorders: Achievements, methods, and challenges

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ABSTRACT

Mitochondrial transplantation is a new treatment strategy aimed at repairing cellular damage by introducing healthy mitochondria into injured cells. The approach shows promise in protecting brain function in various neurological disorders such as traumatic brain injury/ischemia, neurodegenerative diseases, cognitive disorders, and cancer. These conditions are often characterized by mitochondrial dysfunction, leading to impaired energy production and neuronal death. The review highlights promising preclinical studies where mitochondrial transplantation has been shown to restore mitochondrial function, reduce inflammation, and improve cognitive and motor functions in several animal models. It also addresses significant challenges that must be overcome before this therapy can be clinically applied. Current efforts to overcome these challenges, including advancements in isolation techniques, cryopreservation methods, finding an appropriate mitochondria source, and potential delivery routes, are discussed. Considering the rising incidence of neurological disorders and the limited effectiveness of current treatments, this review offers a comprehensive overview of the current state of mitochondrial transplantation research and critically assesses the remaining obstacles. It provides valuable insights that could steer future studies and potentially lead to more effective treatments for various brain disorders.

1. Introduction

Mitochondrial dysfunction is increasingly recognized as a central contributor to the pathology of a wide range of neurological disorders, including traumatic brain injury, ischemia, neurodegenerative diseases, and cognitive impairments (Alshial et al., 2023; Leão Barros et al., 2021; Tian et al., 2022). Mitochondria, often called the cell's powerhouses, are essential for maintaining cellular energy homeostasis, regulating oxidative stress, and supporting neurons' overall function and survival. In brain disorders, impaired mitochondrial function can lead to a cascade of detrimental effects, including energy deficits, increased production of reactive oxygen species (ROS), and the activation of cell death pathways (Grimm and Eckert, 2017). These mitochondrial abnormalities are not merely a consequence of the disease process but are often implicated as critical drivers of disease progression.

Recent advancements in mitochondrial research have opened up new therapeutic avenues, with mitochondrial transplantation (MT) emerging as a promising strategy (reviewed in (McCully et al., 2023)). This innovative approach involves the transfer of healthy mitochondria into damaged or dysfunctional cells to restore their bioenergetic capacity and mitigate the effects of mitochondrial dysfunction. Pioneering work by the group of James McCully (Harvard Medical School, Boston, USA) has shown that this approach can rescue cell viability and function after ischemia-reperfusion injury in the heart (Masuzawa et al., 2013; McCully et al., 2023). Like in the brain, mitochondria play a paramount role in the heart, as they extract more than 75 % of the oxygen in the coronary arteria to meet homeostatic requirements (Fillmore and Lopaschuk, 2013). Thus, the arrest or decrease of coronary blood flow limits oxygen delivery to the heart and results in myocardial ischemia. Therefore, to reverse ischemia-induced mitochondria damage in rabbits, McCully J. and colleagues applied autologous mitochondria directly into the infarct zone of the heart before reperfusion (Masuzawa et al., 2013). They observed an enhanced post-infarct cardiac function and cell viability after MT, with increased oxygen consumption and the induction of protein pathways and cytokine mediators that play critical roles in preserving myocardial energetics. Since this pioneering discovery, clinical trials have been performed on pediatric patients with myocardial ischemia-reperfusion injury who required extracorporeal

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membrane oxygenation (ECMO) (Emani and McCully, 2018; Emani et al., 2017; Guariento et al., 2021). Healthy autologous mitochondria were harvested from non-ischemic skeletal muscle in the patients, isolated using a fast procedure, and injected into damaged myocardium after ischemic injury. The key outcome of these trials was that patients did not show short-term complications related to MT and presented an improvement in ventricular function. Given these encouraging findings in the context of ischemia-reperfusion injury, more studies are necessary to assess MT's safety, efficacy, and optimal dosing in a larger group of patients. The use of MT is increasing in other fields, and studies have been performed on organs like the heart, the muscles, the kidney, the liver, the lungs, and the brain (Liu et al., 2022; McCully et al., 2023).

A recent report published in The Lancet Neurology indicates that 43.1 % of the global population was affected by a brain disorder in 2021, causing more than 11 million deaths (Steinmetz et al., 2024). This study highlights the urgent need to find cures for these conditions, which are often not treatable or preventable and may cause lifelong disability. Because mitochondrial dysfunction undeniably contributes to many neurological disorders (Alshial et al., 2023; Bamshad et al., 2022; Leão Barros et al., 2021; Tian et al., 2022), MT has sparked widespread interest as a potential therapeutic strategy for brain-related pathologies.

Therefore, in this review, we aim to provide a comprehensive overview of the current state of mitochondrial transplantation research in the context of neurological disorders. We first discuss the critical role of mitochondria in brain cells, emphasizing their importance in normal brain function. Next, we discuss studies from the past decade that have investigated the effects of MT in pre-clinical models of brain-related disorders. Namely, we explore the mechanisms through which MT could exert its beneficial effects, including improvements in mitochondrial function, oxidative stress reduction, and neuronal survival enhancement. For this section, a literature search was performed on PubMed for studies investigating MT in the brain, covering the period from 2015 to the present. The search was based on the following keywords: "mitochondrial transplantation" and "mitochondrial transplantation & brain." Only articles focusing on MT in the brain within this time frame were included. Finally, we discuss the significant technical challenges faced in implementing this approach broadly in clinical practice and the specific points that must be overcome in treating brain disorders using MT.

By addressing these essential aspects, we seek to provide a critical and up-to-date synthesis of MT and offer insights into its potential impact on treating brain disorders to stimulate further investigation.

2. Crucial role of mitochondria in the brain

The mitochondrion is an organelle that arose from an endosymbiosis between two bacteria more than 1.5 billion years ago (Lane and Martin, 2010). Therefore, mitochondria are dual-membrane structures enclosing the mitochondria matrix containing a vestigial genome coding for 37 genes (Archer and Longo, 2013). This circular mitochondrial DNA (mtDNA) encodes two ribosomal RNAs, 22 tRNAs, and 13 genes coding for core components of the mitochondria respiratory chain complexes I, III, IV, and V (Suomalainen and Nunnari, 2024). Mitochondria are involved in essential cell functions (Picard and Shirihai, 2022), the main ones being illustrated in Fig. 1.

Mitochondria are particularly important in post-mitotic differentiated cells, such as neurons. Indeed, the integrity of this organelle is essential in cells that no longer divide and cannot "refresh" their mitochondria stock (Bamshad et al., 2022; Grimm and Eckert, 2017). Neurons consume more or less 15 % of the total amount of the body's energy to power processes like action potentials, neurotransmitter release, cytoskeletal dynamics, and synaptic plasticity (Pekkurnaz and Wang, 2022). However, these cells cannot store this necessary energy and must produce adenosine triphosphate (ATP) molecules instantly to supply the energy required by cells (Rangaraju et al., 2014). Neurons rely almost exclusively on mitochondrial oxidative phosphorylation to ensure ATP

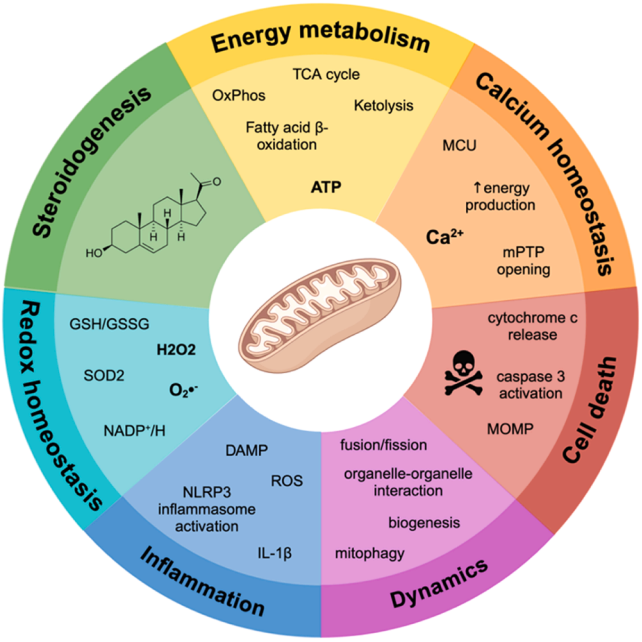

Fig. 1. Main mitochondrial functions. Depicted is the simplified repertoire of mitochondrial functions and associated pathways, proteins, and substrates. Mitochondria are highly dynamic organelles that constantly fuse, divide, and interact with other organelles like the endoplasmic reticulum or the lysosomes. They are considered as a metabolic hub, leading to adenosine triphosphate (ATP) production through OxPhos. Inevitable byproducts of OxPhos are superoxide anion radicals ($O_2\bullet^-$), which can be detoxified by the mitochondria's antioxidant defenses, making mitochondria an important player in the reduction-oxidation (redox) homeostasis. Mitochondria are also involved in inflammation, with mitochondria damage-associated molecular patterns (DAMP) and reactive oxygen species (ROS) triggering the inflammasome activation and the release of interleukin (e.g., IL-1β). Another important function of mitochondria is the regulation of calcium (Ca^{2+}) homeostasis, which is also closely linked to the mitochondria-dependent pathway of cell death with the opening of the mitochondrial membrane, releasing the cytochrome c in the cytosol and leading to apoptosis. Finally, mitochondria play a crucial role in steroidogenesis by producing pregnenolone, the precursor of all steroids. GSH/GSSG: glutathione reduced/oxidised form; H_2O_2: hydrogen peroxide; MCU: mitochondrial calcium uniporter; MOMP: mitochondria outer membrane permeabilisation; mPTP: mitochondria permeability transition pore; $NADP^+$/H: nicotinamide adenine dinucleotide phosphate oxidised/reduced; NLRP3: NOD-like receptor family, pyrin domain containing 3; SOD2: superoxide dismutase 2; TCA: tricyclic acid. Created with BioRender.com.

production in the brain (Bordone et al., 2019; Pathak et al., 2015). Excitatory neurons are the largest consumers of ATP in the brain, accounting for 80–85 % of the total. To support this high demand, glucose is recruited by several cell types, collectively known as the 'neurovascular unit'. These include brain capillary endothelial cells, pericytes, microglia, astrocytes, oligodendrocytes, and neurons. To reach the neurons from the blood, glucose could be directly transported through the extracellular space or through channels into the astrocyte to be primarily metabolized to ATP. In addition, recycling neurotransmitters such as glutamate by the astrocyte to synthesize the glutamine in neurons also contributes to the carbon need of the Krebs cycle and so to ATP production Field (Cunnane et al., 2020). This coordinated effort aims to enhance energy production in the brain's cells, ensuring the optimal functioning of fundamental processes such as synaptic transmission.

Synapses are the primary consumers of ATP in the brain. This is why mitochondria are abundant in synapses and have developed distinctive features, including morphological (Faitg et al., 2021), proteomic (Graham et al., 2017), and enzymatic characteristics (Graham et al., 2017). Mitochondria are transported along the cytoskeleton to the extremity of axons and dendrites to provide a high, localized, and fast

production of ATP and calcium buffering in the synaptic areas (Wang et al., 2023). These mitochondrial functions are essential for the recycling of synaptic vesicles and, therefore, synaptic transmission (Singh et al., 2018). The main mitochondrial functions in neurons are illustrated in Fig. 2.

