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Mechanism and prospects of mitochondrial transplantation for spinal cord injury treatment

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Abstract

Spinal cord injury (SCI) involves a continuous and dynamic cascade of complex reactions, with mitochondrial damage and dysfunction-induced energy metabolism disorders playing a central role throughout the process. These disorders not only determine the severity of secondary injuries but also influence the potential for axonal regeneration. Given the critical role of energy metabolism disturbances in the pathology of SCI, strategies such as enhancing mitochondrial transport within axons to alleviate local energy deficits, or transplanting autologous or allogeneic mitochondria to restore energy supply to damaged tissues, have emerged as potential approaches for SCI repair. These strategies also aim to modulate local inflammatory responses and apoptosis. Preclinical studies have initially demonstrated that mitochondrial transplantation (MT) significantly reduces neuronal death and promotes axonal regeneration following spinal cord injury. MT achieves this by regulating signaling pathways such as MAPK/ERK and PI3K/Akt, promoting the expression of growth-associated protein-43 (GAP-43) in neurons, and inhibiting the expression of apoptosis-related proteins like Grp78, Chop, and P-Akt, thereby enhancing the survival and regeneration of damaged neurons. Additionally, MT plays a role in promoting the expression of vascular endothelial growth factor, facilitating tissue repair, and reducing the secretion of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. Furthermore, MT modulates neuronal apoptosis and inflammatory responses by decreasing the expression of p-JNK, a member of the MAPK family. In summary, by reviewing the detailed mechanisms underlying the cascade of pathological processes in SCI, we emphasize the changes in endogenous mitochondria post-SCI and the potential of exogenous MT in SCI repair. This review aims to provide insights and a basis for developing more effective clinical treatments for SCI.

Background

Mitochondrial dysfunction and secondary damage resulting from SCI can lead to significant impairments in limb function and neurological deficits, potentially resulting in permanent paralysis for the affected patients [1]. Globally, over 27 million people are living with disabilities caused by SCI, with more than 900,000 new cases reported each year [2]. The most common causes of SCI include traffic accidents, falls, and self-inflicted injuries [3]. Currently, treatment options for SCI primarily consist of surgery, pharmacotherapy, hyperbaric oxygen therapy, and physical rehabilitation. However, the effectiveness of these treatments is often limited. Therefore, it is crucial to actively explore the pathological mechanisms underlying SCI and to seek new intervention strategies.

Mitochondria serve as the primary bioenergetic organelles in most cells, generating energy through oxidative

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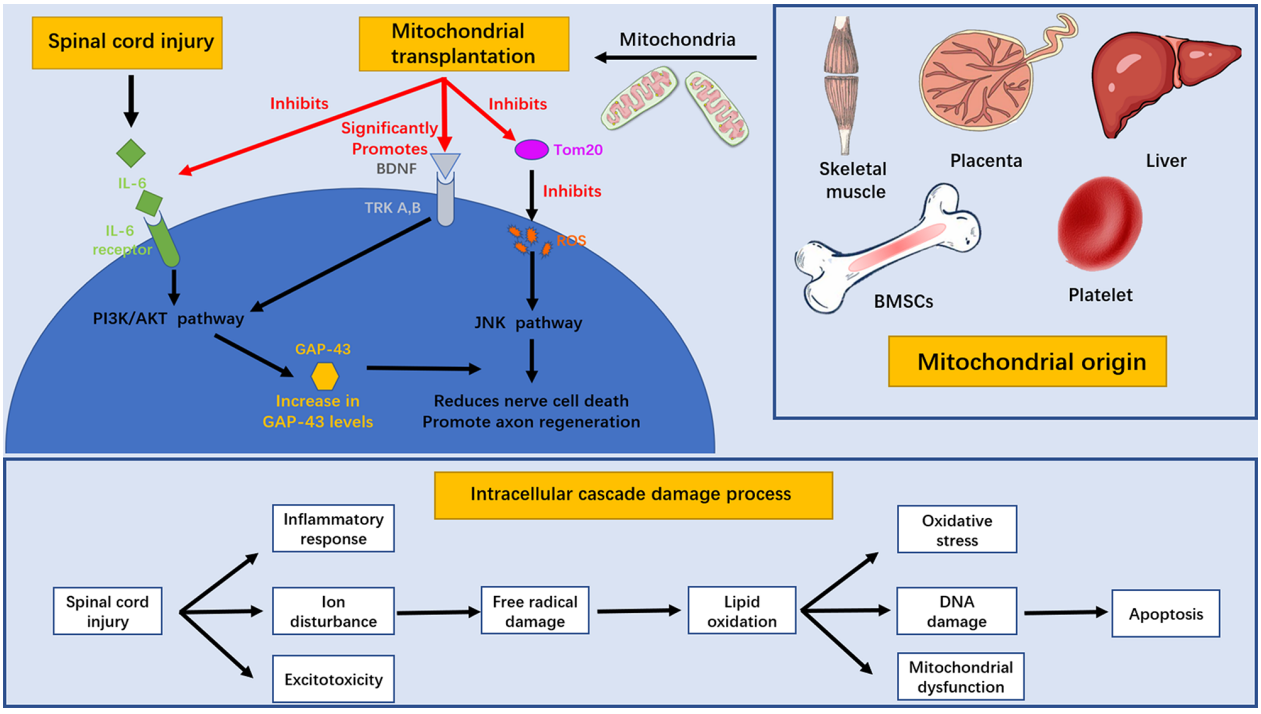
Graphical abstract



