Mesenchymal stem cells and the rescue of mitochondrial damage in different disease models (Review)

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Abstract. Mitochondrial transplantation is based on the fundamental principle of mitochondrial transfer, through which recipient cells take up exogenous mitochondria, thereby restoring cellular function. Several studies have demonstrated that isolated mitochondria can effectively improve cellular function in various diseases characterized by mitochondrial dysfunction as a key factor in pathological progression. The success of mitochondrial therapy depends on the source of donor cells, the quality and quantity of mitochondria, and their competency and compatibility with recipient cells. Mesenchymal stem cells (MSCs) are highly proliferative and possess the potential to differentiate into various cell types, a process requiring competent mitochondria to supply energy and essential building blocks for cellular activities. Consequently, MSC-derived mitochondria exhibit high plasticity and functional capability, rendering them promising candidates for mitochondrial transplantation therapy. The present review discusses the role of mitochondria in health and disease progression. The present review also summarizes current evidence from the literature, highlighting the emerging role of MSCs as a valuable source for mitochondrial therapy in both *in vitro* and *in vivo* pathological models. Given the diverse sources available for MSC isolation, mitochondrial therapy, particularly when combined with stem cell technology, represents a potential avenue for future research in therapeutic and pharmacological development.

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1. Introduction

Mitochondria are the powerhouses of mammalian cells, providing the energy and materials required for cellular function. Mitochondria utilize pyruvate, products from glycolysis, amino acid metabolism and fatty acid oxidation to transfer electrons through the electron transport chain, synthesizing energy in the form of adenosine triphosphate (ATP). Mitochondrial dysfunction causes bioenergetic imbalance and increases oxidative stress, which paves the way for pathogenesis to occur. Multiple diseases arise from mitochondrial damage or are a consequence of impaired mitochondria due to tissue injury. Aging and degenerative diseases are common examples of conditions involving mitochondrial dysfunction. While genetic modifications and the reduction of telomere length are definite hallmarks of aging, impaired mitochondrial function and the accumulation of mitochondrial DNA (mtDNA) mutations critically determine healthy aging outcomes and contribute to longevity (1). Degenerative diseases, such as brain, muscle and macular degeneration are consequences of mitochondrial dysfunction. Modifications in mitochondrial membrane potential, reduced calcium homeostasis and decreased ATP production are associated with mitochondrial dynamic dysregulation and increased levels of reactive oxygen species (ROS). This leads to protein degradation, the loss of intercellular interactions and eventually, apoptosis (2-5). For instance, in the immune system, reduced mitochondrial respiration and metabolism are associated with immune paralysis following septic shock (6,7). In metabolic syndromes, such as type 2 diabetes, mitochondrial oxidative stress promotes glucose intolerance and excessive lipid accumulation in adipocytes, and drives systemic inflammation, which further accelerates insulin resistance (8-10). Mitochondria have also been an unrecognized factor in the progression of skin diseases (11). In pulmonary diseases derived from smoking, cigarette smoke directly blocks complexes I and II, causes mitochondrial depolarisation through altered mitophagy, and induces mitochondrial ROS generation. This consequently results in the apoptosis and necrosis of pulmonary endothelial cells, contributing to the development of chronic and fibrotic

conditions (12-14). In addition, mitochondria exhibiting a low oxygen consumption rate, high levels of mtDNA damage and ROS production are observed in the vascular endothelial cells of preterm infants with bronchopulmonary dysplasia and adverse outcomes (15). Mitochondria are also a key site for calcium homeostasis, as they buffer cytoplasmic calcium ions through interactions with the endoplasmic reticulum (16). The disruption of calcium balance may interfere with mitochondrial respiration and ATP production, leading to the development of pathological conditions and diseases, such as neuron degeneration, cancers, diabetes, and muscular and cardiac dystrophy (17-19). Thus, the ability of cells to maintain competent mitochondrial function and capacity is key to preventing disease progression and negative outcomes.

Mitochondrial transfer refers to the process through which cells exchange mitochondria, serving as a form of cell-cell communication. This transfer may involve the sharing of damaged mitochondria to signal neighboring cells about oxidative damage, while surrounding cells offer functional mitochondria to stressed cells. Receiving mitochondria supports cells in recovering from oxidative stress, improving cellular respiration and ATP production, and consequently, reversing the effects of cellular dysfunction and tissue damage (20-22). The mechanisms of intercellular mitochondrial transfer have been well established and are illustrated in Fig. 1A. The application of mitochondrial transfer has been transformed into mitochondrial transplantation therapy (Fig. 1B), in which exogenous mitochondria are isolated and artificially transferred into cells or tissues. Mitochondrial therapy, which encompasses both mitochondrial transfer and transplantation, is effective in improving cell metabolism, restoring cells from stress and preventing tissue degeneration (23-25). Early clinical trials of mitochondrial therapy have been conducted in ischemic diseases, demonstrating that the injection of exogenous mitochondria effectively improves the conditions of patients and reduces the recovery time (26,27). These data indicate that mitochondrial therapy holds potential for future applications. However, the autologous transfer of mitochondria may be invasive and non-accessible in a number of cases; thus, a source of qualified mitochondrial donors is critical.

Mesenchymal stem cells (MSCs) feature high plasticity and proliferation, which demonstrates their inherent mitochondrial capacity. The ability to acquire, handle and expand MSCs in large quantities in culture, along with a stable and reliable assessment of mitochondrial quality, may further facilitate access to mitochondrial transplantation in various clinical settings, rendering MSCs promising for such therapeutic purposes. The use of MSCs as a mitochondrial source has been shown in *in vitro* and *in vivo* models of different diseases, indicating that mitochondria isolated from MSCs are efficient and safe for translational studies (Fig. 2) (28-30). The present review summarizes data from numerous studies in the literature on mitochondrial transfer using MSCs as mitochondrial donors. Detailed descriptions of the mechanisms underlying mitochondrial therapy are also included. The present review also provides an update on the broad application of mitochondrial donation in various pathological conditions and diseases, indicating that MSCs from different origins are valuable sources for mitochondrial collection and transplantation technology.

2. Mitochondrial transfer from mesenchymal stem cells into different disease models

In pulmonary tissues and lung diseases. Asthma is a chronic condition involving a persistent inflammatory disorder in the airways (31). Mitochondrial dysfunction causes oxidative stress and reduced ATP synthase activity, leading to apoptosis and damage to airway epithelial cells, which results in allergic responses and inflammation (32,33). Through tunneling nanotubes (TNTs), mitochondria transferred from MSCs have been shown to protect the human bronchial epithelium cell line (BEAS-2B) against mitochondrial dysfunction and apoptosis induced by cobalt(II) chloride ($CoCl_2$), which has been used as a hypoxia-mimicking agent (34). Connexin43 (Cx43), a transmembrane protein encoded by the GJA1 gene, is essential for TNT formation and induced pluripotent stem cell (iPSC)-MSC-mediated mitochondrial transfer. This transfer alleviates the symptoms of allergic airway inflammation by recovering mitochondrial function in the bronchi and inhibiting programmed cell death in the lungs (34). The positive effects of mitochondrial transfer have also been reported when inducing airway inflammation by ovalbumin, specifically via the restoration of mitochondrial membrane potential (MMP) and the inhibition of caspase-3 and -9 (34).

The dysfunction of mitochondria, which is associated with changes in mitochondrial morphology and homeostasis and the disruption of MMP in lung cells, is one of the main causes of pulmonary fibrosis (PF) (35). ROS overproduction in the mitochondria is associated with mitochondrial dysfunction, leading to lung damage and inflammatory responses, which contributes to the pathogenesis of PF (36). Increasing mitochondrial biogenesis within human MSCs (hMSCs) using pioglitazone and iron oxide nanoparticles has been shown to enhance mitochondrial transfer to mouse alveolar epithelial cells (TC-1) damaged by bleomycin (BLM), a treatment that induces mtDNA strand breaks and mitochondrial respiratory chain dysfunction (37). TC-1 cells damaged by BLM exhibit restored ATP levels, reduced intracellular ROS levels and recover MMP when they receive functional mitochondria from hMSCs (37).

In the model of chronic obstructive pulmonary disease (COPD), mitochondrial dysfunction due to oxidative stress contributes to tissue inflammation and remodeling (38). Oxidative stress accelerates the inflammatory process by stimulating neutrophils and macrophages (39), leading to apoptosis, autophagy and cellular senescence in the airways (38). Smoking is a well-known contributing factor to the development of COPD and airway structure remodeling. Cigarette smoke medium (CSM) has been shown to alter mitochondrial metabolic regulation, leading to glycolysis and ROS production (40,41). It was previously demonstrated that the transfer of mitochondria from iPSC-MSCs reduced intracellular ROS levels and prevented MMP impairment in airway smooth muscle cells induced by CSM, significantly decreasing apoptosis by 50% (42). Antoehr study demonstrated that BEAS-2B cells treated with 2% CSM for 24 h induced significant inflammatory responses and oxidative stress without leading to cell death, and also received mitochondria from bone marrow-derived MSCs (BM-MSCs) (43). Mitochondrial transfer from BM-MSCs to BEAS-2B cells treated with CSM