Mitochondria also play a crucial role in synaptic plasticity. Indeed, a correlation has been demonstrated between the enhanced aggregation of mitochondria in dendrites and the number of new spines and synapses. Furthermore, during long-term potentiation, one of the two most significant neuroplasticity processes with long-term depression, it has been proven that mitochondrial energy production and calcium pump activity are increased, and mitochondrial gene expression is enhanced

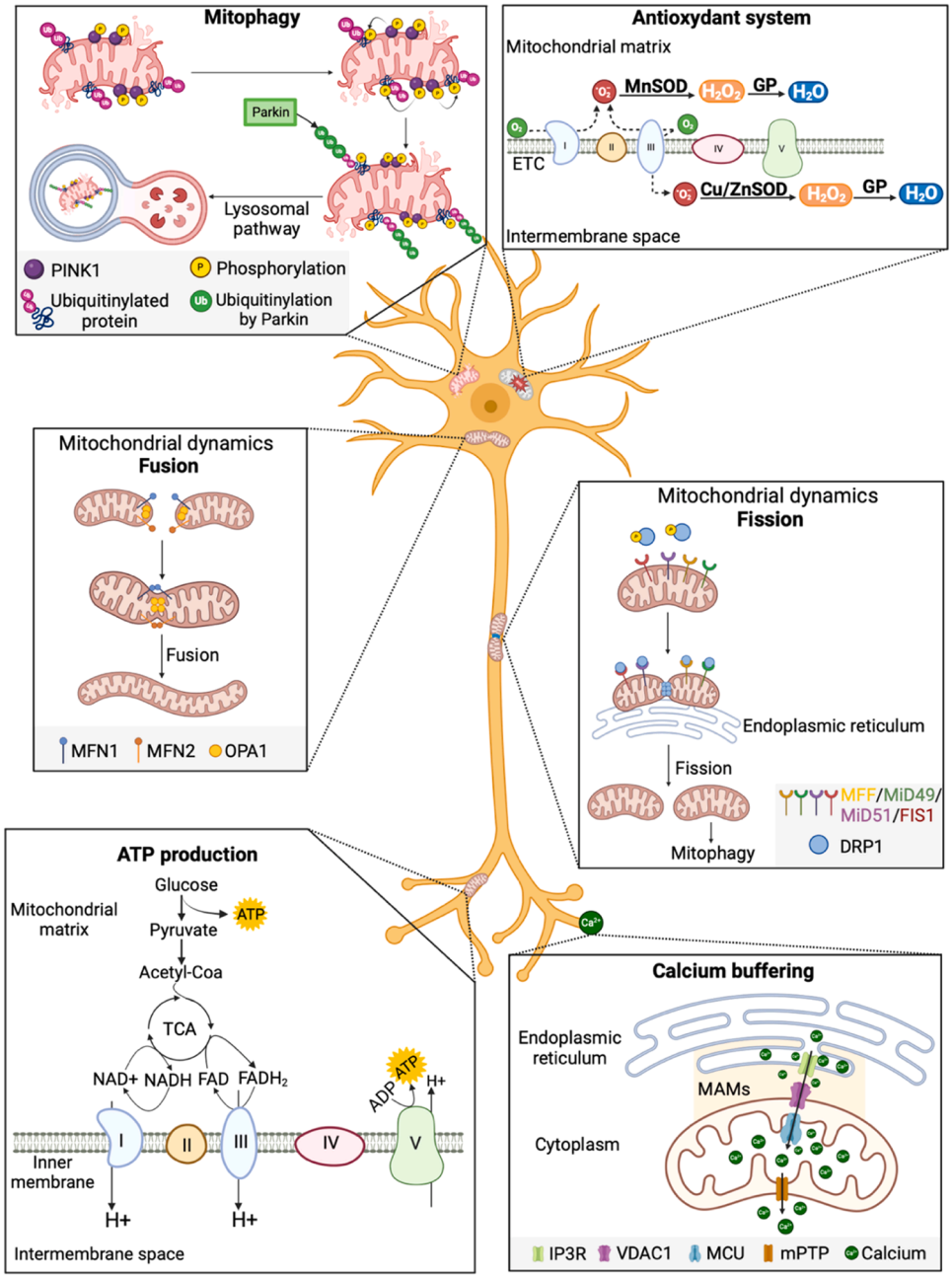

Fig. 2. Pivotal role of mitochondria in maintaining the physiological functions of neurons. ATP production and calcium buffering are particularly important in synapses to regulate synaptic transmission and the recycling of vesicles. To reduce oxidative stress generated by mitochondrial oxidative phosphorylation activity (OxPhos), antioxidant defenses are recruited, including mitochondrial superoxide dismutase (MnSOD) in the mitochondrial matrix or the cytoplasmic SOD (Cu/ZnSOD) in the intermembrane space. Mitochondrial dynamics are required to ensure that all the compartments have access to these fundamental functions. In the somatodendritic area, we can mainly observe an elongated mitochondrial network resulting from the fusion process, which leads to an upregulation of metabolic functions. The fission process is primarily observed in the axon and can be involved in stress conditions. Damaged mitochondria are directed towards the mitophagy process leading to the degradation of mitochondria via the lysosomal pathway. ATP: Adenosine triphosphate, $O_2^{\bullet-}$: superoxide radicals, ETC: Electron transport chain, H_2O_2: hydrogen peroxide, MnSOD: Manganese superoxide dismutase, Cu/ZNSOD: Copper-Zinc superoxide dismutase, GP: Glutathione peroxidase, MAMs: Mitochondrial associated membranes, IP3-R: Inositol-1,4,5-trisphosphate receptors, VDAC1: Voltage-dependent anion channel 1, OMM: outer mitochondrial membrane, IMM: Inner mitochondrial membrane, MCU: Mitochondrial calcium uniporter, mPTP: mitochondrial permeability transition pore, MFN1/2: Mitofusin 1/2, OPA1: Optic atrophy 1, Drp1: Dynamin-related protein 1, MFF: Mitochondrial fission factor, MiD49/51: Mitochondrial dynamics protein 49/51, FIS1: Mitochondrial fission 1 protein, PINK1: PTEN-induced putative kinase, Created with BioRender.com.

(Todorova and Blokland, 2017). Mitochondria also play a role in other plasticity contexts, such as neurogenesis. Scientists have identified a postmitotic period of plasticity for the fate of stem cells, which is influenced by mitochondrial dynamics in the brain (Iwata et al., 2020).

Additionally, there is a metabolic shift from glycolysis to mitochondrial respiration during neurogenesis. Mature cells require more energy, which can be produced through the respiratory process (30–32 molecules of ATP per cycle, in contrast to 2 molecules for glycolysis) (Agostini et al., 2016; Pekkurnaz and Wang, 2022). However, mitochondria can also influence the neurogenesis of stem cells in other ways, such as ROS signaling, biogenesis, and mitophagy (Arrazola et al., 2019). All these contributions to neurogenesis suggest that mitochondria are key regulators of this process.

Mitochondria are also of great importance in glial cells. Astrocytes play a role in many brain functions, including neurotransmitter homeostasis, synaptic modulation, and the blood-brain barrier (Endo et al., 2022). Although astrocytes have a higher glycolytic profile than neurons, astrocytic mitochondria are essential for maintaining lipid waste clearance via mitochondrial oxidation. This process protects against lipotoxicity, which can lead to neuroinflammation and degeneration. Furthermore, astrocytes are involved in synaptic development and transmission (Mi et al., 2023). Consequently, although mitochondria are not the primary energy source for these cells, they are still crucial for maintaining a general equilibrium within the brain.

Mitochondria are also crucial for oligodendrocytes. These cells play a vital role in the brain, forming a specific extension of the plasma membrane around the axons of nerve cells, known as myelin (Rinholm et al., 2016). The metabolic processes of oligodendrocytes are primarily regulated by glycolysis. It is postulated that there is less oxidative stress with glycolytic metabolism, which is beneficial for myelin and axonal integrity (Rosko et al., 2018). Despite their limited number, oligodendrocyte mitochondria play an essential role in supplying the carbon skeletons, lactate, and energy that are vital for the formation of myelin. Furthermore, it has been demonstrated that mitochondria are present in the cytoplasmic ridges along the myelin sheath of oligodendrocytes, exhibiting specific morphological characteristics and markedly reduced mobility compared to neurons and astrocytes (Rinholm et al., 2016). The precise roles of these mitochondria remain unclear so far. However, they may facilitate local lipid synthesis and membrane remodeling during myelination (Nakamura et al., 2023).

The role of mitochondria in microglia has also been described. These brain immune cells have two phenotypes: M1, which is associated with the pro-inflammatory state, and M2, which is more associated with tissue repair (Orihuela et al., 2015). Microglia can switch from oxidative phosphorylation to glycolysis metabolism and, inversely, depending on the energy demand (Baik et al., 2019; Holland et al., 2018). In a resting state, the main pathway used to produce ATP is OxPhos. However, when microglia are activated due to an inflammation or stress signal, they increase their glucose entrance by the glucose transporter (GLUT)-1 and switch their metabolism to anaerobic glycolysis. This glycolytic process increases ATP productivity and the immune response and increases mitochondrial fragmentation and oxidative species (Li et al., 2022). Some studies have shown that inhibiting mitochondrial metabolism is sufficient to switch from the resting microglia phenotype to the pro-inflammatory state. Therefore, mitochondria can influence the phenotype of microglia through their metabolism shift, mitochondrial dynamics, and ROS generation.

Overall, mitochondria play a pivotal role in numerous processes within the brain. Therefore, impairments in mitochondrial function may lead to brain dysfunction, ranging from subtle alterations in neuronal activity to brain cell loss. Thus, mitochondria are an attractive target for therapeutic intervention in treating many brain disorders.

3. Mitochondria transplantation as a therapeutic approach in brain disorders

Given the paramount role of mitochondria in the brain, defects in mitochondrial metabolic activity ultimately lead to neuronal defects. That is why almost all brain pathologies present with mitochondrial abnormalities (Alshial et al., 2023; Leão Barros et al., 2021; Tian et al., 2022). For instance, mitochondrial damage was shown to be a critical player in stroke-induced brain injury (Tian et al., 2022). Mitochondria dysfunction is also a common denominator in aging and brain-related diseases, such as depression, epilepsy, and neurodegenerative diseases (NDs) like Alzheimer's (AD) and Parkinson's disease (PD) (Alshial et al., 2023; Bamshad et al., 2022). Pathological protein hallmarks of NDs, such as amyloid-β (Aβ) peptide, tau protein, or α-synuclein, were even shown to directly interact with mitochondria, leading to defects in mitochondrial transport, mitochondrial dynamics, mitophagy, and mitochondrial bioenergetics (Grimm, 2021; Lurette et al., 2023; Pagani et al., 2011; Szabo et al., 2020). The accumulation of defective mitochondria due to the disruption of the quality control machinery (mitophagy) is a recognized hallmark of various NDs, including AD and PD (Bamshad et al., 2022). Furthermore, evidence suggests that mitochondrial and metabolic dysregulation in the brain may be causative factors in sporadic forms of NDs (Demetrius et al., 2021; Swerdlow et al., 2014).

In this context, many studies have aimed at developing therapeutic strategies to counteract neurodegeneration by improving, preserving, or rescuing mitochondrial bioenergetics in the brain (Cunnane et al., 2020). The therapeutic approaches that have been developed mainly aim to correct mitochondrial dysfunction using mitochondria-targeted drugs (e.g. MitoQ) or multimodal lifestyle changes (e.g. physical exercise, ketogenic diet).

Thus, mitochondria usually represent a target for neuroprotective interventions. However, in the context of MT, they serve as the therapy itself. Table 1 gives an overview of *in vitro* and *in vivo* studies assessing the effects of MT in diverse brain-related disorders. It especially indicates the source of mitochondria used and the tested doses. The main findings are discussed in the next paragraphs.

3.1. Cerebral ischemia and traumatic brain injury

Cerebral ischemia and traumatic brain injury (TBI) are common causes of high mortality and disability worldwide (Dang et al., 2017; Feigin et al., 2021), and their neurological impacts can be devastating and permanent. Several studies on ischemia and TBI have demonstrated the potential therapeutic benefits of MT in these pathologies.

Different techniques are used to induce cerebral ischemia in rodents, including the surgical insertion of a filament to occlude the cerebral artery (CAO: cerebral artery occlusion) (Huang et al., 2016; Nakamura et al., 2020) or the use of a photochemical product (such as rose bengal) to induce artificial ischemia (Chen et al., 2022; Hosseini et al., 2022). In these models, several approaches of MT were tested, such as intracerebral injection (Chen et al., 2022; Huang et al., 2016; Lee et al., 2023; Norat et al., 2023; Pourmohammadi-Bejarpasi et al., 2020; Zhang et al., 2019), or intravenous injection (Huang et al., 2016; Nakamura et al., 2020; Norat et al., 2023; Xie et al., 2021), or nasal delivery (Hosseini et al., 2022; Salman et al., 2023). They were all shown to reduce infarct size in treated animals compared to the untreated controls (Huang et al., 2016; Lee et al., 2023; Nakamura et al., 2020; Norat et al., 2023; Pourmohammadi-Bejarpasi et al., 2020; Salman et al., 2023; Xie et al., 2021; Zhang et al., 2019).