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phosphorylation. In addition to energy production, mitochondria play vital roles in maintaining the cell membrane potential, buffering cellular calcium, producing reactive oxygen species (ROS) and reactive nitrogen species (RNS), and managing oxidative stress. In neurons, up to 93% of ATP is generated through mitochondrial aerobic respiration in the tricarboxylic acid cycle, with only 7% derived from cytosolic non-mitochondrial glycolysis [4, 5]. MT can enhance mitochondrial transport to the injury site and increase ATP production, thereby addressing the local energy metabolism deficits in damaged axons following SCI. Furthermore, MT helps reduce the production of free radicals in injured tissues, enhances antioxidant capacity, alleviates local inflammatory responses, and prevents neuronal apoptosis. These actions can interrupt various pathological cascades caused by secondary injuries, potentially providing critical time to mitigate neuronal damage and promote recovery of central nervous system (CNS) function.

The pathological cascade process of SCI

The molecular cascade of secondary injury begins within the first few minutes to hours following primary injury and peaks approximately two weeks after SCI, although it may persist for several months [6]. The inflammatory response initiated by the injury is primarily driven by the activation of macrophages and microglia, which release pro-inflammatory cytokines. This process further leads to the infiltration and functional enhancement of other immune-related cells, such as polymorphonuclear cells and lymphocytes [7]. The inflammatory response not only determines the secondary pathophysiological changes but also leads to persistent functional impairments in the nervous system [8, 9]. Following SCI, local vascular damage disrupts the transport of glucose and oxygen, leading to impaired mitochondrial function and reduced ATP production within cells. Concurrently, the ion gradients across cell membranes dissipate, resulting in an influx of Ca^{2+} into the cells [10], which in turn causes the generation of excessive ROS and RNS.

After SCI, the excessive production of intracellular free radicals overwhelms the antioxidant system's capacity to neutralize them, leading to oxidative stress damage. Cell membranes and lipoproteins are rich in polyunsaturated fatty acids (PUFA), which are particularly susceptible to lipid peroxidation induced by free radicals, resulting in the formation of lipid oxidation products. The double bond structures in PUFA are easily attacked by ROS, generating lipid alkyl radicals [11]. Subsequently, these lipid alkyl radicals react with molecular oxygen, initiating a

chain reaction. Since this process does not require enzymatic mediation, membrane damage can rapidly propagate to adjacent healthy cells [12]. These products lack surface charge, allowing them to freely traverse cell membranes and cause damage both inside and outside the cells [13]. Additionally, this process can trigger a unique form of non-apoptotic regulated oxidative cell death known as ferroptosis, which is characterized by iron-dependent lipid peroxidation.

Following membrane damage, the activation of voltage-gated Ca^{2+} channels or calcium leakage leads to further increases in intracellular Ca^{2+} levels, which in turn enhances the release of the excitatory neurotransmitter glutamate, resulting in excitotoxic cell death. Prolonged Ca^{2+} overload can also cause the persistent opening of the mitochondrial permeability transition pore (mPTP), compromising the barrier function of the mitochondrial inner membrane. Protons continuously enter the mitochondrial matrix, leading to the loss of the membrane potential, uncoupling of the oxidative phosphorylation chain, and cessation of ATP synthesis.