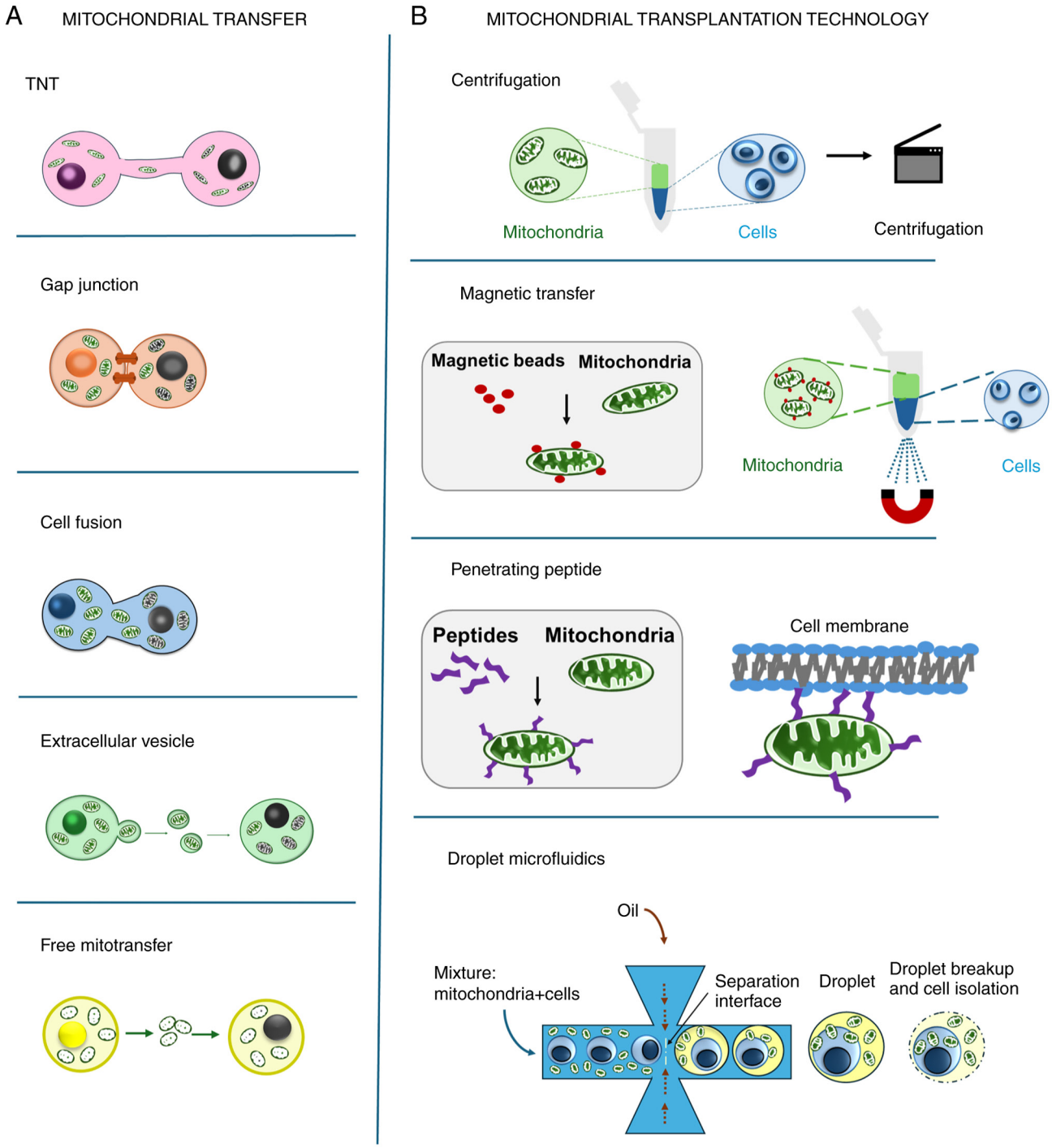

Figure 1. Mechanisms of mitochondrial transfer in the (A) microenvironment and (B) artificial mitochondrial transplantation. (A) Mitochondrial transfer in the microenvironment is facilitated via multiple mechanisms. TNTs form a channel for mitochondria trafficking between cells at certain distances. Cells in close contact can exchange mitochondria via gap junctions on the cell membrane or even fuse their membranes (cell fusion) to allow mitochondrial transfer. Mitochondria can be released via extracellular vesicles or dispersed freely in the microenvironment and taken up by other cells. (B) Mitochondrial transplantation technologies include forced centrifugation, in which centrifugation force increases the mitochondria-membrane contact and induces penetration through the membrane. Magnetomitotransfer enhances penetration by magnetic force. Penetrating peptides wrapping around mitochondria allow mitochondrial transition through the cell membrane. Droplet microfluidics creates isolated spaces, allowing close contact between cells and isolated mitochondria, thereby enhancing the chances of mitochondrial intake. TNT, tunneling nanotube.

showed recovery in intracellular ATP levels (43). This evidence indicated that transferring mitochondria from MSCs can restore mitochondrial dysfunction in the respiratory system by preventing oxidative stress, reducing epithelial cell death, and airway inflammation, and is a potential supportive method in pulmonary diseases.

In damaged cardiac tissue. In cardiac tissue, damage to cardiac muscles can initiate numerous cardiac issues. For example, progressive myocardial damage can be caused by the use of anthracyclines, including doxorubicin, which are commonly used as drugs for the treatment of cancer. Mitochondrial biogenesis inhibition has been shown to

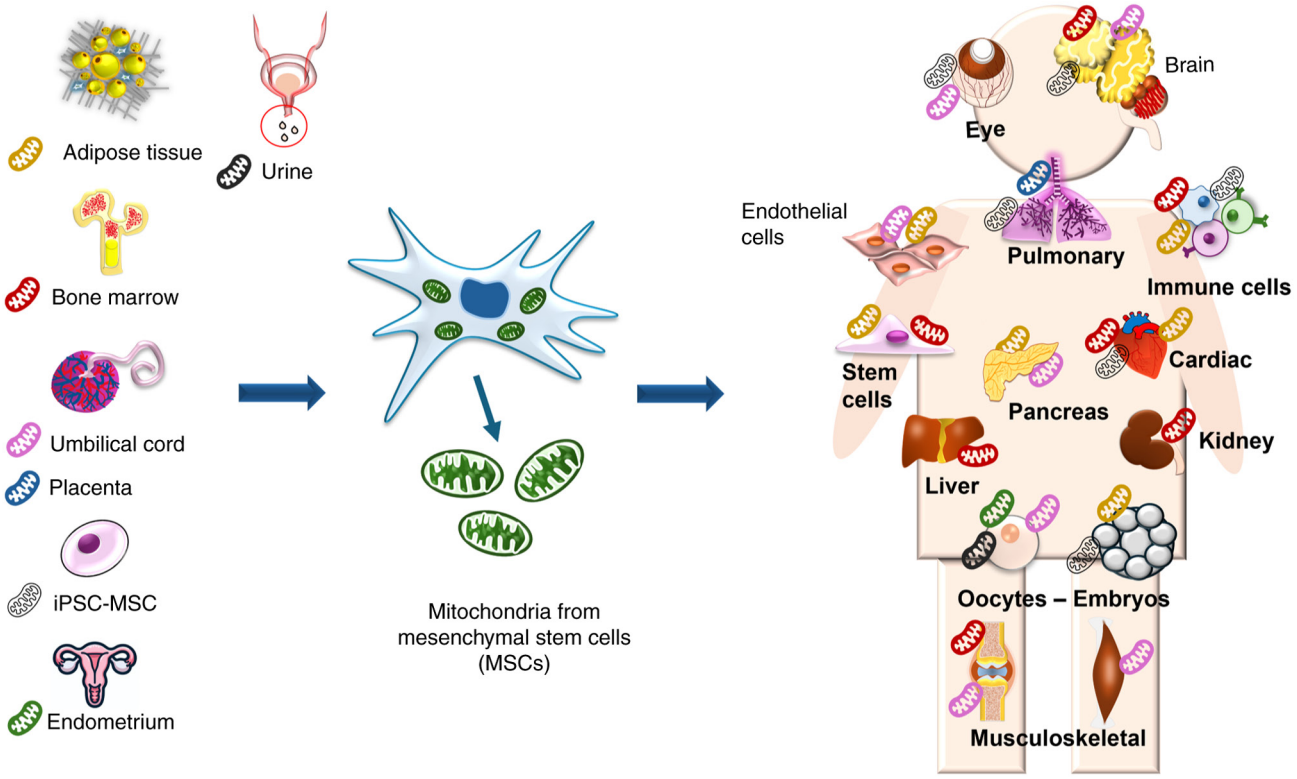

Figure 2. MSC sources for mitochondrial therapy and the associated recipient cells/tissues. Mitochondria were isolated from selected sources of MSCs and transferred/transplanted into different cell types and tissues. The effectiveness of mitochondrial therapy has been examined in various pathological models. MSCs, mesenchymal stem cells.

contribute to this damage (44). The overproduction of ROS caused by doxorubicin induces mitochondrial dysfunction through the impairment of MMP, the opening of mitochondrial permeability transition pore (mPTP), and the alteration of mitochondrial morphology in human vascular endothelial cells (45). Mitochondrial dysfunction caused by doxorubicin has a significant effect on cardiomyocytes as mitochondria comprise 40% of the volume of each cardiomyocyte, and the majority of energy in these cells is generated through mitochondrial respiration (46). In this context, the supplementation of fresh mitochondria could be beneficial. Evidence has indicated that the injection of autologous mitochondria isolated from skeletal muscles into the ischemic hearts of pediatric patients effectively helped them separate from extracorporeal membrane oxygenation (27). However, isolating mitochondria from skeletal muscles may be invasive and impossible in some cases. Thus, a readily available source of healthy mitochondria for transplantation is expected to advance current treatment. As such, MSCs appear as a potential source for mitochondria isolation due to their rapid proliferation. Several studies have demonstrated that MSCs may be a safe source for mitochondrial transfer in cardiovascular conditions (Table I). A previous study demonstrated that functional mitochondrial transfer by iPSC-MSCs protected against doxorubicin-induced damage in cardiomyocytes from neonatal mice, resulting in a marked recovery of the mitochondrial oxygen consumption rate (OCR), ATP production, and optimal mitochondrial respiration in cardiomyocytes (47). It was noted that this effect was distinct from the paracrine activity of MSCs and involved mitochondrial Rho GTPase 1 (Miro1), an outer mitochondrial membrane protein, in the formation of TNTs (47). In another study, the transplantation of mitochondria derived from MSCs reduced apoptosis and ROS levels, while increasing ATP production in cardiomyocytes treated with doxorubicin (48).