These impressive results were accompanied by a protective effect (Zhang et al., 2019) and an improvement of mitochondrial function in the recipient cells of treated mice/rats. Namely, MT was shown to restore the expression of mitochondria complex units I and IV (Salman et al., 2023) and increase ATP production (Chen et al., 2022; Hosseini et al., 2022; Norat et al., 2023; Salman et al., 2023; Zhang et al., 2019)

Table 1
Impact of mitochondrial transplantation on in vitro and in vivo models of brain pathologies.

Pathologies	Mitochondria donor cells / tissues	Models	Method of transplantation	Effects of transplantation	Ref
Traumatic brain injury / Ischemia					
Traumatic brain injury	Allogeneic liver and autogeneic muscle	Primary cortical neurons	Mitochondria added to the culture medium of cells (7*10^6/mL)	Decreased neuronal apoptosis Increased astrocytic BDNF production	(Zhao et al., 2021)
		Male C57BL mice (controlled cortical impact model)	Mitochondria Injected into the cerebral cortex (1,2–1,4*10^6)	Increased ATP, Tom20, and p-JNK levels in mitochondria transplanted cortex Reduced anxiety associated with the trauma Improved cognitive function and spatial memory after a TBI	
	Mouse brain	bEnd3 cells	Mitochondria added to the culture medium of cells	Improved the respiratory function of endothelial cell Increased tight junction proteins	(Zhang et al., 2020)
		PC12 cells	Mitochondria added to the culture medium of cells	Decreased the loss of synaptic plasticity-related proteins (GAP43 & Synapsin 1) Reduced cells apoptosis Promoted angiogenesis	
		Male C57BL/6J mice (controlled cortical impact)	Mitochondria injected into the cortex ipsilateral 10 min after the injury (10μL at 1,1*10^7/μL)	Decreased the leakage and damages of the BBB Decreased brain water content Improved the respiratory function of endothelial cell Improved the synaptic plasticity and memory Reduced apoptosis Prevented brain tissue destruction and preserved the cytoarchitecture of the brain	
	Human umbilical cord-derived mesenchymal stem cell	Adult male Wistar rats. TBI induced by the weight-drop injury device	Mitochondria injected into the intracerebroventricular after the injury	Decreased the number of apoptotic cells Decreased the recovery time and rescued sensorimotor functionality Attenuated microglia activation and prevented astrogliosis Promoted neurogenesis	(Bamshad et al., 2023)
Spinal Cord Injury	PC12 cells or from soleus muscle of Sprague-Dawley rats	Female Sprague–Dawley rats with computer-controlled standard-force injuries (250 kilodynes)	Mitochondria injected into the spinal cord 30 min after injury (50 to 150 μg)	Rescued mitochondrial respiration Neuroprotective effect only in a short-term manner Possibly enhanced neuropathic pain and causing inflammatory responses	(Gollihue et al., 2018)
		Sciatic nerve explant from Sprague-Dawley rats	Mitochondria injected into the epineurium (65 to 269 μg)	Decreased oxidative stress Prevented axonal degeneration and promoted axonal regeneration Reduced pain	
Sciatic nerve crush injury	BHK cells	Male Sprague-Dawley rats with a sciatic nerve crushed by a vessel clamp	Mitochondria injected into the epineurium within 10 min after the injury (195 μg)	Increased the population mature Schwann cell Regained muscle weight Decreased axonal degeneration and restored/ increased the axon traffic capacity and nerve regeneration Decreased oxidative stress and secondary inflammatory response	(Kuo et al., 2017)

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Table 1 (*continued*)

Pathologies	Mitochondria donor cells / tissues	Models	Method of transplantation	Effects of transplantation	Ref
Hippocampal neurons injury	COS-7 cells & primary neuron	Primary neurons of Sprague-Dawley rats	Mitochondria added to the culture medium of cells (25,5 µg)	Reduced muscle denervation Promoted neuronal regeneration Increased mitochondria potential membrane Increased ATP production allowing an early repair of the injured tissue Decreased oxidative stress in the ischemic penumbra	(Chien et al., 2018)
	Pectoralis major muscle	Male Sprague–Dawley rats with middle cerebral artery occlusion	Mitochondria injected into the left lateral ventricle (5*10^6)	Decreased the injury and reduced mitochondria damage and cells death Inhibited astrogliosis and induced neurogenesis during the development of ischemic stroke Reduced the infarct volume Reduced water content in the ipsilateral cerebral hemisphere Improved motor performance, motor coordination and learning	(Zhang et al., 2019)
	N2a or mouse neural stem cells	N2a or mouse neural stem cells	Mitochondria added to the culture medium of cells	Increased cell viability and decreased cells apoptosis Decreased ROS	
		Sprague-Dawley rats with middle cerebral artery occlusion	Mitochondria injected intravenously (around 180-200 µg)	Alleviated neurobehavioral deficits Reduced infarct volume Modified metabolites expression	(Xie et al., 2021)
Cerebral ischemia	Allogeneic mouse liver	Male C57BL/6J mice with photochemical (Rose bengal) induced ischemia	Two bilateral injections of mitochondria with 1 mm distance to lesion center (2*10^7)	Oligodendrocytes internalized mitochondria and increased their survivability, proliferation, and ATP production Increased myelination and preserved myelin, improving locomotion in injured mice in the long term Up-regulated 179 genes expression and down-regulated 196 genes in mitochondria-treated cortex	(Chen et al., 2022)
	Frozen placenta	Male C57BL6 mice with common carotid artery occlusion	Mitochondria injected intravenously (100 µg)	Presence of mitochondria in the brain, the lung, the liver, the kidney, and the heart 2 hours after treatment Reduced infarct volume Recovered motor function with both types of injection	(Nakamura et al., 2020)
	BHK cells	Male Sprague-Dawley rats with middle cerebral artery occlusion	Mitochondria injected into the ischemic striatum (75 µg) or into the femoral artery (750 µg) 24 hours after middle cerebral artery occlusion	Reduced the brain lesion, neuroprotective effect with both types of injection Reduced infarct volume with both types of injection Protected against stress due to oxygen/glucose deprivation Increased microglia cells proliferation and activation	(Huang et al., 2016)
	Mouse bone marrow mesenchymal stem cells	Male C57BL/6J mice with photochemical (Rose bengal) induced ischemia	Nasal delivery of mitochondria each day for 3 days (85 to 340 µg)	Alleviated cognitive impairment, increased plasticity Decreased ROS level, increased ATP level by preventing the loss of mitochondria membrane potential	(Hosseini et al., 2022)

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Table 1 (*continued*)

Pathologies	Mitochondria donor cells / tissues	Models	Method of transplantation	Effects of transplantation	Ref
	Human umbilical cord-derived mesenchymal stem cells	Wistar rats with middle cerebral occlusion	Mitochondria injected into the intracerebroventricular	Minimized the mitochondrial dysfunction and synaptic proteins loss Decreased the number of pyknotic cells, neuroprotection (normal cytoarchitecture/neuron) Reduced the infarct volume and apoptosis Rescued motor and balance neurobehavioral functions Decreased microglia activation and decreased astrogliosis Neuronal recovery/ neurotrophic effect	(Pourmohammadi-Bejarpasi et al., 2020)
	Rat primary astrocytes	Male Sprague-Dawley rats with an occlusion of the internal and common carotid artery	Mitochondria injected two times, 24 hours apart, into the striatum (100 μg)	Decreased the infarct volume Rescued dopaminergic neuron in a Parkinson's disease model (damage of dopamine neurons) Improved body weight after 72h Improved motor coordination and gait Decreased infarct volume and brain edema Improved the BBB Upregulated AMPK, SIRT1 and PGC-1a protein expression	(Lee et al., 2023)
	Male wild-type C57BL/6J mouse liver	Male wild-type C57BL/6J mice with middle cerebral artery occlusion	Nasal delivery of mitochondria 30 min, 24 hours and 48 hours post-stroke (100 μg)	Restored the expression of complex unit I and IV, improved mitochondrial function Decreased inflammation thanks to the inhibition of inflammasomes, astrocyte and microglia activation Antioxidant effect by increasing SULT4A1 protein expression	(Salman et al., 2023)
	Gastrocnemius muscle of C57Bl/6 mice	Adult male or female C57BL/6J mice with middle cerebral artery occlusion	Mitochondria injected by stereotactic or intra-arterial 1 hour after stroke	Passage through BBB by mitochondria occurs only when it is altered. The use of ultrasound promotes this passage Increased ATP production Decreased infarct volume and improve cell viability	(Norat et al., 2023)
Cognitive disorders					
Anxiety and depressive behaviors	Brain of young rats (3 months)	Aged (22 months) male Wistar rats exposed to chronic mild stress	Mitochondria injected in the right lateral cerebral ventricle	Decreased anxiety and depressive behaviors Decreased indoleamine 2 3-dioxygenase activity and Kyn level Increased mitochondria membrane potential Increased dendrites length and density	(Javani et al., 2022)
Cognitive deficit and mood dysfunction after hippocampal damage caused by status epilepticus	Mice hippocampus	Status epilepticus induced by pilocarpine in male C57BL/6J mice	Mitochondria injected intravenously (1 mg/kg)	Decreased cognitive impairment, depression and anxiety caused by status epilepticus Reduced neuronal loss Decreased microglia and astrocytes proliferation Modified metabolites expression Mitochondria crossed the BBB and decreased ROS	(Jia et al., 2023)

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Table 1 (*continued*)

Pathologies	Mitochondria donor cells / tissues	Models	Method of transplantation	Effects of transplantation	Ref
Lipopolysaccharide-induced depression-like behaviors	Mice hippocampus	Male ICR mice treated with lipopolysaccharide	Mitochondria injected intravenously (1 mg/kg)	production induced by status epilepticus Decreased anxiety and depressive behaviors Increased BDNF expression and neurogenesis Decreased oxidative stress and increased ATP production Decreased microglia and astrocytes activation Reduced neuroinflammation	(Wang et al., 2019)
Schizophrenia	Lymphoblasts derived from 3 healthy subjects or from whole brain of rats	Schizophrenia derived induced pluripotent stem cells (SZ-IPSC)	Mitochondria added to the culture medium of cells (1 µg mitochondria for 10^6 cells)	Improved neuronal differentiation and the activation of the Glu-Gln cycle Restored latent inhibition	Robicsek et al., 2018)
		Poly-I:C rats	Mitochondria injected into the cortex (100 µg)	Increased mitochondria membrane potential and prevent of its dissipation Improved glutamatergic neurons expression and differentiation Decreased of cognitive ability in control rats	
Aging	Liver mitochondria of young mice (2 months)	Male BABL/c mice (18 months)	Mitochondria injected intravenously (5mg/kg)	Increased mitochondrial activity in the brain and the muscles Improved the mitochondria enzyme activity Decreased ROS and MDA level Improved learning, memory and sport performances Increased macrophage activation	(Zhao et al., 2020)
	Liver or brain of young C57BL/6J mice (1 month)	C57BL/6J mice (12 months)	Mitochondria injected intravenously (10 or 20mg/kg)	Increased level of succinate Increase mitochondrial complex II expression	(Adlimoghaddam et al., 2022)
Neurodegenerative diseases					
Alzheimer	HeLa cells	Male C57BL/6 mice (injection of amyloid-beta 1-42 peptide in the brain)	Mitochondria injected intravenously (200 µg)	Increased mitochondrial activity in the brain of AD mice Reduced neuronal dysfunction / death and gliosis Improved cognitive function	(Nitzan et al., 2019)
	Brain of C57BL/6 mouse	SH-SY5Y with 10 uM of Aβ1-42 in the medium for 60h	Mitochondria added to the culture medium of cells for 4 hours (1,5 * 10^6/mL)	Increased mitochondrial membrane potential Increased cells viability within 2h and reduced Aβ aggregation Decreased ROS and increased the production of antioxidant compounds (GSH, GSH−Px, SOD, and T−AOC) Increased ATP production Increased the expression of 1,639 genes related to neuronal repair, antioxidant proteins, autophagy, and mitochondrial function, accompanied by a reduction in the expression of 457 genes associated with oxidative stress, cell growth inhibition, apoptosis, and Aβ. Promoted autophagy by	(Yang et al., 2023)