Simultaneously, mitochondrial dysfunction allows water and other small molecules to enter the mitochondrial matrix, causing matrix swelling and rupture of the outer membrane. This results in the release of large amounts of Ca^{2+}, pro-apoptotic proteins, and ROS into the cytoplasm (Fig. 1). Soluble intermembrane space proteins, such as cytochrome c, are then released non-selectively into the cytoplasm [14]. These proteins combine with apoptosome-forming factor 1 (Apaf-1) to form a heptameric structure, which triggers the caspase cascade, ultimately leading to apoptosis [15].

Changes in endogenous mitochondria after SCI

The ion dysregulation induced by SCI leads to the persistent opening of the mPTP, allowing a large influx of protons into the mitochondria, which results in the loss of membrane potential and cessation of ATP synthesis. Concurrently, water and other molecules continuously enter the mitochondrial matrix, causing it to swell until the outer mitochondrial membrane ruptures, resulting in significant mitochondrial damage. Subsequently, large amounts of Ca^{2+}, pro-apoptotic proteins, ROS and RNS are released into the cytoplasm, activating downstream apoptotic pathways. Rajaee et al. established a SCI injury model using Thy1YFP + transgenic mice and found through immunofluorescence staining of tissues that the axonal damage led to the accumulation of mitochondria in the enlarged axon terminals (end bulbs) and the axonal varicosities (axon spheroids). Additionally, excessive

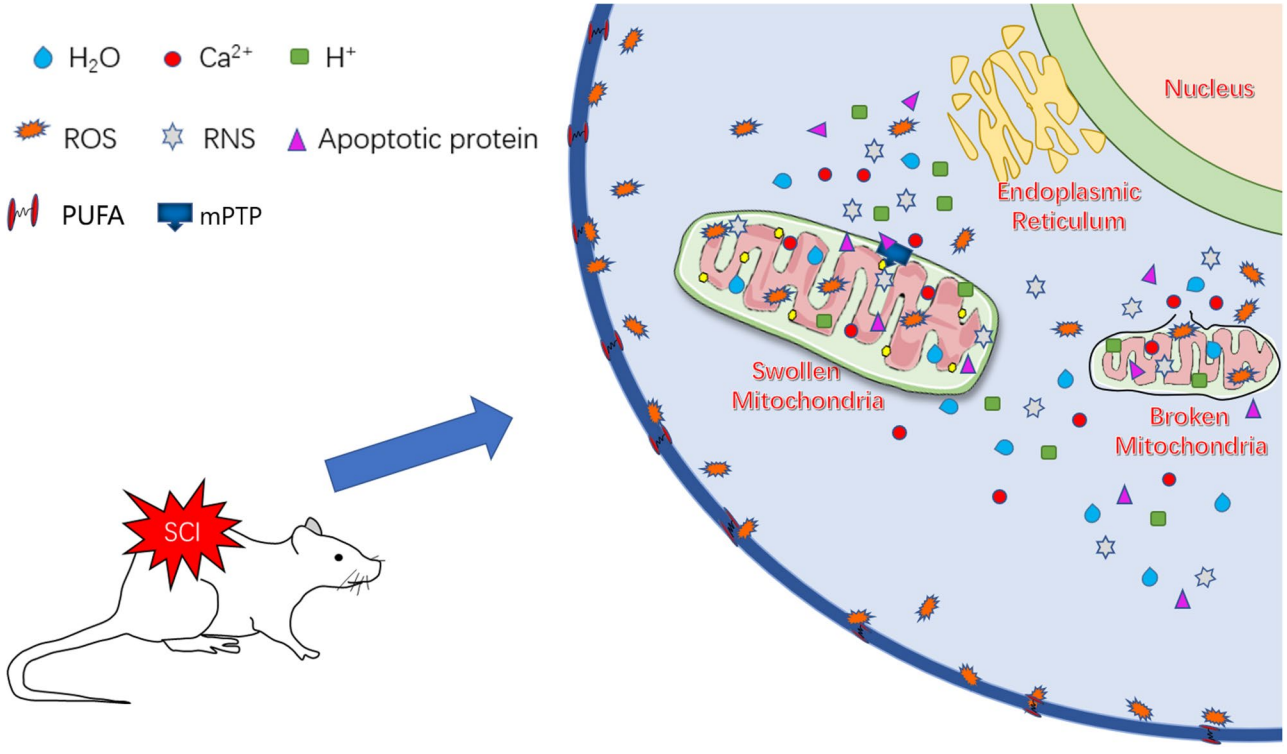

Fig. 1 Following SCI, oxidative stress within cells triggers a cascade of biochemical events. Initially, oxidative stress damages the cell membrane and causes an overload of Ca^{2+}. This calcium overload leads to the persistent opening of the mPTP, resulting in the accumulation of H_2O, H^+, pro-apoptotic proteins, and reactive ROS and RNS within the mitochondria. As the mitochondrial matrix swells, this ultimately causes the rupture of the outer mitochondrial membrane and impairs mitochondrial function. Currently, the ROS generated by oxidative stress and mitochondrial dysfunction attack the PUFA in the cell membrane, initiating a chain reaction. This reaction amplifies and spreads damage, exacerbating the pathological progression of spinal cord injury