Mitochondrial dysfunction is also a key event in simulated ischemia/reperfusion injury (IRI) (49). Abnormal mitochondrial morphology and irregularities in mitochondrial quality control have been identified as cellular mechanisms leading to IRI (50). Mitochondrial ROS production is a primary target of damage caused by hypoxia (51). In an ischemic model, MSCs were shown to reduce the death of H9c2 cardiomyocytes when co-cultured under hypoxic conditions for 150 min via the transfer of healthy mitochondria (52). In another study, BM-MSCs delivered functional mitochondria to injured H9c2 rat ventricular cells, which were cultured in a medium deprived of serum and glucose and incubated under hypoxic conditions for 12 h (53). Co-culturing injured H9c2 cells with BM-MSCs showed significant downregulation of Bax expression and an upregulation of B-cell lymphoma (Bcl-2) expression (53). Furthermore, BM-MSCs also decreased the caspase-3 levels induced by SI/R in H9c2 cells, as this enzyme is an executor of the apoptosis process (53). However, when BM-MSCs were treated with latrunculin A (LatA), which is known to inhibit TNT formation, apoptosis increased (53), suggesting that TNT formation is critical. In another study, when co-culturing human adipose-derived stem cells (hADSCs) with rat cardiomyocytes for 24 h under hypoxic conditions, functional ADSC-derived mitochondria enhanced the OCR of rat cardiomyocytes. This effect was shown to be independent of the paracrine effects from ADSCs (54). On the

Table I. Summary of recipient cell types receiving mitochondrial transfer from MSCs.

System/tissue	Target disease	Defects	Donor cells	Recipient cells	Effects	(Refs.)
Pulmonary	Asthma	$CoCl_2$, OVA	MSCs, iPSC-MSCs	BEAS-2B, hyperplastic goblet cells	- Restoration of mitochondrial function - Inhibition of apoptosis.	(34)
	Pulmonary fibrosis	BLM	hMSCs derived from the placenta	TC-1 cells	- Restoration of mitochondrial function, reduction of ROS.	(37)
	Chronic obstructive pulmonary	CSM	iPSC-MSCs	ASMCs	- Restoration of mitochondrial function. - Inhibition of apoptosis. - Reduction of inflammatory response and oxidative stress.	(42,43)
Cardiac	Myocardia damaged	Doxorubicin	iPSC-MSCs	NMCs, HL-1 cells	- Restoration of mitochondrial function. - Inhibition of apoptosis. - Regulation of autophagy.	(47)
	Ischemic	Phosphatidylserine, hypoxia; H_2O_2	BM-MSCs, ADSCs; hADSCs	H9c2 cells, rCMs, RL4 cells, HUVECs	- Restoration of mitochondrial function. - Reduction of collagen accumulation. - Regulation of autophagy. - Regulation of the HO-1 expression.	(53-55)
Musculoskeletal	Osteoarthritis	Oligomycin, rotenone	BM-MSCs, MSCs	Chondrocytes	- Restoration of mitochondrial function. - Enhancement of collagen and proteoglycan production.	(61,63)
	Tendon injuries	H_2O_2, TNF-α	UC-MSCs, BM-MSCs	Tenocytes	- Restoration of mitochondrial function. - Inhibition of apoptosis. - Enhancement of collagen production. - Reduction of inflammation responses.	(70,71)
	Skeletal muscle atrophy	Dexamethasone	UC-MSCs, MuSCs	Muscle cells	- Restoration of mitochondrial function. - Restoration of muscle bioenergetics.	(81,79)
Brain	Brain ischemic, stroke	OGD, H_2O_2	MMSCs, BM-MSCs	Astrocytes, VSC4.1 cells, neuron-like *p0* PC12 pheochromocytoma cells	- Restoration of mitochondrial function. - Inhibition of apoptosis. - Reduction of inflammation responses.	(88,89, 91)
	Spinal cord injury	Rsl3	UC-MSCs	Ht22	- Restoration of mitochondrial function. - Reduction of the total intracellular iron and free Fe^{2+} level.	(98)

Table I. Continued.

System/tissue	Target disease	Defects	Donor cells	Recipient cells	Effects	(Refs.)
	Parkinson's disease	MPP+, 6-OHDA, rotenone	UC-MSCs, iPSC-MSCs	DA neurons	- Reduced cell death. - Decreased expression of pro-inflammatory cytokines. - Restored intracellular ATP levels.	(104, 106)
	Side-effects of chemotherapeutics	Cisplatin	MSCs	NSCs	- Restoration of mitochondrial function. - Promotion of the survival of NSCs.	(109)
Eye	Ocular disease	Rotenone. Compensates for mitochondrial deficiency	MSCs; iPSC-MSCs	hCECs; neuronal cells in the retinal ganglion cell layer.	- Restoration of mitochondrial function. - Regulation of metabolic processes. - Regulation of Müller cells activation. - Reduction of inflammation responses	(111, 114, 119)
	Mitochondrial mutation disease	mtDNA mutation	WJMSCs, RECs	MF^{Hi}, MELAS neurons, MERRF cybrids	- Restoration of mitochondrial function. - Regulation of metabolic processes. - Inhibition of apoptosis. - Promote cell proliferation.	(155, 156, 158)
Metabolic diseases	Diabetic nephropathy	STZ	BM-MSCs	Proximal tubular endothelial cells (PTECs)	- Inhibition of apoptosis. - Reduction of oxidative stress. - Regulation of SOD2 protein family expression - Regulation of glucose transporter protein family expression.	(29)
	NASH	HFD	BM-MSCs	Mouse hepatocytes	- Restoration of mitochondrial function. - Regulation of MDA expression.	(141, 140)
	SAP	Hypoxia (5% O_2), sodium taurocholate	UC-MSCs	Rat pancreatic acinar cells	- Restoration of mitochondrial function. - Reversal of the reduction of glycerol 3-phosphate, 3-phosphoglyceric acid, and phosphoenolpyruvate and the accumulation of citric. - Increase glycolytic flux.	(146)
		Hypoxia (1% O_2)	ADSCs	Islet cells	- Restoration of mitochondrial function. - Control of insulin production.	(151)
Engraftment function of stem cells		H_2O_2, under serum starvation	hMSCs, ADSCs, BM-MSCs.	hMSCs, ADSCs, BM-MSCs.	- Restoration of mitochondrial function. - Promote cell proliferation. - Enhance stress resistance and anti-aging. - Promote cell cycle progression into the S and G2/M phases.	(169, 167, 170)

Table I. Continued.

System/tissue	Target disease	Defects	Donor cells	Recipient cells	Effects	(Refs.)
Immune	Autoimmune		UC-MSCs, BM-MSCs, MSCs, ASCs	T CD3+ cells, Th17 cells, T $CD4^+$ cells, Tregs	- Differentiate into Tregs. - Control autoimmunity. - Regulate the activity of Th17 cells. - Regulate the activity of T CD4+ cells. - Maintain mitochondrial function in Treg cells. - Enhance Treg function.	(173, 174, 178, 176)
	Diabetes mellitus	high glucose	MSCs	RAW264.7 cells	- Restoration of mitochondrial function. - Regulation of metabolic processes.	(185)
	Acute and chronic inflammatory responses in the testicular	testicular torsion	SLCs	macrophages	- Reduction of oxidative stress. - Enhance testosterone production. - Enhance sperm fertilization capability.	(249)
	Acute and chronic inflammatory responses in the lung	LPS, *E. coli*	BM-MSCs, ADSCs	AMs, MDMs, macrophages	- Enhancement of mitochondrial function. - Enhance the phagocytic ability of macrophages. - Induce differentiation into the M2 phenotype of macrophages.	(187-189, 190, 192)
	Acute and chronic inflammatory responses	Cholesterol	MSCs	7-ketocholesterol-load macrophages	- Enhance the phagocytic ability of macrophages. - Reduction of lipid content. - Enhance energy in macrophages.	(250)

$CoCl_2$, Cobalt(II) chloride; OVA, ovalbumin; MSCs, mesenchymal stem cells; iPSC, induced pluripotent stem cell; BLM, bleomycin; CSM, cigarette smoke medium; ROS, reactive oxygen species; ASMCs, airway smooth muscle cells; NMCs, neonatal mouse cardiomyocytes; BM-MSCs, bone marrow-derived MSCs; rCMs, rat cardiomyocytes; H_2O_2, hydrogen peroxide; HUVECs, human umbilical vein endothelial cells; UC-MSCs, umbilical cord-MSCs; MuSCs, muscle stem cells; MMP+,1-methyl-4-phenylpyridinium; 6-OHDA, 6-hydroxydopamine; mtDNA, mitochondrial DNA; NSCs, neural stem cells; hCECs, Human corneal endothelial cells; WJMSCs, Wharton's Jelly-derived MSCs; MELAS, myopathy, encephalomyopathy with lactic acidosis, and stroke-like episodes; MERRF, myoclonus epilepsy with ragged red fiber syndrome; STZ, streptozotocin; NASH, non-alcoholic steatohepatitis; HFD, high-fat diet; SAP, severe acute pancreatitis; ASCs, adipose-derived stem cells; SLCs, stem Leydig cells.

other hand, mitochondria released by damaged somatic cells, such as hydrogen peroxide (H_2O_2)-treated RL14 cardiomyocytes or human umbilical vein endothelial cells (HUVECs), activate MSCs to transfer healthy mitochondria toward dying cells (55). Heme oxygenase-1 (HO-1) is a rate-limiting enzyme in heme metabolism and exerts a wide range of anti-inflammatory, anti-apoptotic, and immunoregulatory effects in various diseases (56). Co-culturing MSCs with RL4 cells damaged by H_2O_2 and HUVECs leads to the increased expression of HO-1 and enhances HO-1 enzyme activity in MSCs (55). These data indicate that MSCs are promising sources of mitochondria that can be used for mitochondrial transplantation technologies.