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Table 1 (*continued*)

Pathologies	Mitochondria donor cells / tissues	Models	Method of transplantation	Effects of transplantation	Ref
				activating NAD+/SIRT1 pathway Increased BDNF production by activating SIRT1 pathway Increased mice cognitive ability Decreased Aβ aggregation in the brain Decreased ROS production but also increased GSH/GSSG ratio Increased mitochondrial activity and ATP production Promoted autophagy and increased BDNF production by the activation of SIRT1	
		Male C57BL/6 mice with microinjection of 200 μmol/L Aβ1−42 on both sides of the hippocampus every day for 3 days	Mitochondria continuously injected intravenously for 4 days (3 * 10^6/0.2 mL)		
	PC12 cells (allogenic mitochondria) or human osteosarcoma cybrids cells (exogenic mitochondria) conjugated to Pep-1		PC12 cells	Mitochondria added to the culture medium of cells (105 μg)	Reduced oxidative stress and increased neurite growth with allogeneic or xenogeneic mitochondrial (conjugated to pep-1) transplantation
Parkinson	Female Sprague-Dawley rats treated with ascorbic acid to remove dopaminergic innervation in the medial forebrain bundle	(Chang et al., 2016)	Pep-1–conjugated mitochondria injected into the medial forebrain bundle (1,05 μg)	Reduced movement disorder and dopaminergic neurons degeneration Restored mitochondrial functions and decreased oxidative damages in the substansia nigra Xenogeneic mitochondria were less efficient against PD-related defects than allogeneic mitochondria 3 months after transplantation Improvement of the locomotor behavior Increase in neuron survival in the substantia nigra and in the striata Restoration of mitochondrial function Modulated of plasma inflammatory cytokine responses by Pep1-conjugated mitochondria Mitochondria entered in the cells within 30 min leading to an increase of cell viability and ATP content for at least 3 days Increased the respiratory complex I activity, ATP content, GSH level and decreased ROS level, cells apoptosis and necrosis, after 24 hours of treatment	
	Female Sprague-Dawley rat livers	Female Sprague-Dawley rats treated with ascorbic acid to remove dopaminergic innervation in the medial forebrain bundle	Nasal delivery of Pep-1-conjugated mitochondria (200 μg)		(Chang et al., 2021)
		SH-SY5Y	Mitochondria added to the culture medium of cells for 2 hours (10 to 50 μg)		
	HepG2 cells				(Shi et al., 2017)
C57BL/6J mice treated with intraperitoneal injections of 10 mg/kg 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine		Mitochondria injected intravenously (500 μg/kg)	Increased ATP level in the brain but also in the heart, liver, muscle and kidney for at least 3 days Increased endurance of the mice Increased complex I activity and decrease of ROS production		
			Cancer		
Chemotherapy-induced cognitive deficits	Human MSC	male and female C57BL/6J mice treated with cisplatin	Nasal delivery of mitochondria (170 μg)	Reduced the cognitive deficit induced by the chemotherapy. Restoration of spatial and	(Alexander et al., 2021)

(*continued on next page*)

Table 1 (*continued*)

Pathologies	Mitochondria donor cells / tissues	Models	Method of transplantation	Effects of transplantation	Ref
Chemotherapy-induced neuropathy and cognitive deficits	Human astrocytes	Male C57BL/6J mice treated with cisplatin	Nasal delivery of mitochondria coated with dextran-TPPpolymer conjugates (3 µg) or uncoated (170 µg) mitochondria. Treatment 48 and 96 hours after the last dose of cisplatin	working memory Reduced myelin and synaptic damages Reduced mitochondria abnormalities Improved the integrity of synaptosomes Induced hippocampal transcriptome modification (ex: *Nfe2l1, Atp6qp1* and *Apoa2*) Delivered mitochondria coated with dextran-TPP polymer conjugates are distributed to the brain meninges but not in the brain itself Modified the meningeal transcriptome and microenvironment Reduced cognitive deficits and neuropathic pain in cisplatin-treated mice Restoration of white matter integrity Rescued synaptosomal membrane and mitochondrial integrity Increased neurogenesis	(Alexander et al., 2022)
Glioblastoma	Human astrocytes	Human glioma cell line U87 in starvation	Mitochondria added to the culture medium of cells	Decreased expression of genes associated with glycolysis and increased expression of enzymes involved in the TCA cycle (citrate synthase and isocitrate dehydrogenase 2) Improved aerobic respiration and decreased Warburg effect	(Sun et al., 2019)
		athymic BALB/c nude mice treated with U87 cells injection to form a tumor xenograft	Mitochondria injected directly in the tumor	Combination with X ray increased the apoptosis of glioma cells and promoted the radiosensitivity of the cells Inhibited glioma growth when combined with X ray	
			Other		
Sepsis	Allogeneic biopsies of C57BL/6 mice skeletal muscle	M1/M2 BV2 microglia	Mitochondria added to the culture medium of cells (3*10^6)	Shifted microglia from a M1 to a M2 phenotype Increased neuron survival in co-culture with M1 microglia	(Yan et al., 2020)
		Male C57BL/6 mice subjected to cecal ligation and puncture	Mitochondria injected into the left lateral ventricle (4*10^6)	Shifted microglia from M1 to M2 state in the mice with sepsis Reduced behavioral deficits	
Ferroptosis	Immortalized hippocampal HT-22 cells	Immortalized hippocampal HT-22 cells incubated with erastin or RSL3 to induced ferroptosis	Mitochondria added to the culture medium of cells (5 µg)	Increased energy production Decreased cell death Decreased ROS level and lipid peroxidation	(Chen et al., 2023)
	Primary cortical neurons	Primary cortical neurons incubated with RSL3 to induced ferroptosis	Mitochondria added to the culture medium of cells (10 µg)		
Cardiac arrest	Brain or pectoral muscles of donor rats	Primary neuron from male Sprague–Dawley rats	Mitochondria added to the culture medium of cells (0,01mg/mL)	Exogeneous muscle- or brain-derived mitochondria entered in the cells in 24h Increased survival of rats 72 hours after resuscitation from cardiac arrest Attenuated the expression of the mitochondrial fusion	(Hayashida et al., 2023)
	Pectoral muscles of donor rats	Male Sprague–Dawley rats	Mitochondria injected intravenously		

(*continued on next page*)

Table 1 (*continued*)

Pathologies	Mitochondria donor cells / tissues	Models	Method of transplantation	Effects of transplantation	Ref
				proteins Opa1, Mfn1, Mfn2 Enhanced cerebral blood flow early (1h-2h) after cardiac arrest and resuscitation	

BDNF= Brain-derived neurotrophic factor; ATP= Adenosine Triphosphate; TBI= Traumatic brain injury; BBB= Blood-Brain Barrier; ROS= Reactive Oxygen Species; Glu-Gln cycle= Glutamate-Glutamine cycle; MDA= Malondialdehyde; AD= Alzheimer Disease; Aβ= Amyloid beta; GSH= Glutathione; GSH-Px= Glutathione Peroxidase; SOD= Superoxide Dismutase; T – AOC= Total Antioxidant Capacity; GSSG= Glutathione disulfide; PD= Parkinson Disease; TCA= tricarboxylic acid cycle

and mitochondrial membrane potential (Hosseini et al., 2022) in animals treated with MT but not in the control condition.

In CAO models, MT increased the expression of the antioxidant protein sulfotransferase 4A1 (SULT4A1) in C57BL/6 J mice (Salman et al., 2023) and decreased ROS production (Hosseini et al., 2022; Salman et al., 2023; Zhang et al., 2019) in treated mice and rats compared to the untreated condition. Restoring mitochondrial function translated by an antioxidant effect and enhancing ATP production may play a role in the neuroprotective effect of MT observed in the treated animals with CAO. Indeed, in studies with Sprague-Dawley and Wistar rats, the animals treated with MT showed fewer lesions and cell death compared to the untreated condition (Huang et al., 2016; Pourmohammadi-Bejarpasi et al., 2020; Zhang et al., 2019). Besides, mitochondria-treated animals showed a better blood-brain barrier (BBB) post-ischemia and an early repairment of the injured tissue (Zhang et al., 2019) due to improved neurogenesis (Zhang et al., 2019).

Other findings highlighted additional mechanisms of action related to the neuroprotective effects of MT. Chen et al. (2022) showed that the neuroprotective effect of MT may be linked to an increase in the remyelination of the neurons due to the increased survival and proliferation of oligodendrocytes (Chen et al., 2022). This effect is mediated via the upregulation of lipid synthesis genes (such as fatty acid binding proteins 5 and 7, fatty acid synthase, Olig 2, Wnt3, acetyl-Coenzyme A acyltransferase 1B) involved in multiple stages of the oligodendrocyte development. In the same study, authors observed an up-regulation of 179 genes and a down-regulation of 196 genes in mitochondria-treated mice cortex (Chen et al., 2022) compared to the untreated mice. In line, Xie et al. (2021) showed that MT reprogrammed cellular metabolism in Sprague-Dawley rats, particularly lipid metabolism (Xie et al., 2021). Other reprogrammed pathways include peroxisome proliferator-activated receptors (PPAR) signalling, insulin signalling, gluconeogenesis, glycolysis, and cholesterol metabolism, as well as pathways related to fat intake and digestion.

Salman M. et al. showed an increase in the expression of AMP-activated protein kinase (AMPK), Sirtuin 1 (SIRT1) and Peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1a) in mitochondria-treated mice compared to untreated mice. These three proteins are known to decrease cell apoptosis and have inhibitory effects on inflammation and oxidative stress, thereby improving cell survival. They also observed a reduction in the NLR family pyrin domain containing 3 (NLRP3) pathway in MT-treated mice, which plays a critical role in inflammation associated with ischemic stroke (Salman et al., 2023). These results explain the reduced inflammation observed in mitochondria-treated mice (Salman et al., 2023) and rats (Zhang et al., 2019). They could also explain the reduction in microglial activation and astrogliosis observed after MT (Salman et al., 2023; Zhang et al., 2019).

In another study, Huang P.-J., et al. noticed an increase in microglia activation in a rat model of CAO without further mechanistical analysis (Huang et al., 2016). These beneficial cellular effects of MT were also visible at the organism level. Indeed, several studies highlighted an improvement in cognitive and motor function compared to the untreated condition (Hosseini et al., 2022; Huang et al., 2016; Pourmohammadi-Bejarpasi et al., 2020; Salman et al., 2023; Xie et al., 2021; Zhang et al., 2019).

The beneficial effects of MT were also observed in several *in vitro* models. In primary mouse cortical neurons, Zhao, J., et al. showed that MT reduced neuronal apoptosis and increased astrocytic BDNF production (Zhao et al., 2021). Similar findings were observed in rat primary neurons (Chien et al., 2018). In parallel, Zhang, B., et al. showed that MT increases the expression of tight junction proteins and improves the respiratory function of bEnd3 cells. They also showed that MT could alleviate the loss of synaptic plasticity-related proteins (Growth Associated Protein 43 (GAP43) & Synapsin 1) and reduce the apoptosis of the PC12-treated cells compared to the untreated (Zhang et al., 2020).