polyglutamylation of microtubule proteins was observed, indicating a disruption in axonal transport, which is a significant feature of axonal degeneration [16].

Under physiological conditions, mitochondria within axons can move bidirectionally. In mature axons, approximately 20–30% of the mitochondria are capable of either moving or pausing in response to the demands of biological growth and variations in individual energy metabolism [17, 18]. Recent studies have revealed that axonal mitochondria are distributed linearly, with approximately 87% of the mitochondria being stationary. The number of mobile mitochondria decreases progressively from the proximal to the distal end of the axon [19]. Endogenous mitochondrial transport primarily relies on the interactions between microtubules, motor proteins, adaptor complexes, and their associated "anchors" [20]. This transport can be categorized into anterograde and retrograde modes, aimed at redistributing mitochondria to meet the physiological demands of the CNS as well as external stimuli and injuries. Anterograde transport primarily provides neurons with sufficient ATP to ensure their survival. In peripheral axons with terminal synapses, mitochondria tend to move unidirectionally in an anterograde manner [21]. Retrograde transport plays a crucial role in maintaining the integrity and quality of mitochondria within axons. Damaged mitochondria can undergo fission driven by dynamin-related protein 1 and mitochondrial fission protein 1. They are then transported back to the cell body via a retrograde axonal transport mechanism, which involves mitochondrial Rho GTPases, transport motor proteins, and molecular motors. Once in the cell body, these damaged mitochondria can either restore their integrity by fusing with healthy mitochondria mediated by Mitofusins and optic atrophy protein 1, or they can be degraded through mitophagy [22]. Mitochondrial fission facilitates the separation of damaged mitochondria from healthy ones, while mitochondrial fusion allows for the exchange of components such as DNA, proteins, and metabolites between two mitochondria, enabling mutual repair. This mechanism creates a constantly dynamic network that regulates the morphology and quantity of mitochondria within axons, which is crucial for maintaining mitochondrial integrity and cell survival under stress conditions [23].

The interruption of anterograde transport in axons exacerbates local energy metabolism disorders at the injury site, and retrograde transport becomes impossible, preventing damaged mitochondria from fusing again to restore the respiratory chain and inhibit mitochondrial apoptosis. Additionally, mitochondrial dysfunction-induced fission further inhibits microtubule stability and axonal regeneration [24]. In mature mammalian neurons, regeneration following injury requires rapid alterations in the growth cone, including sealing the damaged cell membrane, reorganizing the cytoskeletal structure, transmitting retrograde growth signals, activating regeneration programs, and transporting materials necessary for regeneration [25]. These physiological activities require a substantial supply of ATP. Damaged mitochondria not only reduce ATP production but also release various ROS, leading to apoptosis and axonal degeneration. Therefore, it is crucial to clear these damaged mitochondria promptly after injury. In this process, the synaptic protein Syntaphilin (Snph) plays a key role in the specific static anchoring of mitochondria within axons [26, 27]. Research by Zhou et al. has shown that the expression of Snph is elevated in mature neurons [28], Its expression is tightly regulated in the CNS, remaining low during embryonic development and up to 7 days after birth. However, it peaks during adulthood, showing high expression levels the CNS [29]. Zhou et al. demonstrated that by knocking out the Snph gene in mice and establishing a SCI animal model, enhanced mitochondrial transport in damaged axons can alleviate local energy deficits and improve axonal regeneration capabilities [28], At the same time, it reduces and curtails the secondary pathological processes caused by axonal injury and mitochondrial dysfunction (Fig. 2). In fact, neuronal activity and synaptic interactions heavily rely on mitochondrial metabolism, including mitochondrial axonal distribution and transport (fission-fusion) as well as ATP production along the axon. When mitochondrial function is impaired following SCI, each step in these processes is altered [30].