In disorders of the musculoskeletal system. Osteoarthritis (OA) is a common musculoskeletal disorder related to the aging process, which is characterized by cartilage degradation, joint pain, and impaired function (57). Chondrocytes play a functional role in the synthesis, deposition and formation of the extracellular matrix of cartilage tissue (57). The mitochondria of chondrocytes in the OA model exhibit a reduced activity of mitochondrial respiratory chain (MRC) enzymes (complex I, II, III, IV and ATP synthase), along with decreased MMP (58). Furthermore, mitochondria exhibiting a swollen morphology and loss of cristae regularity have also been observed in chondrocytes in models of OA (58). Mitochondrial dysfunction and energy metabolism disruption markedly contribute to the pathogenesis of OA, including cartilage degeneration, increased synovial inflammation and the calcification of the cartilage matrix (59). The abnormal alteration in the metabolic process of cartilage cells is a response to inflammation and is correlated with the process of cartilage degeneration (60). In a previous study, the bilateral anterior cruciate ligament and medial meniscus were resected in 8-week-old rats to induce OA pathogenesis (61). Functional mitochondria from BM-MSCs rescued OA chondrocytes from mitochondrial dysfunction by restoring the normal morphology of mitochondria, MMP, MRCI, II, and III activity, citrate synthase, and ATP content (61). Another study indicated that mitochondrial dysfunction in chondrocytes in OA is characterized by a reduced type II collagen secretion (58). It should be noted that type II collagen and proteoglycans are key components of cartilage tissue (62). OA chondrocytes co-cultured with MSCs showed a significant increase in the concentration of type II collagen and proteoglycan compared to the OA chondrocytes group (61). Another study indicated that inhibiting mitochondria in chondrocytes with agents such as rotenone or oligomycin promoted MSCs to transfer functional mitochondria to chondrocytes with mitochondrial dysfunction (63). Although chondrocytes adapt to low oxygen conditions, a number of their functions are still oxygen-dependent (64). Thus, culture conditions, such as hyperoxia and hyperglycemia, affected the mitochondrial transfer from MSCs to chondrocytes because chondrocyte homeostasis responds to the low oxygen levels and nutrient-deficient conditions *in vivo* (63).

Tendon injuries often occur in the severely hypoxic zone, characterized by mitochondrial dysfunction and increased oxidative stress (65). Mitochondrial dysfunction is characterized by an increase in ROS, decreased superoxide dismutase activity, and a reduced number of mitochondria, all of which contribute to tendon pathology (66). In a previous study on a murine model of supraspinatus tendinopathy, mitochondrial dysfunction led to the altered expression of genes related to morphology and abnormal mitochondrial quantity associated with the development of tendinitis (67). Another study indicated that H_2O_2 activated the apoptotic pathway by inducing oxidative stress and the depolarization of MMP in mouse models of Achilles tendinopathy (68). Tenomodulin (TNMD) is a marker specific to tendons and contributes to the durability and aging of tendon tissue at the tissue level (69). TNMD is associated with the structural and functional properties of collagen 1 (COL1) (69). A reduction in the levels of tenomodulin is a sign of pathogenesis. Mitochondrial transfer from BM-MSCs to H_2O_2-damaged tenocytes triggered anti-apoptotic mechanisms and restored mitochondrial function by recovering MMP and ATP levels (70). Functional mitochondria derived from MSCs enhanced the expression of TNMD and collagen 1 and reduced the expression of matrix metalloproteinase 1 in tenocytes treated with tumor necrosis factor-α (TNF-α) (71). Moreover, functional mitochondria from MSCs also reduced levels of pro-inflammatory cytokines, such as interleukin (IL)-1β and IL-6 (70), demonstrating an anti-inflammatory effect.

Mitochondria contribute to several key functions for the survival of muscle cells, such as ATP production, substrate biosynthesis, metabolism and participation in the regulation of apoptosis (72). Skeletal muscle atrophy is characterized by a reduction in muscle mass and strength and is associated with mitochondrial dysfunction as mitochondria occupy a significant portion of muscle cell volume (72,73). The reduction in mitochondrial mass, MMP, ATP production and mitochondrial glucose metabolism activity are characteristic features of muscle atrophy (74). ROS overproduction related to mitochondrial dysfunction is the main mechanism associated with muscle atrophy (75-77). Moreover, mitochondrial dysfunction has also been implicated in the pathology of muscular dystrophy (78). The restoration of mitochondrial bioenergetics has been shown to ameliorate the progression of muscular dystrophy in mice (79). Dexamethasone is an agent that induces muscular atrophy through a process of pyroptosis, a form of programmed cell death involving inflammation as the initial process (80). A previous study demonstrated that mitochondrial transplantation derived from umbilical cord-derived MSCs (UC-MSCs) promoted myofiber hypertrophy and reduced intracellular lactate concentration in dexamethasone-induced atrophied muscles (81). This also contributed to enhancing the expression of muscle-specific markers, such as desmin and activated adenosine monophosphate-activated protein kinase, which aided the functional recovery of atrophied muscles (81).

These data indicate that the use of mitochondria isolated from MSCs may be beneficial in different types of pathology in the musculoskeletal system. The addition of MSC mitochondria aids in the restoration of various cell types, the construction of different functional parts, and the reduction of tissue destruction caused by immune responses to stress.

In conditions of the brain. Ischemic stroke is associated with a reduction in cerebral blood flow, leading to severe oxygen and glucose deprivation (OGD) in neurons (82-84). OGD has been shown to cause neuronal mitochondrial dysfunction, such as reduced mitochondrial complex I activity, MMP collapse, decreased ATP synthesis and increased oxidative

stress (85). Transient focal cerebral ischemia is characterized by irreversible neuronal loss, leading to persistent neurological impairment in individuals (86). The *in vitro* model of brain ischemia is a state of OGD closely related to oxidative stress due to the overproduction of ROS (87). In a previous study, mitochondrial damage in astrocytes caused by OGD, which resulted in fragmented mitochondria, stimulated the transfer of functional mitochondria from multipotent MSCs (MMSCs) to astrocytes (88). The functional mitochondria from MMSCs not only restored bioenergetics, but also normalized the proliferation of neuron-like *ρ0* PC12 pheochromocytoma cells, which carried damaged mitochondrial DNA and generated most of their energy through anaerobic glycolysis (88). Injured astrocytes received more functional mitochondria from MMSCs when MMSCs overexpressed Miro1 (88). Furthermore, BM-MSCs also transferred functional mitochondria to VSC4.1 motor neurons injured by OGD (89). BM-MSCs exhibited an increased CD157 expression when co-cultured with VSC4.1 motor neurons injured by OGD, an effect that enhanced the mitochondrial transfer capacity of BM-MSCs (89). Mitochondria derived from BM-MSCs could alleviate apoptosis and inflammation in damaged VSC4.1 motor neurons and promoted the outgrowth of VSC4.1 motor neurons, but only affected their length without changing their number (89). The mitochondrial transfer from iPSC-MSCs increased intracellular ATP levels in PC12 cells following $CoCl_2$-induced hypoxic damage (90). Furthermore, the mitochondrial transfer from MSCs improved mitochondrial respiration, ATP production, and the basal metabolic rate in neurons after H_2O_2-induced injury (91).

Spinal cord injury (SCI) is a severe type of central nervous system injury and is associated with oxidative stress caused by the excessive production of ROS (92). Mitochondrial dysfunction related to mitochondrial homeostasis leads to the inactivation of ATP-dependent ion pumps and is closely associated with the activation of cell death (93). Mitochondrial quality control and the mitochondria-related process of ferroptosis play a crucial in SCI (94). Ferroptosis is an iron-dependent cell death process that occurs due to the accumulation of damaged phospholipids on the cell membrane and is associated with SCI (95-97). In a previous study, UC-MSCs were shown to transfer mitochondria to HT22 neuronal cells under the stimulation of the ferroptosis inducer Rsl3 when co-cultured (98). UC-MSCs helped to restore mitochondrial mass, promoted mitochondrial fusion, restored MMP, and balanced intracellular ROS and ATP levels in ferroptosis neurons (98). Furthermore, mitochondrial transfer from UC-MSCs reduced ferroptosis by decreasing the total intracellular iron content and free Fe^{2+} levels in neurons undergoing ferroptosis (98). Inhibiting ferroptosis using dihydroorotate dehydrogenase in injured neurons has been shown to normalize mitochondrial morphology and MMP (96).

Parkinson's disease (PD) is a condition related to the degeneration of the nervous system of the brain, and damaged mitochondria are one of the causes of PD (99,100). Mitochondrial dysfunction has been identified as a major factor contributing to the death of dopaminergic (DA) neurons (101). The dysfunction of mitochondrial respiratory chain complex I is a major cause of PD pathogenesis (102). The impairment of mitophagy and oxidative stress are hallmarks of PD (103). Mitochondria derived from UC-MSCs reduce DA cell death caused by 1-methyl-4-phenylpyridinium, 6-hydroxydopamine and rotenone (104). Furthermore, mitochondria derived from UC-MSCs also reduce the mRNA expression of TNF-α and nitric oxide synthase, and decrease the expression of IL-6 and IL-8 induced by lipopolysaccharide (LPS) in murine microglia BV2 cells (104). The reduced expression of pro-inflammatory cytokines has been shown to alleviate oxidative stress, inflammation and normalize mitochondrial dysfunction in a mouse model of PD (105). In a previous study, astrocytes derived from iPSC-MSCs provided functional mitochondria to DA neurons damaged by rotenone, a compound that inhibits complex I (106). Notably, the neuroprotective effect of astrocytes was not due to paracrine activity, but primarily to the transfer of mitochondria to DA neurons (106). The transfer of mitochondria from iPSC-MSCs-derived astrocytes restored ATP levels impaired by rotenone in DA neurons (106).

In addition, cisplatin is a chemotherapeutic agent used to treat cancer; however, it is known to cause morphological changes and mitochondrial dysfunction in mouse neurons (107). Cisplatin has been shown to cause excessive ROS production and alter the mitochondrial content of cells (108). The donation of MSCs was shown to normalize the membrane potential of neural stem cells (NSCs) treated with cisplatin, which had shown a marked decrease in basal respiratory capacity, ATP levels, and MMP (109). Furthermore, excessive expression of Miro1 in MSCs increased mitochondrial transfer and promoted the survival of NSCs (109). In summary, these findings indicate that the transfer of functional mitochondria from MSCs can improve mitochondrial dysfunction and neuronal survival under various pathological conditions in brain tissue (106).