In a mouse model of TBI (controlled cortical impact model), MT had positive effects at a cellular and organism level. Compared to the control mice, animals treated with MT showed better mitochondrial function, with more ATP production and less Tom20, a mitochondrial import receptor, and phosphorylated- c-Jun N-terminal kinases (JNK), a signaling molecule involved in ROS generation (Zhao et al., 2021). Similarly, Zhang B. et al. also observed that the treated mice had fewer signs of apoptosis, less brain damage, and less water in their brains than the control mice. In addition, they demonstrated the ability of MT to promote angiogenesis and improve the respiratory function of endothelial cells in treated mice (Zhang et al., 2020). In parallel, the study of Bamshad C. et al. performed on rats (TBI induced by a weight-drop injury device) highlighted an MT-induced reduction of apoptosis, prevention of microglia activation, and astrogliosis. MT also limited brain tissue destruction, allowing the preservation of the cytoarchitecture of the brain but also promoting neurogenesis (Bamshad et al., 2023). At the organism level, the above-mentioned studies also demonstrated the capacity of MT to improve cognitive function and spatial memory after TBI (Zhang et al., 2020; Zhao et al., 2021), to reduce the anxiety associated with the trauma (Zhao et al., 2021), to reduce the recovery time, and to rescue sensorimotor functionality.

Of note, Gollihue J.L. et al. observed adverse side effects after MT in rats with a spinal cord injury (Gollihue et al., 2018). Indeed, even though they rescued mitochondrial respiration and had a neuroprotective effect in the short term (48 hours), MT increased the sensitivity of treated animals, potentially increasing neuropathic pain and inflammatory responses in the long term. These results contradict those obtained by Kuo C.-C. et al. in a rat model of sciatic nerve crush. They observed that rats treated with MT had a pain reduction paralleled by a decrease in the inflammatory response and oxidative stress compared with untreated rats. In addition, treated rats had a regain in muscle mass that was protected from denervation, an increase in mature Schwann cells, and an increase in axonal trafficking (Kuo et al., 2017).

Taken together, these findings obtained in cerebral ischemia and TBI models highlight the potential of MT as a therapeutic approach. More longitudinal studies are needed to investigate long-term effects (including adverse side effects) and underlying mechanisms.

3.2. Cognitive disorders

A major issue of aging is the increasing risk of dementia and mood dysfunction (anxiety and depressive behaviors) that may be due to several biological processes, such as metabolic disorders, an increase of oxidative stress and inflammation, neuroendocrine abnormalities, impairments of neuroplasticity, and mitochondrial dysfunction (Javani et al., 2022).

Several studies have shown the capacity of MT to alleviate these cognitive disorders. Indeed, MT allowed the restoration of the expression of mitochondrial complex protein II, which is impaired in aging, improving mitochondrial function in the old mouse brain and suggesting a potential link between complex II and aging (Adlimoghaddam et al., 2022).

In rodent models of anxiety and depression disorders, MT was shown to limit neuronal loss and improve neurogenesis and plasticity, leading to an improvement in cognitive ability and a reduction in depression and anxiety by restoring and enhancing mitochondrial activity, paralleled with a decrease in ROS levels and an increase in brain-derived neurotrophic factor (BDNF) production (Javani et al., 2022; Wang et al., 2019; Zhao et al., 2020). Moreover, the positive effects of MT on depression and anxiety are not only due to the increase in plasticity. Indeed, Javani G. et al. have shown that MT decreases indoleamine 2 3-dioxygenase activity and kynurenine level, which are known to play a crucial role in the modulation of emotional states and are linked to depression and aging-related diseases (Javani et al., 2022).

Interestingly, Jia X. et al. found that the effects of MT were partly mediated by modulation of metabolite levels in a model of pilocarpine-induced status epilepticus in mice (Jia et al., 2023). They observed that MT reduced the level of sphingomyelin (d18:1/18:0) in the brain, which is a sphingolipid linked to neurodegenerative disorders in the brain and is increased in the cerebrospinal fluid of Alzheimer's disease patients (Koal et al., 2015). This decrease may be due to a mammalian-neutral sphingomyelinase located on mitochondria, which degrades sphingomyelin by hydrolysation (Wu et al., 2010). MT also decreased the level of methylmalonic acid, which is known to cause oxidative damage in synaptosomes and to play a role in cognitive impairments and seizures (O'Shea et al., 2012). Still, in Jia's study, mitochondrial transplantation decreased microglia and astrocyte activation (Jia et al., 2023). Besides, MT upregulated D-fructose 1,6-bisphosphate, which possesses anti-inflammatory effects and reduces inflammatory pain-like behavior (Veras et al., 2015).

However, these results contradict those from Zhao Z. et al., who showed that MT could potentially have a pro-inflammatory effect via activating macrophages, leading to enhanced cellular immunity to exogenous particles (Zhao et al., 2020). This could be explained by the action of a low level of sphingomyelins, which has been shown to increase microglial proliferation (Dannhausen et al., 2015). However, it highlights that, despite the encouraging results obtained with MT, some potential side effects could exist, and they will be discussed later in this review.

In induced pluripotent stem cells derived from schizophrenic patients, MT improved neuronal differentiation and restored the glutamate-glutamine cycle, a fundamental interaction between astrocytes and glutamatergic neurons that is disrupted in schizophrenia. In a rat model of schizophrenia (poly-I:C rats), MT improved the cognitive abilities of schizophrenic animals but had a deleterious effect in control rats. The reasons for this harmful effect are still unknown, but it could be due to the use of heterologous mitochondria that could induce an inflammatory response (Robicsek et al., 2018).

3.3. Neurodegenerative diseases

Many studies have highlighted the role of mitochondria in neurodegenerative diseases (NDs), where a major hallmark is decreased neuronal energy (Mochel and Haller, 2011; Parihar and Brewer, 2007; Pathak et al., 2013; Szabo et al., 2020). For this reason, using mitochondria as a therapy to restore neuronal bioenergetics is an interesting approach to treating NDs. Studies have been conducted to evaluate the therapeutic effect of exogenous mitochondria transplantation in this context *in vitro* and *in vivo* models of AD and PD.

Nitzan K. et al. demonstrated MT's therapeutic potential in a mouse model of AD, in which Aβ peptide was intracerebroventricularly injected (Nitzan et al., 2019). Indeed, after the transplantation, the authors observed an improvement in mitochondrial activity, a reduction in neuron disorganization and loss, a reduction of gliosis in the hippocampus of treated mice, and an improvement in cognitive abilities. Interestingly, transplanted mitochondria were also found in the liver of these mice, increasing the mitochondrial activity of this organ.

These data are in line with another study performed in both neuronal cells (*in vitro*) and mice (*in vivo*) treated with Aβ (Yang et al., 2023). Indeed, in a study by Yang X. and colleagues, MT has been shown to increase mitochondrial activity, ATP production, and antioxidant defenses and to decrease ROS levels and Aβ aggregation. These effects were probably linked to the capacity of MT to modulate gene expression. Indeed, four hours after MT in vitro, 1639 genes related to neuronal repairment, antioxidant proteins, autophagy, and mitochondrial function were remarkably upregulated. In parallel, 457 genes associated with oxidative stress, cell growth inhibition, apoptosis, and Aβ were downregulated. Besides, authors have shown that the SIRT1 pathway plays an essential role in the positive effect of MT by promoting autophagy and BDNF production *in vivo* and *in vitro*, thus leading to an increased cognitive ability of AD mice treated with mitochondria (Yang et al., 2023).

In the context of PD, Chang J.-C. et al. have evaluated the effect of transplanting allogeneic and xenogeneic Pep-1 conjugated mitochondria in PC12 cells and rats exposed to 6-hydroxydopamine (6-OHDA) (Chang et al., 2016). Positive effects were observed with both allogeneic (isolated from PC12 cells) and xenogeneic (isolated from human skin fibroblasts) mitochondria. *In vitro*, MT improved cell survival and neurite growth under 6-OHDA exposure. *In vivo*, an improvement of mitochondrial function was observed in 6-OHDA-treated rats, namely a normalization of the protein level of mitochondrial complexes and mitochondrial dynamics, as well as mitochondrial homeostasis and turnover, and a decrease in mitochondrial oxidative damages on neurons from the substantia nigra. Furthermore, mitochondria-treated PD rats showed an improvement in locomotor activity. Interestingly, the effect of MT using allogeneic mitochondria was more robust and persistent than with xenogeneic mitochondria. Thus, the origin of the mitochondria and the nuclear genome of the donor seems to play a role in the efficiency of the mitochondria and should be taken into account in the context of long-term treatment (Chang et al., 2016).

Of note, mitochondria transplanted into the medial forebrain bundle were found also in the substantia nigra, reflecting the ability of mitochondria to transfer between cells (Chang et al., 2016). This is consistent with other studies demonstrating intercellular transfer of mitochondria and other cellular compounds between cells (Fairley et al., 2022; Gao et al., 2019; Hayakawa et al., 2016). In a follow-up study, Chang J.-C and colleagues recapitulated the experiment by injecting intranasally exogenous mitochondria, conjugated or not, to Pep-1 (Chang et al., 2021). They observed improvements in the locomotor behavior of the rats with both conjugated and unconjugated mitochondria, as well as increased survival and recovery of dopaminergic neurons after lesions in the substantia nigra and striatum. These effects were likely due to the restoration of mitochondrial function by promoting the expression of complex 1, which is reduced in PD. Moreover, intranasal infusion of Pep-1-conjugated mitochondria attenuated the plasma inflammatory cytokine response.

Again, in PD models, Shi X. et al. showed the ability of transplanted mitochondria to enter inside neuronal cells (SH-SY5Y cells) within 30 minutes. This MT increased cell viability by enhancing anti-necrotic and anti-apoptotic activity in a dose-dependent manner. Besides, ATP

production, GSH level, and complex I activity were increased in 1-methyl-4-phenyl-pyridinium (MPP+)-treated cells after MT. A similar effect was observed in MPTP-treated mice, with a decrease in ROS production (possibly due to the increase of GSH level) in the brain and other organs (heart, liver, muscles, kidneys). Although the treated mice did not show any improvement in spontaneous locomotor activity, they did show an increase in cognitive capacity and endurance. This increase could be explained by the presence of transplanted mitochondria in the muscle, which, by increasing ATP production, would increase the endurance of the mice (Shi et al., 2017). Of note, Lee E.-H. and colleagues have shown that MT rescues dopaminergic neurons in a stroke model, which could also be beneficial in PD (Lee et al., 2023).

3.4. Cancer

Approximately 75 % of cancer patients suffer from cognitive impairment, including loss of memory, concentration, processing speed, executive and psychomotor functions, and visuospatial abilities. This was linked to the neurotoxic effects of chemotherapy, which significantly impact patients' quality of life (Henderson et al., 2019). MT completely reversed the chemotherapy-induced cognitive deficits in mice (Alexander et al., 2021). Indeed, MT did not only reduce symptoms in cisplatin-treated mice (a commonly used anti-tumor drug) but also reversed myelin damage, synaptic/synaptosomal damage, and mitochondrial abnormalities. Interestingly, mitochondria transplantation altered several gene expression in the mouse hippocampus. While cisplatin treatment changed the expression of 1813 genes in the mouse hippocampus, MT reversed the cisplatin-induced change expression in 676 genes. Among these 676 genes, *NFE2L1* (nuclear factor erythroid 2-related factor 1) was one of the most impacted genes, along with telomerase, *ERK/MAPK*, as well as genes related to synaptogenesis signaling, which could explain the improvement in cognitive functions (Alexander et al., 2021). Of note, *NFE2L1* is known to have neuroprotective properties against oxidative stress by triggering antioxidant genes through the glutathione synthesis pathway (Lu, 2009). Furthermore, *NFE2L1* is essential for the preservation of mitochondrial homeostasis (Hu et al., 2022). In a follow-up study from the same group, experiments were repeated using nasal delivery of mitochondria coated with dextran-TTP (Alexander et al., 2022). This method resulted in the distribution of mitochondria only in the brain meninges, but similar effects were observed compared to their previous study (Alexander et al., 2021). MT restored neurogenesis, white matter integrity, mitochondrial integrity, and synaptosomal membrane function, improving cognitive capacity and reducing chemotherapy-induced neuropathic pain in cisplatin-treated mice. Furthermore, there was a noted change in the transcriptome, with 2433 genes affected (1619 upregulated and 814 downregulated) in the meningeal transcriptome by MT. Additionally, out of the 668 genes affected by chemotherapy, 286 were normalized by MT. The most significant changes were seen in pathways regulating the NFE2L2 (nuclear factor erythroid 2-related factor 2)-mediated oxidative stress response, axonal guidance, semaphorin signaling, and xenobiotic metabolism. The latest consisted of changes in the constitutive active / androstane receptor (CAR), pregnane X receptor (PXR), aryl hydrocarbon receptor (AHR), and retinoid X receptor (RXR) signaling pathways. MT also altered the meningeal microenvironment, particularly macrophage pathways related to C-C chemokine receptor type 5 (CCR5) signaling, antigen presentation, and phagosome maturation. An increase in interleukin (IL)-15, known for its role in cognitive function, was also observed. Notably, IL-15 deficiency in mice leads to memory and behavioral disorders and impacts neurogenesis and neurotransmission (Pan et al., 2013). Finally, changes in the vascular system were detected in angiogenesis and in pathways regulating blood flow (vasodilation, purinergic receptor, and endothelin signaling pathways), which play a beneficial role in the health of the brain. Nervous system pathways involving glutamate receptors, opioids, and synaptogenesis signaling were also changed after MT.