Exogenous mitochondrial transplantation

Sources and methods of exogenous mitochondrial transplantation

Previous experiments have demonstrated the importance of timely restoration of energy supply and mitochondrial transport at damaged sites [28]. At the same time, mitochondria can undergo intercellular transfer under physiological conditions, indicating their viability in recipient cells. This capability provides a prerequisite for MT therapies in the CNS [31]. MT involves the direct implantation of healthy mitochondria to replace or rescue dysfunctional mitochondria at the injury site. This approach aims to introduce healthy mitochondria with normal respiratory function into damaged tissues, thereby aiding in the restoration of cellular function. The benefits of this method include reducing ROS production, increasing ATP generation, and enhancing calcium buffering capacity [32], This approach aims to prevent the cascade of pathological processes following SCI. Animal studies have demonstrated the efficacy of MT in alleviating inflammatory responses, reducing apoptosis and ferroptosis, and improving biological behaviors in animals after SCI. Currently, MT can be categorized

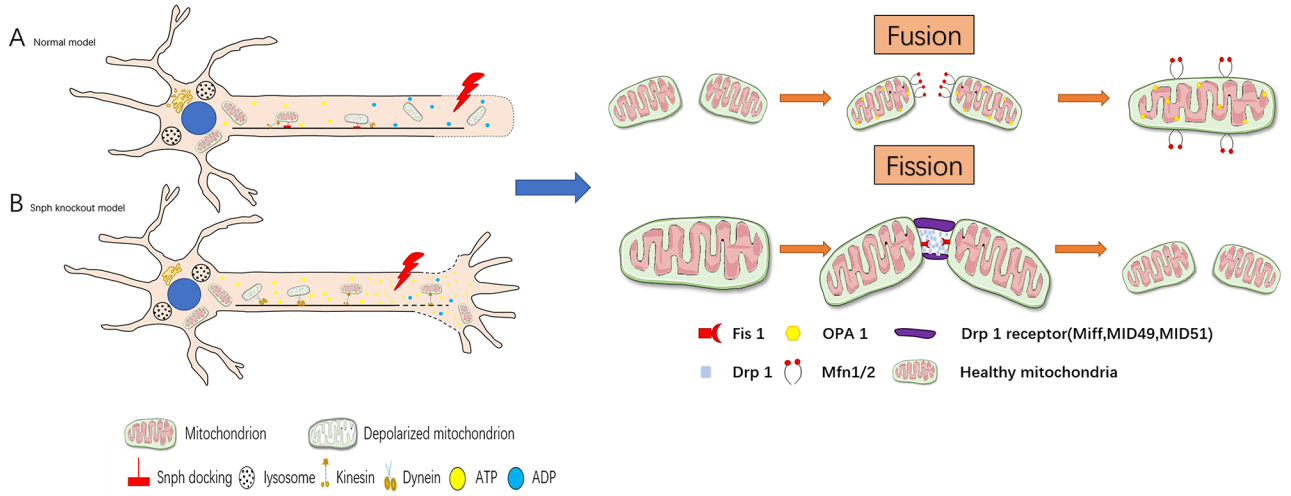

Fig. 2 Endogenous mitochondrial transport and fission-fusion

into two main types: direct and indirect transplantation. Direct transplantation involves the transfer of mitochondria themselves, while indirect transplantation utilizes other carriers to deliver the mitochondria. Various experiments have shown that the mitochondria used in direct transplantation primarily originate from different cell lines and allogeneic tissues, including skeletal muscle, placenta, liver, brain, and platelets. In contrast, indirect transplantation often employs mesenchymal stem cells (MSC) or hydrogels as carriers for the mitochondria. The routes of transplantation include various injection methods such as arterial, ventricular, venous, vitreous, nerve sheath, and spinal cord injections. In summary, the sources of exogenous mitochondria and the methods of transplantation are diverse, but they remain in the experimental stage in animal studies, with no established protocols or guidelines available yet. Future research is needed to identify the optimal sources of mitochondria and the most effective transplantation methods.