In conditions of the eyes. Mitochondrial damage and abnormalities in mitochondrial homeostasis are among the causes of ocular diseases (110,111). The risk of mitochondrial damage increases when the cornea is exposed to ultraviolet rays (112). Corneal endothelial cells (CECs) play a crucial role in maintaining the transparency of the cornea; therefore, a decline in their function will negatively impact vision (110). Metabolic activity and mitochondrial respiration, such as the tricarboxylic acid cycle and acetyl coenzyme A-related enzymes, are closely related to the survival and function of CECs (113). Therefore, the addition of functional mitochondria is expected to support the recovery of eye disorders where impaired mitochondria have been identified to play a role. In a model of human corneal endothelial cells (hCECs) damaged by rotenone, the inhibition of mitochondrial complex I and increased ROS production were shown to promote the uptake of MSC mitochondria through TNT, whereas healthy hCECs could not accelerate similar effects (111,114). Rotenone-induced ROS promote NF-κB, which enhances TNT formation via the upregulation of TNF-α-induced protein 2 (TNF*α*ip2) (114). The underlying mechanism has been previously reported (115). The contribution of functional mitochondria from MSCs improves basal respiration, ATP production, and the expression of mitochondrial component proteins, such as complex I, mitochondrial matrix components and the mitochondrial membrane (111). The transfer of functional mitochondria from MSCs is the primary mechanism for protecting CECs from the effects of rotenone, although the paracrine effects of MSCs

are also a contributing factor (114). However, the transferred mitochondria are either digested by lysosomes in the host cell or excreted after 8 days (111), suggesting that the therapeutic effect of exogenous mitochondria may be limited to the short term in CECs.

Degeneration of retinal ganglion cells (RGCs) is the cause of optic atrophy (116). The dysfunction of mitochondrial NADH dehydrogenase and complex I in the retina is related to an innate immune and inflammatory response and is associated with neuropathies, which has been shown to cause RGC degeneration in mice (116-118). It was previously demonstrated that neuronal cells in the RGC layer directly received mitochondria from the injected iPSC-MSCs to compensate for mitochondrial dysfunction in the retinas of mice deficient in NADH dehydrogenase Fe-S protein 4 (119). On the other hand, Müller cells, the main glial cells of the retina, play a crucial role in maintaining neurovascular homeostasis in the retina (120). The abnormal activation of Müller cells, which may also lead to excessive ATP release, has been shown to contribute to the apoptosis of RGCs and is a pathogenic factor in glaucoma (121,122). In addition, inflammation should be accounted for in ocular and macular diseases. IL-17 has been shown to increase the production of glial fibrillary acidic proteins, vascular endothelial growth factor, and glutamate, leading to abnormal activation and dysfunction of Müller cells (123). IL-1β contributes to the recruitment of macrophages in the retina of *in vivo* models (124). Mitochondrial transfer from iPSC-MSCs reduced the abnormal activation of Müller cells in mouse retinal and downregulated pro-inflammatory cytokines such as IL-17 and IL-1β (119). These data demonstrated that mitochondrial transfer could alleviate ocular pathological conditions both by restoring ocular cell function and reducing inflammatory effects.

In models of metabolic disorders. Mitochondria play a crucial role in the functional activity of renal tubular epithelial cells (TECs) (125,126), and the disruption in mitochondrial activities has been shown to cause the aging of renal TECs, leading to renal complications and pathogenesis (127-129). Hyperglycemia causes mitochondrial dysfunction, characterized by a reduction in intracellular ATP and MMP, changes in mitochondrial morphology, and the excessive production of ROS in renal TECs, which contribute to diabetic nephropathy (130). A recent study revealed that high glucose levels increased oxidatively modified proteins in mitochondria and intracellular ROS in TECs (131). Streptozotocin (STZ) is an agent that causes alterations in MMP and mitochondrial NAD and NADH enzyme activity, leading to the inhibition of ATP synthesis, and thereby inducing oxidative stress and apoptosis in pancreatic β-cells (132). The use of STZ to model diabetes has been shown to lead to cellular metabolic changes and mitochondrial dysfunction in renal cells (133). In that context, mitochondrial transfer from BM-MSCs was previously been shown to inhibit apoptosis and ROS production in damaged proximal TECs induced by STZ (29). This was achieved by promoting the expression of mitochondrial superoxide dismutase 2 and Bcl-2, which are involved in regulating the process of apoptosis of proximal TECs (29). Furthermore, BM-MSCs-derived functional mitochondria improved the expression of megalin, a surface receptor protein in TECs that participates in the reabsorption of proteins from urine (134), as well as sodium-glucose cotransporter-2 (SGLT2), a member of the glucose transporter family in proximal TECs (29). Since high glucose levels have been shown to reduce the expression of megalin (which is also associated with glucose transport via SGLT) (135), the recovery of megalin and SGLT2 is a sign of improved TEC function.

Non-alcoholic steatohepatitis (NASH) has been shown to be a result of dysfunctional mitochondria, which includes alterations of enzymatic activity, changes in mitochondrial shape and quantity, and disrupted calcium regulation (136,137). In the NASH disease model, impaired mitochondria facilitate hepatic lipid accumulation by promoting ROS production and lipid peroxidation processes (138). High-fat diets over a long period of time have been shown to cause mitochondrial deformation and alter the levels of proteins involved in mitochondrial dynamics (139). It was previously shown that when fatty hepatocytes were co-cultured with BM-MSCs, mitochondrial transfer was observed through cell-to-cell contact, which promoted lipolytic activities via enhancing oxidative capacity and mitochondrial biogenesis (140,141). Mitochondria from BM-MSCs restored several mitochondrial abnormalities in the hepatocytes of mice fed a high-fat diet, including MMP, mtDNA copy number, OCR and ATP levels (140). Functional mitochondrial-derived BM-MSCs also restored impaired calcium activity in steatotic cells (140), an effect which is important for glucose production and lipogenesis (142).

Severe acute pancreatitis (SAP) is an inflammation of the pancreas that can lead to mortality. SAP is often linked to smoking, gallstone disease, alcohol consumption, obesity, diabetes, and hyperlipidemia (143). The excessive accumulation of intracellular ROS is associated with pyroptosis in pancreatic cells during acute inflammation (144). The dysregulation of the mPTP caused by excessive intracellular calcium levels results in changes in MMP, which is associated with the progression of SAP (145). The transfer of mitochondria via extracellular vesicles (EVs) from hypoxia (5% O_2)-treated hUC-MSCs (hypo-EVs) was previously shown to restore ATP levels and OCR, and to maintain relatively stable MMP in sodium taurocholate-induced damaged rat pancreatic acinar cells (PACs) (146). EVs carrying mitochondria also promoted the normalization of glycolytic activity in PACs (146).

Allogeneic islet transplantation provides a promising opportunity for a limited group of patients with type I diabetes (147). Allogeneic transplantation of human islets requires short-term cultivation to ensure safety assessments (148). However, islet functions are influenced by various environmental conditions during this period, which may induce oxidative stress and inflammation (148). The insulin-secreting ability of pancreatic islet β-cells is associated with mitochondrial mass and respiratory capacity (149,150). It is also primarily regulated by mitochondrial ATP production in response to extracellular glucose levels (150). ADSCs have been shown to transfer mitochondria through extracellular vesicles to mouse islet cells exposed to hypoxia (1% oxygen), resulting in enhanced OCR and insulin secretion of islet cells when stimulated with 20 mM glucose (151). These data suggest that mitochondrial transfer can also be used as a supportive technique in optimizing islet pre-transplantation conditions.

In cells with mtDNA mutation or damage. Mitochondrial myopathy, encephalomyopathy with lactic acidosis, and stroke-like episodes (MELAS) is the acronym for a clinical subgroup of mtDNA diseases affecting several body systems (152). MELAS is often a result of point mutations in the mtDNA and is thus inheritable from the affected mother (152). The transition from adenine to guanine at nucleotide 3243 in the mtDNA of the *MT-LT1* gene encoding *tRNAleu (UUR)*, is among the most frequently observed pathogenic mutations in individuals with MELAS (153). This alteration leads to the impaired translation and synthesis of ETC protein subunits, resulting in reduced mitochondrial energy production (154). Patients with MELAS have fibroblasts (MELAS fibroblasts) with a high mutation burden, featuring mitochondrial dysfunction and increased ROS production (155). It was previously shown that Wharton's jelly-derived MSCs (WJMSCs) transferred mitochondria via TNTs into MELAS fibroblasts pre-treated with rotenone, resulting in an increased protein expression of the respiratory complexes, which suppressed ROS production and enhanced MMP (155). Furthermore, this also enhanced the proliferation of fibroblasts and reduced the expression of cleaved caspase-3 and TUNEL, thereby suppressing apoptosis (155). The results of another study suggested that highly purified MSCs have a greater ability to transfer mitochondria into MELAS neurons compared to traditional MSCs (156). Furthermore, co-culturing with RECs or MSCs significantly enhanced the viability of MELAS neurons (156).

Myoclonus epilepsy with ragged red fiber syndrome (MERRF) is a result of a transition from adenine to guanine at nucleotide 8344 (mt8344A>G) within the mitochondrial $tRNA^{Lys}$ coding gene (157). This mutation has been shown to increase ROS production and oxidative stress, along with compromised mitochondrial bioenergetics (157). MERRF cybrids, which were created by fusing ρ^0 cells lacking mtDNA with human platelets in a medium devoid of pyruvate and uridine, were unable to survive in a galactose-added and glucose-free medium. This suggests that the mt8344A>G mutation leads to mitochondrial dysfunction (158). The MERRF mutation impairs the translation of 13 proteins encoded by mtDNA and produces abnormal translation products (159). The transfer of mitochondria from WJMSCs into MERRF cybrids decreases intracellular ROS, re-establishes MMP, and enables the growth of MERRF cells in glucose-free environments (158).

In clinical applications, hematopoietic stem cells (HSCs) were utilized for mitochondrial transplantation into the HSCs of patients with large-scale mtDNA deletion, such as Pearson or Kearns-Sayre syndromes (160,161). Recipient HSCs were then infused back into the patients, improving their quality of life (160,161). This evidence suggests a novel therapeutic application of mitochondrial transplantation for currently incurable diseases. While MSCs have not yet been used in such clinical trials, they can be collected from multiple sources and easily expanded. Their mitochondria vary in both morphology and functional capacity, and can be selected to suit HSC biology, making them a potential source for mitochondrial transplantation into HSCs for similar cases. Although replacing or supplementing defective mitochondria in all body systems appears challenging and warrants further research, mitochondrial transplantation holds therapeutic potential in mitochondrial pathogenesis.