In addition to the neuroprotective aspect shown against chemotherapy-induced cognitive deficits, MT appears also beneficial against glioblastoma. Indeed, Sun C. et al. have shown that MT reduced the Warburg effect (up-regulation of glycolysis) in glioma and increased mitochondrial respiration (Sun et al., 2019). In addition, transplantation exacerbated the radiosensitivity of gliomas, leading to a better reduction in glioma proliferation and size after X-ray irradiation. However, unlike the other studies, starvation treatment was required for the mitochondria to enter the cells.

3.5. Other brain-related disorders

Beneficial effects of MT were also observed in pathological models that indirectly affected the brain. Recently, Chen T. et al. studied the impact of MT on ferroptosis, a type of oxidative cell death that can occur in neurodegenerative diseases (Chen et al., 2023). When compared to healthy cells, more mitochondria were internalized in ferroptotic HT-22 cells and primary cortical neuron cells, together with an increased interaction between endogenous and exogenous mitochondria. This incorporation of mitochondria led to a neuroprotective effect and prevented cell death in a dose-dependent manner. This effect occurs through the increase of ATP production and the decrease of ROS and lipid peroxidation (a hallmark of ferroptosis) levels in cells. Moreover, this neuroprotective effect disappears when the mitochondrial complex I, III or V were inhibited (Chen et al., 2023).

The effects of MT were also studied in the context of sepsis, especially regarding brain-related impairments. Indeed, evidence has shown the deleterious impact of microglia activity on neurons through their M1 pro-inflammatory phenotype, increasing neuroinflammation, which can harm the neurons in the context of neurodegenerative diseases (Colonna and Butovsky, 2017; Hickman et al., 2018). Alteration of microglial mitochondria was shown to modify the microglia phenotype and impede the activation/transition to the M2 phenotype, which would be beneficial in neurodegenerative diseases to mitigate this deleterious inflammation (Ferger et al., 2010).

In this context, Yan C. et al. have evaluated the protective effect of MT on neurons *in vitro* and *in vivo* models of sepsis. They found that mitochondrial content increased in M2 microglia but decreased in M1 microglia (Yan et al., 2020). This discovery could explain the observation of Baik S. H. et al., who showed that M1 microglia metabolism is reprogrammed towards a more glycolic metabolism (Baik et al., 2019). This may be due to the lack of mitochondria in M1 microglia, which then increase their glycolytic activity to compensate for the lack of ATP production. After MT, a neuroprotective effect was observed in sepsis mice by restoring an M2 phenotype and promoting the transition from an M1 to an M2 phenotype (Yan et al., 2020). Hence, treated mice showed a significant increase in cognitive ability compared to untreated mice. In the context of neurodegenerative disease, in addition to restoring the bioenergy of neurons, MT would limit the deleterious effects of inflammation on neurons by promoting an M2 phenotype in microglia.

Finally, since cardiac arrest leads to fatal whole-body ischemia if left untreated, people who survive exhibit long-term cardiovascular and neurological issues. As MT has already shown promising results in brain ischemia, Hayashida K. et al. investigated the effect of MT on neurological outcomes after resuscitation from cardiac arrest. After confirming *in vitro* the ability of exogenous mitochondria (from brain or pectoral muscle) to enter into primary neurons from rats, they tested *in vivo* the effect of MT on rats resuscitated from cardiac arrest. At the cellular level, treatment with MT resulted in a decrease in the expression of mitochondrial fusion genes *OPA1*, *MFN1*, *MFN2*, and an enhanced cerebral flood flow one to two hours after resuscitation from cardiac arrest. However, the significant finding of this study is the ability of MT to enhance rats' survival 72 hours after resuscitation from cardiac arrest (Hayashida et al., 2023).

Together, these preclinical studies demonstrate that MT can

potentially treat a wide range of brain disorders. Fig. 3 summarizes the primary and often similar effects of MT observed in animal models of various brain pathologies.

4. Mitochondria transplantation: from bench to bedside

As discussed above, MT showed promising outcomes in several *in vitro* and *in vivo* models of brain-related disorders. However, before being used as a treatment in humans, MT must overcome several technical challenges and questions (Fig. 4). In this section, we discuss challenges faced in the general application of MT, not only those inherent to brain disorders.

4.1. Source of mitochondria

The first paramount question to answer is: which source of mitochondria should be used for transplantation? Ideally, transplanted mitochondria should come from the same tissue from the target organ to maximize/optimize the effects of the transplantation. As discussed in a recent review from the group of J. McCully (McCully et al., 2023), mitochondria from autologous tissue from the patient's own body would be the most clinically relevant source for transplantation. This is indeed

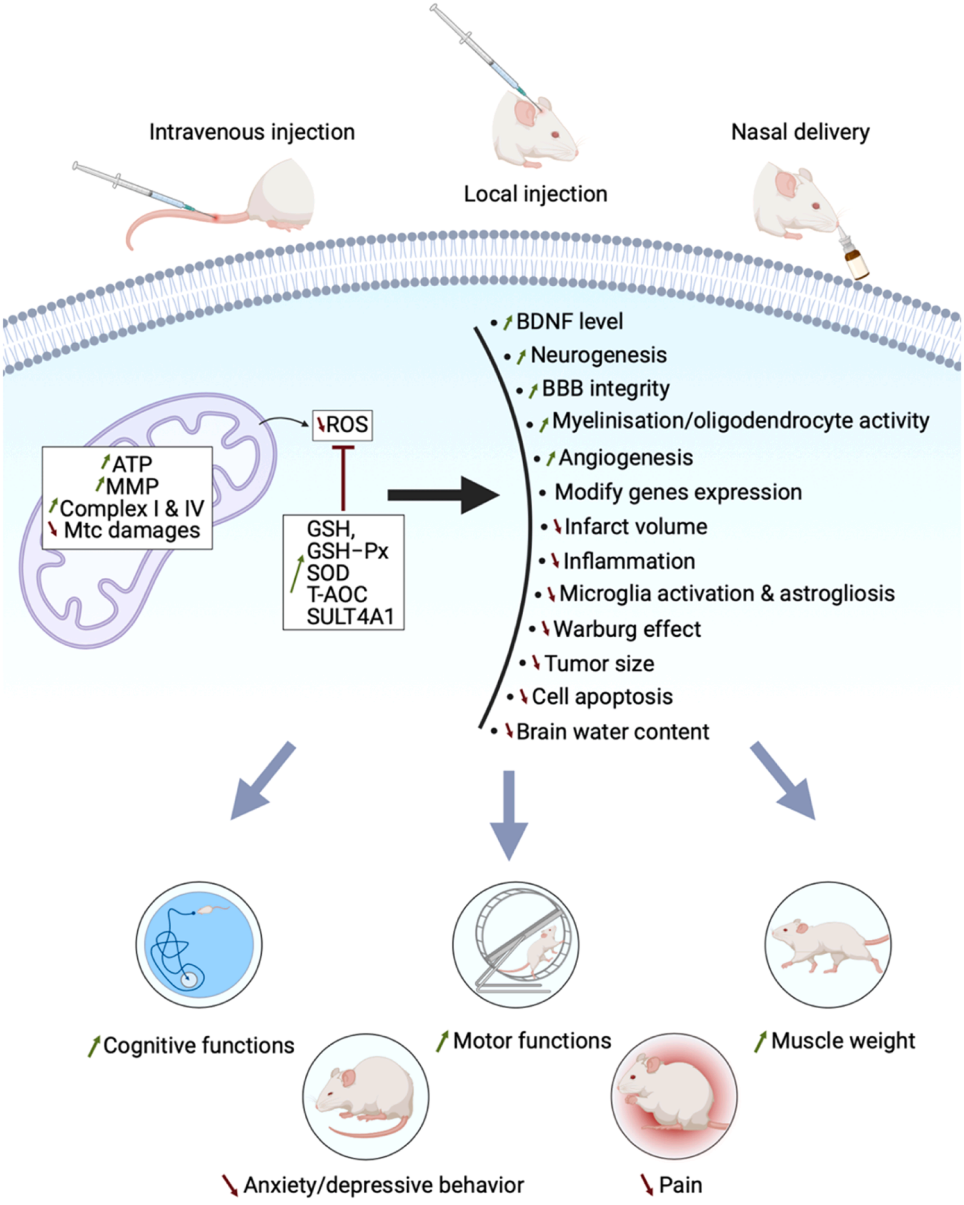

Fig. 3. Redundant effects of mitochondrial transplantation in pre-clinical models of several brain pathologies. Common results appear in animal studies assessing mitochondrial transplantation (MT) effects across various brain pathologies, although different injection methods (intravenous, local, nasal) and protocols (mitochondrial source, concentration, animal models) were used. At the mitochondrial level, MT restores and enhances mitochondrial activity, limits mitochondrial damage, reduces the production of reactive oxygen species (ROS), and increases the expression of antioxidant compounds (GSH, GSH-Px, SOD, SULT4A1). At the cellular level, MT exerts neuroprotective effects through various actions, such as modifying gene expression, reducing inflammation, decreasing cell apoptosis, and promoting neurogenesis. At the organismal level, these beneficial effects are physiologically translated into improved cognitive and motor function in the treated rodents, as well as a reduction in anxiety/depressive behaviors and pain in some pathologies such as traumatic brain injury, cancer, or depression. MMP: Mitochondrial membrane potential, Mtc: Mitochondrial, GSH: Glutathione, GSH-Px: Gluthatione peroxidase, SOD: Superoxide dismutase, T-AOC: Total antioxidant capacity, SULT4A1: sulfotransferase 4A1, BDNF: Brain-derived neurotrophic factor, BBB: blood-brain barrier. Green arrow ↗: increase, red arrow ↘: decrease. Created with BioRender.com.