Application of exogenous mitochondria in Non-SCI cases

In recent years, MT has emerged as a promising therapeutic approach, demonstrating significant potential and value. Compared to other strategies in regenerative medicine, MT offers notable advantages, including ease of operation and rapid isolation and purification of mitochondria, which can be completed within 30 min. These characteristics make MT highly suitable for clinical applications, meeting the urgent needs of medical practice [33]. MT is a rapidly advancing field, showing promising progress in various animal models, including ischemic heart injury, Parkinson's disease, skeletal muscle aging, and burn injuries. For instance, James et al. successfully established a myocardial ischemia model by ligating the left anterior descending artery of rabbits for 30 min. Following this, the research team used an insulin syringe to inject 0.8 ml of mitochondria, at a concentration of $7.7\times10^6 \pm 1.5\times10^6$/ml, into the damaged area in 8 separate injections over the course of 1 min [34, 35], The results showed that compared to the injury group, the myocardial oxygen consumption capacity in the transplantation group significantly increased (by 2.04 times), indicating the potential positive role of mitochondria in repairing ischemic myocardial tissue. Additionally, the study found that mitochondria promoted the recovery of myocardial fatty acid metabolism by inhibiting the expression of key genes involved in fatty acid metabolism, such as Cpt-1b and Fads1. This suggests that MT may contribute to metabolic restoration in damaged heart tissue [36]. Hyeyoon et al. isolated mitochondria from human umbilical cord MSC using centrifugation and intravenously injected them into a Parkinson's disease mouse model at doses of 0.5 μg, 2.5 μg, and 10 μg. The results indicated that the mitochondria improved behavioral deficits in the Parkinson's mice and alleviated dopaminergic cell damage and neuroinflammation by promoting neuroprotection and inhibiting inflammatory responses [37].

Tasnim et al. demonstrated the role of mitochondria in promoting skeletal muscle bioenergetics in aging rodent models through experimental studies. They extracted mitochondria from the quadriceps of young female C57BL mice using ultracentrifugation and directly injected them into the hind limb muscles of aged mice to assess the effects of exogenous mitochondria on aging. The results showed that compared to the placebo group, the mice in the MT group exhibited significantly improved exercise endurance, indicating that mitochondria can ameliorate skeletal muscle aging caused by progressive mitochondrial dysfunction [38]. Furthermore, the study found that mitochondria can promote the healing of deep second-degree burn wounds in the absence of

tissue toxicity. Li et al. isolated mitochondria from mouse liver using differential centrifugation and subsequently injected them into the subcutaneous tissue of a mouse model with back burns at a dose of 10 μg/g/day for three consecutive days. They recorded wound images, wound size, and body weight daily until day 21. The results indicated that MT significantly reduced the inflammatory response in the burn mouse model, as evidenced by a decrease in the secretion of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) and a significant increase in the secretion of the anti-inflammatory cytokine IL-10. Additionally, the MT group exhibited the highest expression levels of vascular endothelial growth factor, suggesting that MT contributes to promoting wound healing and tissue recovery. Furthermore, MT significantly downregulated the expression of TGF-β1, indicating its potential role in scar formation. Moreover, histological analysis using HE staining of mouse liver and kidney tissues indicated that mitochondria did not exhibit toxicity in the mouse model [39]. Additionally, other studies have shown that MT also has significant therapeutic effects in diseases such as pulmonary hypertension, renal ischemia-reperfusion injury, liver damage, and heart failure.

Application of exogenous mitochondria in SCI

Although the application of MT in the treatment of SCI is still in its early stages, animal studies have shown encouraging results. By transplanting exogenous mitochondria to replace damaged mitochondria, it is possible to reduce the production of intracellular ROS, provide a new source of exogenous mitochondrial DNA, and enhance energy production and calcium buffering capacity. These effects collectively promote cell survival and regeneration [40]. Jenna et al. isolated mitochondria from PC12 cells and rat soleus muscle using differential centrifugation. Within 30 min of successfully modeling SCI, they injected exogenous mitochondria at doses of 50 μg, 100 μg, or 150 μg into the medial and lateral gray matter of the injured spinal cord using a glass microinjection syringe, with injection points spaced 2 mm apart in the anteroposterior direction. The results showed that exogenous mitochondria maintained energy supply to the injured spinal cord in a dose-dependent manner, significantly reducing the proportion of cells in the G1 phase. Additionally, they preserved the activity of antioxidants such as catalase and glutathione peroxidase in the damaged tissue, promoting oxidative phosphorylation function in the injured spinal cord to maintain at 90% of the sham-operated level. This finding provides new possibilities for rescuing local energy metabolism disorders following SCI through MT. The study also indicated that the fluorescently labeled exogenous mitochondria resided in various spinal cord cell types, including microglia, endothelial cells, astrocytes, pericytes, and oligodendrocytes [41]. In fact, the spinal cord is composed of a diverse mix of cell types, each of which plays a crucial role in the overall health and function of the spinal cord. For instance, macrophages are responsible for phagocytosing debris and foreign substances, and they play a key role in mediating immune responses [42], Endothelial cells provide tissues with blood and oxygen, while pericytes wrap around endothelial cells to constrict blood vessels and regulate blood flow. Oligodendrocytes play a vital role in insulating axons, which enhances the efficiency of signal transmission [43], Astrocytes contribute to the maintenance of the blood-brain barrier and help regulate ionic homeostasis in the extracellular fluid [44]. Maintaining the energy metabolism and survival of any of the aforementioned cell types through MT could be crucial for the survival and regeneration of injured neurons, as well as for the overall restoration of function.