In enhancing the function of cell engraftment therapy. Stem cell therapies have often been ineffective due to low cell survival and engraftment (162,163). The excessive production of ROS in damaged tissues usually decreases the viability of transplanted MSCs (164). Additionally, MSC functional characteristics may be compromised with prolonged isolation and *in vitro* cultivation, or due to the age of the donor or disease conditions (165,166). In this context, it has been shown that healthy hMSCs could donate mitochondria to those pre-treated with H_2O_2 through TNT formation (167). The treatment of hMSCs with mesenchymal stem cell adjuvant has been shown to enhance their mitochondrial transfer into other H_2O_2-induced damaged hMSCs, resulting in a significant reduction in intracellular ROS levels, maintenance of MMP, and an increase in TNT length and formation (167). Mitochondrial Drp 1 phosphorylation (Drp1 S616) is involved in mitochondrial fission and fragmentation (168). It was previously demonstrated that functional mitochondria derived from healthy hMSCs reduced mitochondrial fragmentation and Drp1 S616 phosphorylation in damaged hMSCs (167). The mitochondria derived from ADSCs supplied ATP to fulfill metabolic needs, thereby enhancing the overall metabolic activity of the recipient ADSCs through glycolysis (169). Moreover, ADSCs that received donated mitochondria showed enhanced proliferation and mobility in serum starvation conditions, demonstrating enhanced stress tolerance, anti-aging capabilities and multidirectional differentiation potential in ADSCs treated with doxorubicin (169). It should be noted that mitochondria can be artificially introduced into BM-MSCs *in vitro*, and within certain limits, the addition of extracellular mitochondria could enhance the capacity of the recipient cells to take up more mitochondria (170). Receiving mitochondria also increases BM-MSC proliferation and migration, promoting cells to enter the S and G2/M phases, and resisting the replicative senescence of BM-MSCs (170). In addition, mitochondrial transfer also enhances the osteogenic differentiation potential and mitochondrial functions, including OCR and ATP production in BM-MSCs (170).

A recent study demonstrated that the transfer of mitochondria from MSCs to endothelial cells, either by direct cell-to-cell contact or artificial transplantation, significantly enhanced the engraftment ability of the cells in the *in vivo* environment (171). The stimulation of these effects was shown to be related to mitophagy; however, the precise mechanism remained unknown. These data suggested that boosting mitochondrial activity by mitochondrial transfer and donation can also support cell survival in an *in vivo* environment, proposing a potential application for mitochondrial therapy in cell transplantation technology.

In conditions of the immune system. MSCs possess the capacity to modulate immune responses, particularly those of T-cells, indicating their therapeutic potential in treating autoimmune disorders, preventing graft rejection and managing graft vs. host disease (GVHD) (172). One mechanism of immunoregulation by MSCs may be attributed to their ability to transfer mitochondria to immune cells, regulating cell

function and consequent immune outcomes. It was previously demonstrated that $CD3^+$ T-cells receiving mitochondria from UC-MSCs increased the expression of CD25 (a factor for T-cell activation) and FoxP3 [a marker of T-regulatory cell (Treg) differentiation], compared to $CD3^+$ T-cells not receiving mitochondria from UC-MSCs (173). Since Tregs participate in maintaining tolerance and preventing autoimmunity, they are involved in various pathological conditions, including GVHD (174). Treg cell differentiation induced by mitochondria transferred from UC-MSCs enhanced the ability to inhibit the proliferation of peripheral blood mononuclear cells (173). As previously demonstrated, mitochondrial transfer also markedly improved the survival rate of mice with GVHD, while decreasing tissue inflammation (173). The key strategy employed by Tregs to preserve immune homeostasis is the inhibition of conventional T-cell (Tconv) proliferation (175). A previous study demonstrated that ADSCs transferred mitochondria to Tregs during co-culture, 85% of which remained functional, allowing Tregs to efficiently inhibit the proliferation of Tconvs (176). The insufficient presence of HLA class II antigens on ASCs restricted the uptake of mitochondria by >80% (176). Thus, mitochondrial transfer from MSCs supports T-cells in regulating uncontrolled immunity.

In addition, it should be noted that both $CD4^+$ and $CD8^+$ T-cells participate in immune responses in GVHD, autoimmune disorders and tissue rejection (177). It was previously demonstrated that mitochondria donated by BM-MSCs suppressed T-helper 17 (Th17) cells, a class of $CD4^+$ T-cells involved in the progression of autoimmune conditions, while promoting the formation of Treg cells (178). In a co-culture system, BM-MSCs transferred mitochondria to pathogenic Th17 cells, leading to increased OCR and a decrease in IL-17 expression in Th17 cells (178). The inhibition of IL-17 production was related to the interconversion into Tregs (178). In another study, mitochondria transferred from MSCs also helped to inhibit the response of $CD4^+$ T-cells and reduced the production of interferon-γ (IFNγ), a cytokine that activates M1 macrophages, and promoted $CD8^+$ T-cell function (172). The differentiation of IFNγ-producing $CD4^+$ Th1 cells relies on the key transcription factor, T-bet, the expression of which is increased upon encountering antigens to promote gene expression, particularly IFNγ, thus determining the differentiation of the effector subset Th1 (179). In a previous study, co-culturing with MSCs that were primed with TNFα and IFNγ for 48 h inhibited T-bet expression following $CD4^+$ T-cell activation and suppressed Th1 differentiation (172).

Diabetes mellitus is chiefly characterized by increased macrophage infiltration in the kidneys. Implementing strategies to prevent the pro-inflammatory (M1) phenotype or to shift them to an anti-inflammatory (M2) state has been proposed to help reduce kidney injury in diabetic mice (180). Metabolic and physiological changes in mitochondria are essential for regulating macrophage polarization, proliferation and survival (181). While M1 macrophages utilize glycolysis for energy, M2 macrophages depend on mitochondrial oxidative phosphorylation (182,183). Mitochondrial dysfunction in macrophages derived from diabetic mice has been shown to lead to M1 polarization and resulted in subsequent inflammation (184). In that context, in another study, mitochondria transferred from MSCs to RAW264.7 macrophages pre-treated with high glucose helped the cells to reduce ROS production and restore MMP and ATP levels by regulating gene expression of the glycolytic and citric acid cycles (185). RAW264.7 macrophages induced by high glucose that took up mitochondria exhibited lower levels of cytokine secretion, such as IL-1β and TNF-α, two cytokines which are critical for mitigating inflammation (185).

Alveolar macrophages (AMs), found in the lung lumen adjacent to the epithelium, function to phagocytose debris and help resolve inflammation (186). Dysfunctional AMs with an irregular mitochondrial function frequently contribute to severe inflammation in the lungs (186). It has been shown that MSCs transferring mitochondria to macrophages can enhance their phagocytosis, which may uncover a mechanism behind the antimicrobial effects of BM-MSCs (187). Furthermore, mitochondrial transfer from MSCs can boost the anti-inflammatory and antibacterial functions of macrophages by promoting their differentiation into the M2 phenotype (188). As previously demonstrated, when MSCs and primary human monocyte-derived macrophages (MDMs) were co-cultured for 4 h, the mitochondrial transfer from BM-MSCs through TNTs enhanced the ability of macrophages to kill up to 80% of extracellular *Escherichia coli* bacteria (187). Notably, macrophages co-cultured with MSCs exhibited a substantial and consistent enhancement of both OCR and ATP production (187). This was consistent with a report that macrophages receiving mitochondria from exosomes secreted by MSCs in the co-culture settings significantly increased OCR and reduced proton leak (189). This functioned as a survival strategy in response to oxidative stress, where donated mitochondria were re-utilized through a fusion process to enhance the bioenergetics of macrophages (189). Exosomes derived from ADSCs could transfer mitochondrial components to murine alveolar macrophages, which then fused with the macrophage mitochondria (190). Murine alveolar macrophages in acute lung injury exhibited an increased number of mitochondria, improved mitochondrial morphology, and increased membrane potential after receiving mitochondria from ADSCs (190). Moreover, mitochondria played a critical role in the metabolic programming of immune cells and in reshaping cellular phenotypes and function (191). The transfer of mitochondria via ADSC-derived exosomes caused LPS-stimulated macrophages to transition from a pro-inflammatory M1 phenotype to an anti-inflammatory M2 phenotype (190). Furthermore, mitochondria have been shown to be transferred from MSCs to macrophages via EVs, which boosted oxidative phosphorylation (OXPHOS), leading to enhanced phagocytosis of macrophages (192). These data demonstrate that MSCs employ multiple mechanisms to transfer mitochondria to immune cells, which often have high mobility in circulation. Thus, questions regarding the driving factors for mitochondrial transfer from MSCs to immune cells warrant future research, potentially opening a potential opportunity for therapeutic application.

In conditions of the reproductive system. The reproductive system consists of various organs and structures that are distinct in males and females. Different cell compartments in the reproductive system are responsible for specific functions that support the formation and production of offspring. The two key cell types directly responsible for fertilization are

sperm and eggs. While mitochondria are crucial for sperm maturation, survival, and mobility, oocyte mitochondria are critical for fertilization and embryonic development, which are also majorly inherited by the fetus (193). Thus, both mtDNA content and mitochondrial function are essential for successful fertilization, pregnancy and live births. Mitochondria in oocytes produce energy mainly via OXPHOS, as glycolysis is only unblocked at the early stage of blastocyst formation. ATP production is associated with egg quality, as aged and poor-quality eggs have significantly lower mtDNA content and produce much less ATP compared to normal and healthy oocytes (194). This could potentially result in low or no fertilization (195,196). Aging is one of the major contributing factors to reduced female fertility, as it directly affects mtDNA replication and mutation, and changes mitochondrial metabolism (197).