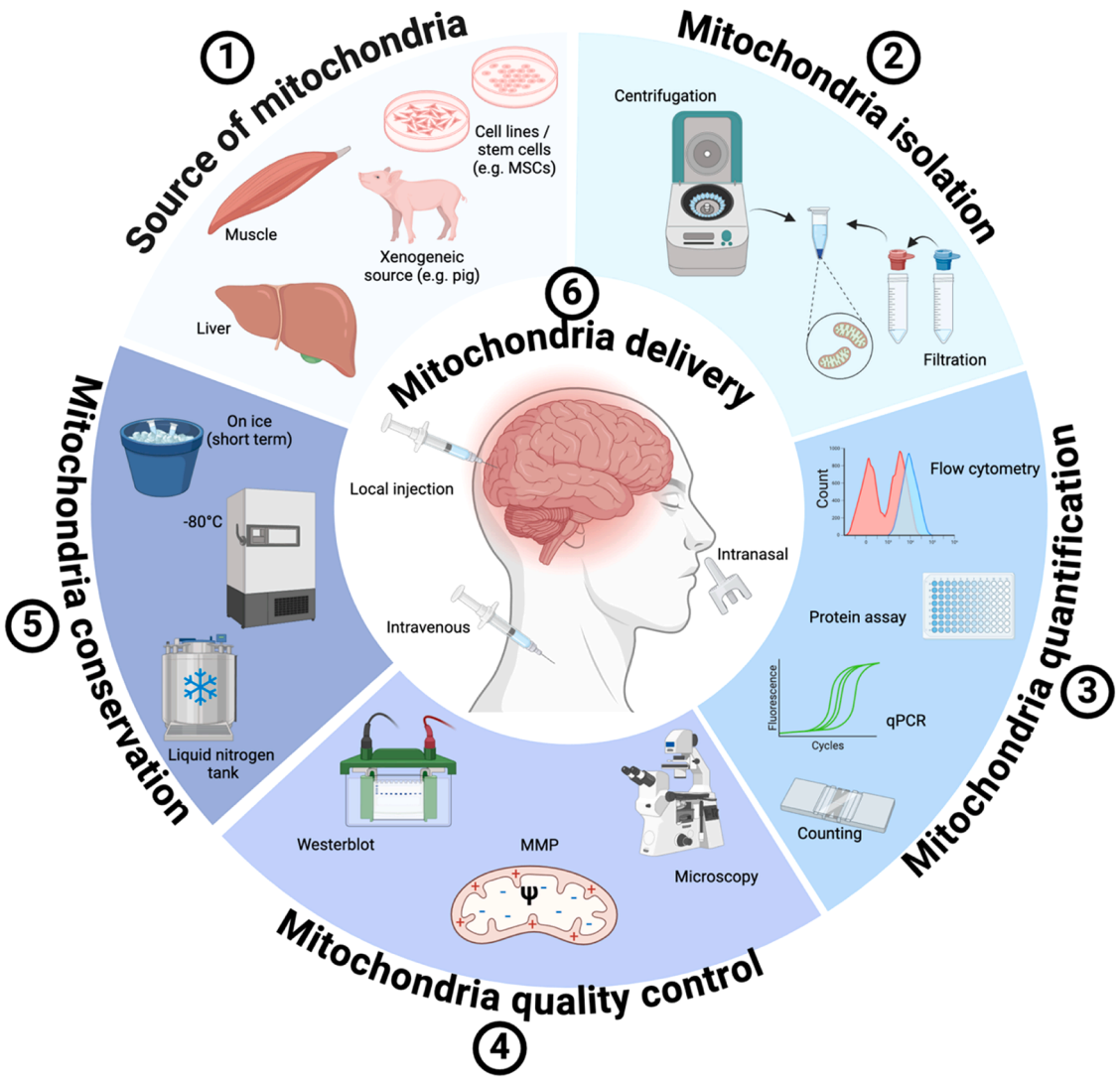

Fig. 4. Key stages and challenges in developing mitochondrial transplantation as a therapeutic strategy for brain disorders. The diagram shows the various steps and processes that need to be developed and improved before mitochondria transplantation can be used for patients with brain disorders. This involves (1) identifying the most suitable source of mitochondria (such as muscle tissue, liver tissue, or cell lines); (2) refining the protocol for isolating mitochondria to obtain viable ones for transplantation; (3–4) establishing efficient methods for counting and evaluating mitochondrial quality control; (5) perfecting procedures for the short- and long-term preservation of mitochondria; and finally, (6) determining the best delivery methods for mitochondrial transplantation (such as local brain injection, intravenous administration, or nasal inoculation). MMP: mitochondrial membrane potential. Created with BioRender.com.

feasible in the context of MT in cardiac diseases in which a surgical incision is anyway necessary to access the heart. Thus, mitochondria can be isolated from muscle (e.g. pectoralis major, rectus abdominus) or liver tissues and reinjected in the ischemic site.

This approach is more challenging in the case of brain-related diseases. Indeed, brain-derived mitochondria cannot be easily accessed and cannot be used as a primary source for mitochondrial transplantation. Besides, in neurodegenerative disorders like AD, mitochondrial dysfunctions were also found in peripheral cells (fibroblasts, peripheral blood mononuclear cells, platelets) (Bell et al., 2021), suggesting that autologous MT is not an option in that case.

Sources of mitochondria employed in studies depicted in Table 1 include cell lines (e.g. PC12 cells, BHK cells, COS-7 cells, N2a cells, HT22 cells) or non-brain tissues (muscle, liver) and showed positive outcomes in animal models of brain disorders. Thus, the use of heterologous sources of mitochondria would be an appropriate alternative to brain-derived mitochondria and would be readily available without the need for a surgical intervention. Allogeneic mitochondria (from human cells, e.g., mesenchymal stem cells) should be used for more clinical relevance. Nevertheless, animal studies have shown that xenogeneic MT induced similar positive effects than allogeneic MT (Alexander et al., 2021; Bamshad et al., 2023; Chang et al., 2016).

From a clinical perspective, identifying the source of mitochondria represents a significant challenge. It is imperative to avoid complications associated with surgical procedures to obtain isolated mitochondria. However, using mitochondria derived from animal sources raises substantial ethical concerns and may increase the risk of immune rejection. It is essential to ascertain which mitochondrial sources are most suitable for transplantation in a specific organ. Indeed, it is established that cells with defined functions, such as the retina or neurons, do not require the same ATP level to maintain their functions (Hosseinian et al., 2022).

Furthermore, there is a lack of studies demonstrating the proportion of active transplanted mitochondria in recipient cells relative to the total amount of transplanted mitochondria. The procedure's efficiency may also be contingent upon the source of the isolated mitochondria. Xenotransplantation has yielded promising outcomes in animal models. This approach is based on the assumption that mitochondria originate from a

common ancestor. Yet, evidence suggests that evolutionary divergence has led to variations in mitochondrial DNA replication capabilities among species. Therefore, further investigation into xeno-transplantation is crucial before its application in humans to ascertain this technique's long-term stability and efficacy (Hosseinian et al., 2022).

The source of mitochondria also raises a crucial question about the risk of a potential immune response in mitochondrial transplantation. However, it was shown that neither syngeneic nor allogeneic transplanted mitochondria triggered direct or indirect alloreactivity, and no damage-associated molecular patterns were observed in transplanted mice, which is consistent with the observations of the studies in Table 1. Interestingly, this observation was made for both single and serial injections of mitochondria (Ramirez-Barbieri et al., 2019), suggesting that mitochondrial transplantation may be feasible without the risk of immune reaction.

4.2. Mitochondria isolation

One of the main challenges of MT is to isolate and count mitochondria with sufficient precision and in a short period to avoid loss of mitochondrial capacity or deleterious damages that could lead to unwanted side effects. Indeed, it has been reported that isolated mitochondria can remain active when kept on ice for only one to two hours (Doulamis and McCully, 2021; McCully et al., 2017). Mitochondrial isolation by centrifugation (differential and/or gradient centrifugation) is the most widely used method. However, this method is time-consuming, requiring around 90–120 minutes to complete, ultimately reducing mitochondrial activity and viability. To solve this issue, Preble JM and colleagues were the first to propose a faster isolation protocol using differential filtration instead of centrifugation, which can be achieved in 30 minutes (Preble et al., 2014). Still used nowadays (Hayashida et al., 2023; Norat et al., 2023; Salman et al., 2023), this protocol appears to be the most suitable for mitochondrial isolation due to the short process time by limiting the number of centrifugations, which can harm mitochondria. With this protocol, less than 0.01 % of isolated mitochondria are fractured or damaged, and less than 0.001 % contamination of non-mitochondrial particles was obtained (McCully et al., 2016; Preble et al., 2014).

Of note, commercial kits allow the isolation of mitochondria, which are based on centrifugations (Minet and Gaster, 2010; Zhang et al., 2020). However, they take longer to isolate mitochondria than McCully's technique.

4.3. Mitochondria counting

Determining mitochondrial number is the second step of the process and is essential before the transplantation. However, due to the short time window of mitochondrial viability on ice, it isn't easy to have a method that combines efficiency and quickness. One efficient way would be to use the qPCR method to determine the quantity of mitochondria based on the quantification of the mitochondrial DNA (Chen et al., 2022) or to quantify the number of mitochondria by flow cytometry (Xie et al., 2021). However, this approach required a certain amount of mitochondria and time. A faster way would be to count mitochondria using a hemocytometer or by staining them and using a fluorescent microscope (Zhang et al., 2020; Zhang et al., 2019). Nevertheless, besides the staining time that can be long depending on the dye, the risk of errors is high for both methods and can vary from one experimenter to another, especially when the mobility and the fusion/fission capacity of the mitochondria are considered.

A good compromise between time and efficiency is measuring the total amount of mitochondrial protein (e.g., using a Bradford test), as it has been used in several studies (Chang et al., 2013; Gollihue et al., 2018; Lee et al., 2023; Nitzan et al., 2019; Salman et al., 2023; Shi et al., 2017). Thus, the risk of error due to the fusion/fission capacity of the mitochondria is reduced.

4.4. Mitochondrial viability and purity

Mitochondrial viability and purity are other important parameters that should be assessed before mitochondrial transplantation. The easiest and quickest way to assess mitochondrial viability is to use dyes based on mitochondrial membrane potential, such as Mitotracker fluorescent probes or JC-1 dye, which accumulate only in active polarized mitochondria (Cottet-Rousselle et al., 2011). Two methods can be used to assess the purity of isolated mitochondria: western blots (Micakovic et al., 2019; Nitzan et al., 2019) and microscopy (Huang et al., 2016; Preble et al., 2014; Sun et al., 2019).

4.5. Short to long-term mitochondria conservation

Because isolated mitochondria remain active on ice for approximately one to two hours, mitochondrial transplantation is not suitable for time-consuming surgical procedures.

In their study, Gnaiger E. et al. showed the ability of a specific buffer to preserve mitochondrial capacity for a longer time. Indeed, mitochondrial respiratory capacity was maintained for 24 h by keeping mitochondria in a HEPES–sucrose-based buffer containing antioxidants, ATP, histidine, colloidal agents, and cytochrome C, at 0°C. Nevertheless, after 24 hours, the mitochondrial activity started to decrease (Gnaiger et al., 2000).

Cryopreservation of isolated mitochondria has been a longstanding challenge due to their sensitivity to the freezing and thawing processes. These processes can damage the structure and function of mitochondria, necessitating the optimization of protocols and buffers used. However, it has been demonstrated that cryoprotective agents can affect mitochondrial bioenergetics (Nukala et al., 2006). Selecting and using an effective cryoprotective agent is crucial to mitigate the harmful effects of ice crystal formation during the freezing of mitochondria. Common agents such as glycerol and dimethyl sulfoxide (DMSO) have been employed, showing a protective effect on mitochondrial structure and oxidative phosphorylation activity at 10 % concentration.

An old report from Greiff and Myers in the 60's suggested that DMSO appears more suitable due to its lower toxicity at higher concentrations (30 %) compared to glycerol (Greiff and Myers, 1961). In this study, mitochondria were isolated from Sprague-Dawley rat livers, slowly frozen at −76°C, and stored for 18 days at −65°C. No loss of OxPhos activity was detected after thawing. Different outcomes were observed in a more recent study from Nukala V.N. et al. (Nukala et al., 2006). Here, mitochondria were isolated from rat cerebral cortex and slowly frozen at −80°C for one week in 10 % DMSO. The mitochondrial structure was maintained after thawing, but a significant reduction in mitochondrial respiratory capacity and a loss of cytochrome c compared to the non-frozen conditions were observed. These different results could be due to the difference in the freezing procedure or the origin of mitochondria (liver or brain) used between both studies.

In another approach, Yamaguchi, R. et al. isolated mitochondria from mouse liver, which were rapidly frozen in liquid nitrogen and then stored at −80°C. In their study, various freezing mediums were tested, but only the medium containing 300 mM of trehalose could maintain mitochondrial structure and retain cytochrome c for at least 45 minutes at 22°C and 37°C after thawing. However, the mitochondria presented a loss of ATP and a decline in bioenergetic function, although they could still produce ATP post-thaw (Yamaguchi et al., 2006). Nevertheless, trehalose seems to be an interesting compound for mitochondrial cryopreservation. Indeed, in a recent study, Cloer C.M., et al. were able to preserve mitochondria for one year by directly storing them at −80°C in a trehalose buffer (300 mM trehalose, 10 mM HEPES, 10 mM KCl, 1 mM EGTA, 0.1 % BSA), without damaging the mitochondrial structure or losing mitochondrial functions (Cloer et al., 2023).