Further research has revealed that mitochondrial transfer between cells is mediated through tunneling nanotubes, microvesicles, and gap junctions [45]. Li et al. isolated fresh mitochondria from primary rat bone marrow mesenchymal stem cells (BMSC) using a mitochondrial isolation kit and labeled them with MitoTracker Red. After establishing a SCI model through a contusion method, they injected 1×10^6 BMSC into the center of the injured spinal cord of one group of rats, while injecting 3×10^6 mitochondria extracted from BMSCs into the center of the injured spinal cord of another group. The results showed that mitochondria could be transferred from MSC to damaged motor neurons via gap junctions, enhancing their energy metabolism. This was evidenced by an increase in both basal and maximal respiratory rates in the rats. Additionally, the BBB scores of the rat models significantly improved after transplantation, indicating that MT facilitated the recovery of motor function. MT can also inhibit the expression of apoptosis-related proteins such as Grp78, Chop, and P-Akt, effectively reducing the number of apoptotic cells in the early stages of SCI and promoting cell survival. Furthermore, MT significantly decreases the formation of late-stage glial scars in the lesion area, reduces the size of the lesion cavity, and promotes myelin regeneration by increasing the number of cells expressing neurofilament. Additionally, studies have shown that during the process of MT, the levels of GAP-43, which is highly expressed in neuronal growth cones, are significantly elevated. This protein plays a critical role in myelin regeneration. GAP-43 facilitates dynamic changes in the cytoskeleton by interacting with microtubules and actin filaments, thereby supporting the formation of neuronal growth cones and axonal extension. Moreover, GAP-43 regulates cell survival and growth through various signaling pathways, including the MAPK/ERK and PI3K/Akt pathways, further promoting the repair of spinal cord injuries [46].

Mitochondria are also extensively involved in ferroptosis by coordinating iron homeostasis, energy metabolism, and lipid synthesis [47, 48]. Yao et al. directly injected 3×10^5 MSC into the injury site of spinal cord-injured mice using a stereotaxic microinjection device. They found that neuronal ferroptosis progressed in a manner dependent on mitochondrial quality control (MQC). MQC reflects the cellular response to both internal and external stressors, encompassing mitochondrial-nuclear crosstalk, the remodeling of mitochondrial networks through mitochondrial dynamics, and organelle-level mitophagy [49, 50]. Due to the severe deterioration of MQC in neurons following SCI, the overall mitochondrial network cannot be compensated for through axonal transport. This leads to mitochondrial dysfunction, imbalanced mitochondrial dynamics, and excessive autophagy, ultimately mediating neuronal ferroptosis. Mitochondria delivered through MSC transplantation can fuse with neuronal mitochondrial membranes, restoring mitochondrial homeostasis. This process inhibits mitochondrial fission and mitophagy, ultimately alleviating neuronal ferroptosis and promoting functional recovery after SCI [51]. Additionally, scanning electron microscopy further confirmed the transfer of mitochondria between MSC and neurons via tunneling nanotubes at the nanoscale. Following SCI, the accumulation of myelin debris significantly inhibits the regeneration of axons and myelin, becoming a major obstacle to neural regeneration [52]. Macrophages can remove this myelin debris [53]. However, excessive autophagy can lead to lipid accumulation and dysregulation of intracellular lipid homeostasis, resulting in the generation of pro-inflammatory and foam-like macrophages [54, 55]. Research has found that mitochondrial dysfunction may lead to the sustained activation of M1 macrophages, increasing the inflammatory response and resulting in chronic inflammation and tissue damage. Additionally, increased oxidative stress affects the polarization state of macrophages, leading to the overactivation of M1 macrophages and the suppression of M2 macrophages. Previous experiments by Li et al. also confirmed that transplanted mitochondria are internalized by neurons in vivo, with less internalization occurring in macrophages [56]. Xu et al. obtained mitochondria from mouse bone marrow-derived macrophages using a centrifugation method. They then mixed these mitochondria with the peptide cysteine-alanine-glutamine-lysine (CAQK) and incubated the mixture to construct engineered mitochondria at a concentration of $2–5\times10^6$/ml. These engineered mitochondria were used to intervene in SCI in mice. The results indicated that CAQK could optimize the targeted affinity of the transplanted mitochondria to the injury site, significantly enhancing the phagocytic activity of macrophages towards myelin debris, reducing lipid accumulation, and improving mitochondrial dysfunction [57].