Mitochondria can be isolated from healthy donors and directly injected into the eggs or embryos of unhealthy individuals who may carry mutations interfering with mitochondrial function. The technology is effective in supplementing oocytes with healthy mitochondria to improve oocyte quality and fertilization rate, and to increase chances of live births and offspring with normal phenotypes, providing hope to infertile women and those with inherited diseases (198). Multiple studies have been conducted on both animal and human models, aiming to examine the applicability of mitochondria isolated from various cell types to identify the most suitable source of mitochondria specifically for oocyte improvement; a number of these sources were from MSCs of different origins. Even though the current technology focuses on the autologous grafting of mitochondria due to concerns about mtDNA and nuclear DNA mismatch (199), the therapy has yielded positive results in assisting cases of aged and low-quality oocytes. For example, in animal models, for instance, the mitochondria isolated from MSCs derived from UC-MSCs were directly injected into metaphase I oocytes of aged mice, which consequently resulted in improved mitochondrial function and development of early embryos (200). On the other hand, mitochondria derived from ADSCs were shown to be effective in improving oocyte competence, fertilization rate, and blastocyst development in both aged-MII and cryopreserved oocytes (201,202). MSCs (EnMSCs) were also a source of cells that have been tested in mice. The increase in oocyte quality and maturation associated with an enhanced birth rate and embryonic development suggested that mitochondrial transfer from EnMSCs was effective in rescuing infertility due to the poor quality of germinal vesicle oocytes (203). Additionally, mitochondria isolated from iPSCs were also shown to be a good source for mitochondrial transfer due to their compatibility with the mitochondrial morphology in oocytes and embryos (204). Furthermore, advancements have been made to bring the technology of mitochondrial therapy to humans. Particularly, mitochondria from urine-derived MSCs and oogonial stem cells were isolated for use in aged human oocytes. The results revealed an improvement in pregnancy rates, embryonic development and live birth rates (205-209). These data highlight the promising potential of mitochondrial transplantation technology in supporting the reproductive system, particularly in addressing female infertility. Future research is also anticipated to advance mitochondrial therapy in the male reproductive system.

3. Mechanisms of mitochondrial donation from MSCs

Previous *in vitro* studies have demonstrated the role of MSCs in rescuing damaged cells by transferring their healthy mitochondria (53,210). In cells exposed to mitochondrial toxicity stimulators, mitophagy is activated to eliminate dysfunctional mitochondria. These dysfunctional mitochondria, which can be composed of mtDNA and other mitochondrial components, help maintain mitochondrial homeostasis (211). These mitochondrial components are released into the microenvironment and function as stress signals, which can prompt nearby MSCs to provide support (47,55,212) (Fig. 3). Following internalization by MSCs, damaged mitochondria or their parts undergo autophagy, thereby triggering MSCs for mitochondrial transfer to rescue injured cells (55,171). The activation of autophagy enhances the formation of TNTs in MSCs, which is essential for the mitochondrial transfer process (212). Autophagy also activates the expression of HO-1, a cytoprotective enzyme, and increases mitochondrial biogenesis in MSCs through the regulation of peroxisome proliferator-activated receptor gamma coactivator-1-α and mitochondrial transcription factor A expression (55). These data suggest that the degradation of external mitochondria within MSCs by autophagy is a key trigger of mitochondrial transfer. Doxorubicin-induced injured cardiomyocytes also exhibit an increased expression of TNF-α, which stimulates the formation of TNTs in MSCs (47). Similar to doxorubicin, cells treated with hydrogen peroxide (H_2O_2) were also shown to be rescued by MSCs (55). In fact, the overproduction of ROS in mitochondria has been demonstrated as a severe signal of cellular stress (88,213,214). OGD/reoxygenation causes ROS overproduction in injured cells, which stimulates the uptake of healthy mitochondria from MSCs (213,215). Additionally, high levels of abnormal ROS from oxidative stress can cause mitochondrial fragmentation, leading to mitochondrial transfer from MSCs (88). A previous *in vitro* study demonstrated that the inhibition of OXPHOS upregulated related adhesion promoters, a mechanism central to mitochondrial transfer from MSCs to acute myeloid leukemia (AML) cells (216). Specifically, under the pressure of chemotherapeutic OXPHOS inhibition, ROS levels increase, and the conversion of LC3-I to LC3-II occurs as a sign of autophagy. This process promotes MSCs to transfer mitochondria to OCI-AML3 cells (171,216). However, in the event that N-acetyl-L-cysteine (NAC) is used to decrease ROS production, the mitochondrial uptake in damaged cells is impaired (214,215). These data indicate that various stress signals are crucial for the mitochondrial transfer rescue effect mediated by MSCs.

The molecular mechanism of TNT formation involves Miro1, an outer mitochondrial membrane protein essential for mitochondrial transport and donation (217,218). Following the increased levels of Miro1 induced by oxidative stress, MSCs enhance their capacity for mitochondrial transfer through TNTs (47,55,88,219). *Miro1* deletion has been proven to inhibit MSC mitochondrial transfer and impair the microtubule movement of donated mitochondria (217,218). It should be noted that the expression of Miro1 and TNFαip2 are interrelated

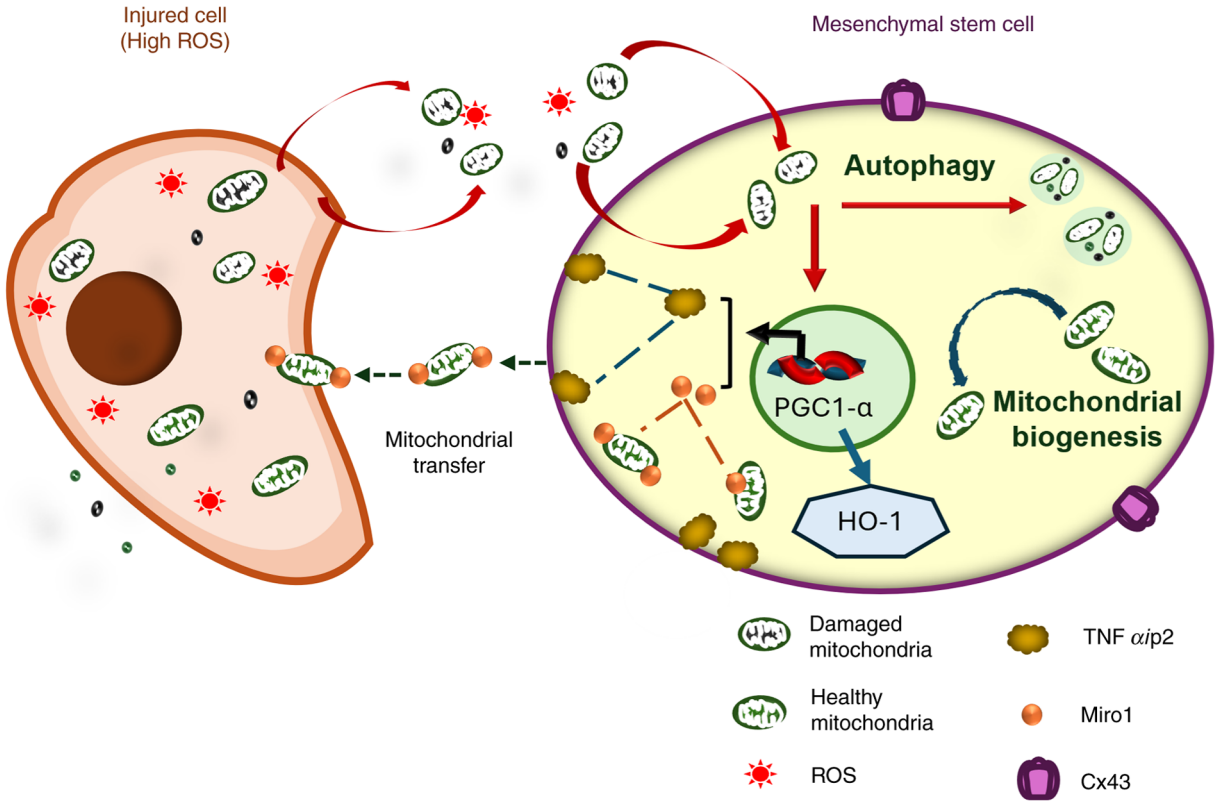

Figure 3. Mechanisms of MSC mitochondrial transfer rescue effects. Injured cells release damaged mitochondria or their components into the surrounding microenvironment as a distress signal. MSCs respond to these stress signals by activating the mitochondrial transfer mechanism via the upregulation of PGC1-α and the expression of HO-1. The expression of Miro1, TNFαip2 and Cx43 is also upregulated in MSCs to facilitate the transfer of healthy mitochondria to rescue stressed cells from damage. MSCs, mesenchymal stem cells; ROS, reactive oxygen species; PGC1-α, proliferator-activated receptor gamma coactivator-1-α; HO-1, heme oxygenase 1; Miro1, mitochondrial Rho GTPase 1; TNFαip2, TNF-α-induced protein 2; Cx43, connexin43.

in mitochondrial transfer (219). TNFαip2 is a marker of TNT formation that regulates intercellular interactions (114). TNF-α-induced oxidative stress causes significantly high *TNFαip2* expression (220). When *TNFαip2* is deleted in MSCs, the overexpression of *Miro1* also decreases mitochondrial transfer, and the control of ROS levels is impaired both *in vitro* and *in vivo* (217). *NF-κB* and *TNFαip2* overexpression increase ROS levels, which subsequently leads to TNTs formation, and NAC reverses this process by reducing ROS (47,114,221). Furthermore, there is an association between the phosphorylation of NF-κB and TNT formation inhibition (114,221,222). The expression of TNFαip2 is directly related to mitochondrial transfer capacity between cells through TNTs (219,220). The N- and C-terminal region of the TNFaip2 protein have different contributions to the remodeling of the MSC's plasma membrane to form TNTs (223).