In a separate study, Schieber O., et al. (1994) preserved the structure

and activity of isolated tobacco leaf mitochondria using 7.5 % ethylene glycol. In this case, mitochondria were rapidly frozen in liquid nitrogen and stored for three months (Schieber et al., 1994).

Overall, these studies highlight that cryoprotective agents and freezing media are essential but not the only points to optimize the freezing process of mitochondria. Indeed, even if an excellent cryoprotective agent can maintain mitochondrial structure, it may not be able to protect against cytochrome c leakage and loss of mitochondrial respiratory capacity. Thus, the freezing process (slow or fast), the storage time, the thawing process (fast or slow), and the media are key points to consider to preserve mitochondrial activity.

4.6. Mitochondria delivery

Different methods have been attempted to transplant isolated mitochondria into cells. *In vitro*, a simple co-incubation of isolated mitochondria with recipient cells has been demonstrated to be an effective approach. The internalization of isolated mitochondria can be enhanced by implementing various strategies. One is magnetomitotransfer, a technique that uses beads to bind to mitochondrial outer membrane protein TOM22 (Macheiner et al., 2016). The utilization of cell-penetrating peptides, such as Pep-1, has also been established, facilitating the delivery of mitochondria through electrostatic and hydrophobic interactions with the cell membrane (Kim et al., 2023). Furthermore, biocompatible polymers, such as dextran, can be employed as a coating for isolated mitochondria to preserve their functionality and enhance cell uptake. While these approaches offer distinct advantages, a limitation is their *in vivo* applicability or the necessity for further investigation.

The last but significant limitation and source of concern that must be overcome to use MT against brain-related disorders in the clinic is the delivery method. Indeed, in most studies discussed above, MT was made by local injection in the brain. However, in the context of clinical treatment, this invasive mode of injection may not be the most suitable due to the severe risk of injury. Another method that was employed is the intravenous administration of mitochondria. However, *in vivo* studies have shown the lack of organ specificness as exogenous mitochondria were found in the muscle, heart, liver, kidney, and brain (Nakamura et al., 2020; Nitzan et al., 2019; Shi et al., 2017; Zhao et al., 2020). Despite the positive effects observed in these organs, the risk is that mitochondria will accumulate in other organs than the brain, requiring higher doses, which could lead to an inflammatory reaction.

The nasal route is an interesting alternative. It is noninvasive, simple, and requires a smaller amount of mitochondria (Alexander et al., 2022; Alexander et al., 2021; Chang et al., 2021). Indeed, Chang J-C. et al. showed that the rostral migratory stream provides a conduit for intranasal mitochondrial delivery, guiding internalized mitochondria into the striatum (Chang et al., 2021).

The delivery approach presents a significant challenge, as it must be as efficient as possible while minimizing the risk of adverse effects. Developing a drug delivery system that targets specific cells or tissues could prove beneficial in treating numerous diseases. It may also be of interest to combine different delivery pathways, for example, a local injection to elicit an acute response and then continue the treatment by the intranasal route to maintain the effect over the long term. Further investigations are required in this area to ascertain whether mitochondrial transplantation could be used as a treatment for brain diseases.

5. MT against neurological disorders: practical considerations and future directions

In the previous section, we discussed some challenges not specifically inherent to MT in brain pathologies but extending to its general application for other diseases. Risks and challenges regarding the use of MT are also described elsewhere, especially in the context of IRI, tissue injury, and diseases associated with mtDNA mutation or cancer (Liu et al., 2022; McCully et al., 2023).

Regarding specifically the practical use of this approach against neurological disorders, especially chronic conditions, the most critical points are probably finding a good source of mitochondria, using off-the-shelf (frozen) mitochondria, determining the best delivery method, and assessing the long-term safety of repeated treatment (Fig. 4). Indeed, as mentioned earlier in the section “Source of mitochondria”, it is possible in some contexts to use mitochondria from the patient’s own body for transplantation. To our knowledge, the first human trial is currently underway to confirm the safety of autologous mitochondrial transplantation in brain ischemia (registered at ClinicalTrials.gov: NCT04998357). In this clinical trial, mitochondria are isolated from the patient’s muscle tissue adjacent to the surgical access site during standard-of-care endovascular treatment of cerebral ischemia. Mitochondria are then isolated at the bedside and infused into the brain artery via micro-catheter during reperfusion. This study assesses whether MT reduces the infarct volume and induces adverse events during and after mitochondria infusion, such as severe adverse vascular events, severe systemic adverse events, and adverse events related to muscle biopsy. Study completion is estimated at the end of 2026.

As stated before, using autologous mitochondria would not be possible in chronic neurological conditions that present mitochondrial impairments not only in brain cells but also in peripheral cells (fibroblasts, blood-derived cells) (Bell et al., 2021; Larrea et al., 2024). Therefore, a sustainable source of viable mitochondria for MT is needed. McCully and colleagues have reported that it would be possible to use allogenic and even xenogeneic mitochondria for transplantation. In the context of IRI in animal models, they detected no signs of acute rejection or inflammation after MT from allogenic or xenogeneic sources (Bechet et al., 2024; Ramirez-Barbieri et al., 2019). As previously mentioned (Table 1), xenogeneic mitochondria (XM) were also used for transplantation in the brain of a PD rat model, showing beneficial effects but with less robust and persistent efficacy than allogeneic mitochondria (Chang et al., 2016). XM may represent an alternative source for MT in brain disease, but, to our knowledge, have never been used in human clinical trials. Because mitochondria possess their own DNA, using XM in human clinics should be carefully assessed, especially regarding the long-term effects of xenogeneic mtDNA in humans. Of note, since pig-to-human transplantation has already been performed in the clinic (e.g. heart xenotransplantation), using pig cells as mitochondria sources would be a potential alternative to human cells.

Human mesenchymal stem cells (MSC) appear to be an appropriate mitochondria source, given that these cells naturally transfer mitochondria to other cell types (Liu et al., 2024). One can imagine having a human or pig MSC culture ready for MT in a clinical setting. However, this implies having a cell culture facility, laboratory space, and devices to quantify mitochondria and assess mitochondrial quality control (see also Fig. 4) near the patient’s bedside (at least in the same building), since isolated mitochondria can only be kept on ice for less than two hours (Doulamis and McCully, 2021; McCully et al., 2017). Furthermore, cognitive disorders, neurodegenerative diseases, and brain cancer are chronic conditions, meaning that repeated MT would have to be performed on a long-term basis to treat these diseases.

With this regard, the long-term culture of MSCs might not be sustainable and can be challenging because changes occur in these cells’ properties, including proliferation and morphological changes, after passaging, which might also affect mitochondria (Gu et al., 2016). Therefore, the possibility of using off-the-shelf mitochondria will be critical for applying MT in practice for chronic neurological conditions. Progress has recently been made in this area, with the successful development of a new method of freezing and storing viable mitochondria isolated from porcine heart tissue (Cloer et al., 2023). This method needs to be tested with other mitochondrial sources and in the context of brain diseases.

Given the complexity of the central nervous system and the presence of the blood-brain barrier (BBB), finding the most effective delivery

route to ensure targeted and efficient mitochondrial integration into the affected brain areas may be the rate-limiting step for the application of MT against chronic brain disorders in human clinics. Although studies showed that mitochondria administrated intravenously are found in the brain (Adlimoghaddam et al., 2022; Shi et al., 2017; Zhao et al., 2020), a considerable amount of mitochondria was needed (0,5 – 20 mg/kg), and the mechanisms by which mitochondria cross the BBB and enter the target cells are still unknown. Studies are currently ongoing in our group to unravel this point. Namely, we use an *in vitro* human BBB model to elucidate whether and how mitochondria cross the BBB and by which pathway transplanted mitochondria enter the target cells (neurons). With this investigation, we hope to identify molecular targets that may promote the crossing of the BBB by mitochondria and enhance their entry into neurons. As already discussed in the section "Mitochondria delivery," the nasal route seems appropriate for repeated MT compared to i.v. or local injection because of its non-invasiveness, which would not necessarily require qualified medical staff, the need for a smaller amount of mitochondria, and the possibility to bypass the BBB. This promising delivery alternative would require further investigation concerning the effects of repeated MT in chronic brain diseases.

Another critical point to consider is the viability of the transplanted mitochondria once in the target tissue and a fortiori in the brain. Indeed, mitochondria play an essential role in calcium homeostasis and are sensitive to high calcium concentrations, leading to mitochondrial swelling and/or cytochrome c release. Given that extracellular calcium concentration in the brain can reach 2 mM (Egelman and Read Montague, 1999), finding ways to protect the "naked" transplanted mitochondria would enhance mitochondrial viability, increasing the efficacy of MT and reducing unwanted side effects that unhealthy mitochondria may trigger. To solve this issue, ways of engineering mitochondria were proposed to protect them from the extracellular environment and enhance their entry into cells. Such engineering approaches include cell-penetrating peptide Pep-1, synthetic liposomes, polymer packaging, or cationized gelatin nanospheres (Zhao et al., 2024). In the context of stroke, a very recent review discusses the use of hydrogels and nanoparticle-assisted delivery to enhance the therapeutic effects of MT (Ulger et al., 2024). Namely, the authors report that the respiratory capacity of the mitochondria released from hydrogel was higher than that of mitochondria not encapsulated in hydrogel, showing the potential of this approach in preserving mitochondrial integrity and its application in stroke therapy. Other exciting studies have used synaptosomes or extracellular vesicles to deliver mitochondria into target cells (Morrison et al., 2017; Picone et al., 2021). These leads should be further explored in the future.

Finally, longitudinal studies are needed to assess the long-term effect of repeated MT in chronic neurological diseases. Although several studies have shown the beneficial effects of MT on inflammation in acute brain injury (Salman et al., 2023; Zhang et al., 2019), there is no evidence showing the safety of long-term treatment, especially regarding immune and inflammatory responses in chronic brain disorders. Elucidating the fate of transplanted mitochondria once in the host cells would also help understand MT's lasting (or not lasting) effects. In this regard, investigations are ongoing in our group to decipher how the neurons deal with transplanted mitochondria. Namely, we assess whether exogenous mitochondria fuse with the endogenous mitochondria network or whether they are degraded. We specifically aim to unravel the molecular signals leading neurons to either integrate exogenous mitochondria in their own mitochondrial network or to degrade them.

6. Conclusion

Taken all together, the recent reports discussed in the present review demonstrate that MT is a promising therapeutic strategy against various neurological disorders. Thanks to its highly diversified mode of action, this approach has proved effective in improving overall cellular function, promoting tissue repair, and improving clinical outcomes in several pathologies while enhancing cognitive function. Although the future of MT is promising, several challenges must be addressed to facilitate its widespread clinical adoption. Especially in the context of brain disorders, and even more for chronic neurological conditions like depression, schizophrenia, AD, PD, or brain cancer, significant challenges are still faced concerning namely the source of mitochondria to use, the possibility of using off-the-shelf mitochondria for repeated treatments, the delivery method to pass the BBB and enhance the viability of transplanted mitochondria, and the lasting effects of MT. Despite these remaining difficulties, the positive results highlight the significant therapeutic potential of MT. Continued research and development are essential to overcome current limitations and ensure the safety and efficacy of this technique. With further advances, MT is poised to become a powerful therapeutic tool, offering new hope and better outcomes for patients suffering from a range of brain disorders.

Author contributions

Aurélien Riou: Writing-original draft, conceptualization; Aline Broeglin: Writing-original draft, conceptualization; Amandine Grimm: Writing-review and editing, funding acquisition, conceptualization, supervision.

Declaration of Competing Interest

The authors declare they have no competing interests.

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