After SCI, mitochondrial dysfunction can lead to the accumulation of ROS, which in turn activates JNK. As a member of the MAPK family, JNK is involved in cellular stress responses, proliferation, and apoptosis. The upregulation of Tom20 expression may help maintain mitochondrial function and reduce ROS levels, thereby inhibiting the excessive activation of JNK. The relationship between Tom20 expression and JNK phosphorylation involves multiple signaling pathways, including MAPK, PI3K/Akt, and NF-κB. These pathways are interconnected and collectively regulate the stress response, survival, and apoptosis of neural cells following SCI. To target this potential therapeutic pathway and molecular mechanism, Zhao et al. used a mitochondrial isolation kit to obtain mitochondria from mouse allogeneic liver. They directly injected $1.2–1.4\times10^6$ mitochondria into the cerebral cortex of mice. The results showed that MT significantly upregulated the expression of brain-derived neurotrophic factor in reactive astrocytes and reduced the expression levels of Tom20 and phosphorylated JNK [58].

Samir et al. also discovered that a hydrogel composition consisting of 1% sodium hyaluronate (MC) and 1% methylcellulose (HA) promotes the local diffusion and incorporation of mitochondria into host cells. This process enhances the metabolic activity of the cells without adversely affecting mitochondrial integrity [59], This further demonstrates that MT can maintain the energy supply of damaged tissues. To address the challenge of low efficiency in mitochondrial transfer to target cells, Zhu et al. proposed a novel approach using photobiomodulation (PBM) to facilitate the transfer of mitochondria into neurons and enhance the effects of MT. They rapidly isolated and purified mitochondria from rat platelet sources using a discontinuous Percoll gradient, and immediately injected them into the center of the injured spinal cord using a microinjection syringe and stereotaxic apparatus after establishing the SCI model. The results showed that the combination of PBM and MT produced specific downstream effects, including increased ATP production, reduced oxidative stress, and decreased levels of neuronal apoptosis, thereby promoting tissue repair and recovery of motor function [60].

Conclusion

After SCI, mitochondrial dysfunction leads to metabolic disturbances and cell death in spinal cord neurons. Transplanting exogenous mitochondria can correct this dysfunction, restore energy supply, and further regulate factors such as inflammation, apoptosis, and oxidative stress, demonstrating significant potential in the treatment of SCI. However, there is currently a lack of

guidance regarding the sources, dosages, administration methods, and timing of MT. Moreover, research on MT for SCI is still in its preliminary stages, with relatively few relevant cellular and animal studies conducted. Although existing studies indicate that MT has the potential to improve energy metabolism, reduce cell death, modulate inflammatory responses, and promote tissue regeneration, the specific molecular mechanisms and signaling pathways require further investigation.

Nevertheless, there is reason to believe that the transplantation of exogenous mitochondria will bring new hope for the treatment of SCI. Future research should focus on establishing more systematic experimental models to comprehensively explore the various potential roles of MT in SCI repair and investigate its potential clinical applications. This will provide important scientific evidence for understanding the critical role of mitochondria in SCI repair and advance development of related therapeutic strategies.

Abbreviations

SCI	Spinal cord injury
ATP	Adenosine triphosphate
MT	Mitochondrial transplantation
ROS	Reactive oxygen species
RNS	Reactive nitrogen species
CNS	Central nervous system
PUFA	Polyunsaturated fatty acids
mPTP	mitochondrial Permeability Transition Pore
Snph	Syntaphilin
MSC	Mesenchymal stem cells
BMSC	bone marrow mesenchymal stem cells
GAP-43	growth-associated protein-43
MQC	Mitochondrial quality control
CAQK	the peptide cysteine-alanine-glutamine-lysine
JNK	c-Jun N-terminal kinase
PBM	photobiomodulation

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Conception and design of the study: XW, QW. Drafting or revising the manuscript: QW, XW, ZS, LZ. All authors have approved the final article.

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