Additionally, after receiving stimulation from injured cell signals, MSCs also promote cell-to-cell interactions and mitochondrial transfer capacity. Connexin 43 (Cx43) has been shown to be related to the transfer of mitochondria between cells (63,224). ROS overproduction caused by LPS in injured cells promotes the mitochondrial transfer from MSCs through Cx43 regulation (214). Cx43 knockdown in MSCs interrupts the mitochondrial transfer from MSCs to injured chondrocytes (63,225). In the event that MSCs upregulate Cx43 expression by iron oxide nanoparticles, the mitochondrial transfer ability of MSCs will be enhanced (226). On the other hand, various mechanisms can be utilized by other cells, particularly cancer cells, to steal mitochondria from their neighboring cells in the microenvironment (227-231); however, these mechanisms have not been implicated in the MSC-mediated mitochondrial rescue pathway. Questions remain as to whether these mechanisms exist between MSCs and other cells.

4. Fates of donated mitochondria in host cells

There are two separate fates for donated exogenous mitochondria once internalized inside recipient cells: Integration into the host mitochondrial network or degradation through mitophagy and autophagy processes. Within the host cells, exogenous mitochondria can fuse with the host mitochondrial network, and this fusion can occur via different mechanisms across various types of cells (232-234). This process is associated with the expression of mitofusin (MNF)1, MNF2 and optic atrophy 1 (OPA1) (235). Under oxidative stress conditions, cells downregulate the expression of these mitochondrial fusion proteins, particularly MFN1 and OPA1 (232). In the majority of cases, this downregulation is affected by the presence of exogenous mitochondria. A previous study demonstrated that following exogenous mitochondrial transplantation, the recipient cells contained nearly 12% mtDNA from donor cells after 24 h (171). Notably, this exogenous mtDNA cannot be detected on day 7. Lysosomes of host cells

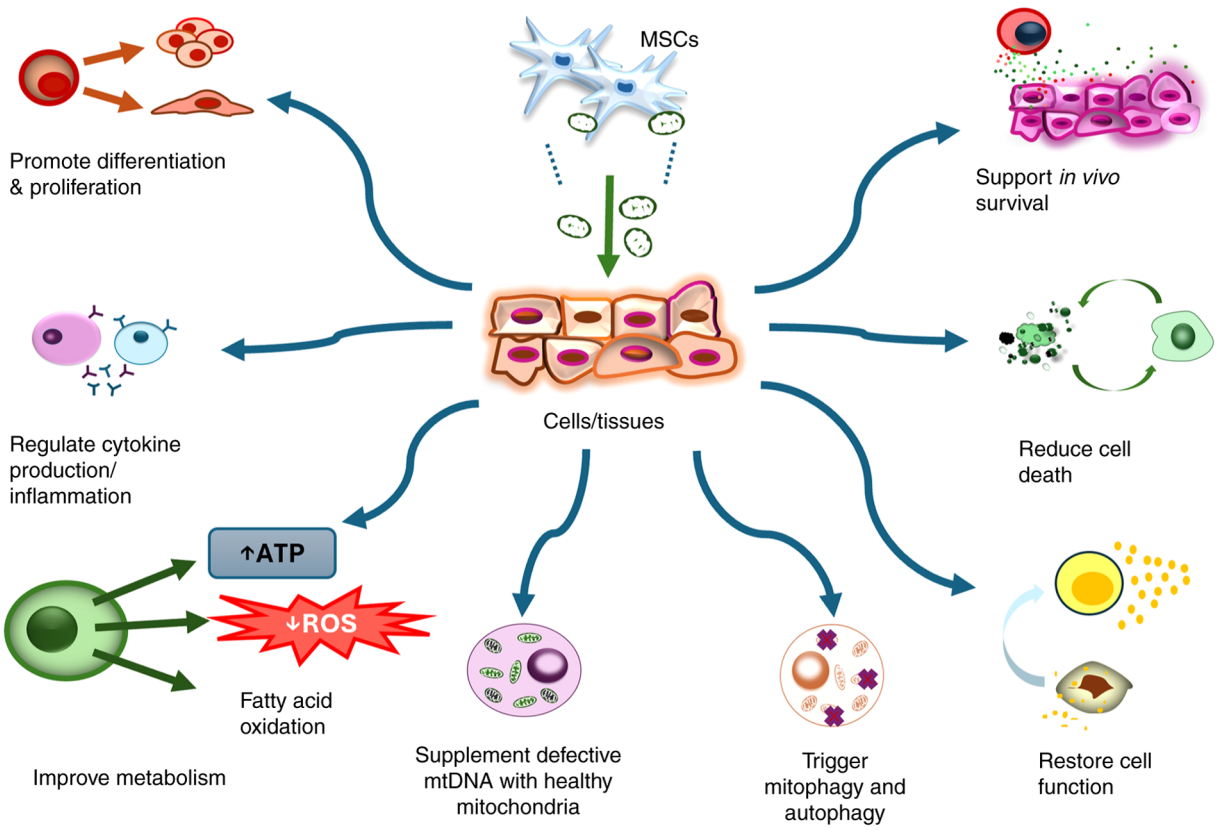

Figure 4. Regenerative mechanism in mitochondrial therapy using MSCs. Cells or tissues receiving mitochondria from MSCs exhibit improvement and restoration in several aspects. The supplementation with healthy mitochondria from MSCs can directly replace defective mtDNA and improve metabolism and fitness, supporting ATP generation and ROS reduction. As mitochondrial biogenesis improves in recipient cells, cell survival is significantly enhanced, particularly *in vivo*, thereby restoring cell and tissue function. Cells that received donated mitochondria from MSCs showed enhanced differentiation and proliferation, simultaneously reducing apoptosis. Mitochondria supplementation also helps to regulate the immune response and cytokine secretion, resulting in positive outcomes. The degradation of internalized mitochondria further activates mitophagy and autophagy in recipient cells, thereby indirectly regulating cellular homeostasis and improving cell function. MSCs, mesenchymal stem cells; mtDNA, mitochondrial DNA; ROS, reactive oxygen species.

degrade parts of exogenous mitochondria (232,233,235). On the other hand, it has been shown that at ~6-12 h following transplantation, exogenous mitochondria enter the autophagy process in host cells (171). There is evidence to indicate that donated mitochondria from MSCs inside endothelial cells undergo mitophagy mediated by the PINK1-Parkin pathway, which facilitates biogenesis in the recipient cells and enhances their engraftment *in vivo* (171). Future research is warranted to elucidate the precise mechanisms through which host cells take up and regulate the use of exogenous mitochondria within their cytoplasm.

5. Conclusion and future perspectives

Mitochondrial transfer and transplantation appear to be an innovative and promising tool for targeting mitochondria-related pathological conditions (25,236-238). However, identifying a qualified and ready-to-use source of mitochondria has been a challenge for clinical translation. Difficulties in obtaining mitochondrial sources can limit the reproducibility of the approach, increase the need for invasive procedures in patients, and hinder the quality control of the transplanted mitochondria. In clinical trials, ready-to-use mitochondria may help to improve the feasibility and efficacy of their application, ensuring timely treatment (239). A recent study demonstrated that storable human mitochondria, as a ready source of exogenous mitochondria, are effective in a mouse model of Leigh syndrome (240). Thus, a stable and quality source of mitochondria is key to the success of mitochondrial transplantation. In this context, MSCs have emerged as potential donors of mitochondria in mitochondrial therapy, and preclinical data indicate that their use is effective across a range of cell types, diseases and conditions. A summary of recipient cell types receiving mitochondrial transfer from MSCs is presented in Table I. However, although the exact mechanisms underlying tissue regeneration through mitochondrial transfer are not yet fully understood, it is proposed to involve several rescuing effects (Fig. 4).

Despite this promising application, it should be noted that mitochondrial transfer and transplantation may also pose significant health risks in the case of misuse. Mitochondrial therapy, whether utilizing mitochondria from MSCs or other cell types (both autologous or allogenic), may encounter various challenges, including the acceleration of the immune response and the promotion of tumor metastasis (241-243). For instance, allogenic mtDNA has been shown to accelerate the innate immune response in mice (244), and even in cases of autologous transplantation, an mtDNA mutation in the cells of the donor could elicit an immune response that is dependent on host major histocompatibility complex (245). Although

allogenic mitochondrial transplantation has been shown in several studies, it is important to understand the mechanism and effects of the treatment, and screening for mtDNA is crucial to ensure safety in clinical applications. In addition, several ethical questions have also been raised, primarily in the field of assisted reproductive technology, concerning the retention of exogenous mitochondria and the potential for mtDNA/nuclear DNA mismatch within host cells (243,246,247). Given the relevance of these issues in other clinical applications, further research is required to clarify the mechanisms of exogenous mitochondrial interaction with the host cells and determine the effective dosages for different cases. Furthermore, optimizing the procedures and routes of application for specific pathological conditions is crucial to enhance the accessibility of this technique in diverse clinical settings.

Although challenges persist, progress has been achieved to improve the safety and broad application of mitochondrial transfer and transplantation. Firstly, research has focused on optimizing the cellular uptake of exogenous mitochondria through various techniques of artificial transplantation (Fig. 1B). These technologies focus on improving mitochondrial permeabilization across the cell membranes by utilizing both mechanical forces and penetrating peptides. While none of these methods are currently suitable for clinical application, ongoing efforts are focused on refining existing techniques and developing new materials and technologies. Current approaches, however, have successfully achieved mitochondrial transplantation into isolated cells. This success holds promise for improving cell function in therapeutic areas, such as stem cell and immune cell therapies. Furthermore, research is being conducted to understand the mechanism of intercellular mitochondrial transfer, aiming to enhance the rescue of damaged cells in *in vivo* settings (248). For instance, stimulating mitochondrial transfer from MSCs, such as enhancing the formation of TNT, increasing the secretion of EVs, and promoting cell fusion, could be advantageous for multiple applications. Most importantly, future research is required to verify the effectiveness of different stem cell types and their culture conditions, while clarifying and defining appropriate mitochondrial quality measures. With the current progress, it is expected that MSCs will provide a cell source for mitochondrial transplantation, offering a new approach to regenerative medicine and adding an essential element to stem cell therapy.

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Authors' contributions

CMT was involved in the conceptualization of the study, in the preparation of the figures, and in the writing of the original draft of the manuscript. VTTN was involved in the conceptualization of the study, in the preparation of the figures visualization, in the writing of the original draft of the manuscript, and in the writing, reviewing and editing of the manuscript. Both authors have read and confirmed the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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