Trends in
Molecular Medicine

CellPress

Review

Targeting mitochondrial transfer as a promising therapeutic strategy

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Despite the primary impression of mitochondria as energy factories, these organelles are increasingly recognized for their multifaceted roles beyond energy production. Intriguingly, mitochondria can transfer between cells, influencing physiological and pathological processes through intercellular trafficking termed 'mitochondrial transfer.' This phenomenon is important in maintaining metabolic homeostasis, enhancing tissue regeneration, exacerbating cancer progression, and facilitating immune modulation, depending on the cell type and microenvironment. Recently, mitochondrial transfer has emerged as a promising therapeutic target for tissue repair and antitumor therapy. Here, we summarize and critically review recent advances in this field. We aim to provide an updated overview of the mechanisms and potential therapeutic avenues associated with mitochondrial transfer in various diseases from the perspective of different donor cells.

Highlights

Mitochondrial transfer plays a crucial role in metabolic homeostasis, tissue regeneration, cancer progression, and immune modulation.

Mesenchymal stem/stromal cells are key donor cells in mitochondrial transfer, providing therapeutic benefits in neurological, cardiovascular, and respiratory diseases.

Cancer cells hijack mitochondria from surrounding cells, contributing to tumor growth, invasion, and chemotherapy resistance.

Artificial mitochondrial transfer/transplantation and stem cell-mediated mitochondrial transfer show promise in preclinical and clinical settings.

An overview of mitochondria and mitochondrial transfer

Mitochondria, membrane-bound organelles found in almost all eukaryotic cells, are well-documented for producing energy through cellular respiration and regulating various cellular metabolic processes. The function of mitochondria can be traced back to their evolutionary origins approximately 1.5 billion years ago, derived from an ancient **endosymbiosis** (see Glossary), where *Proteobacteria* were engulfed and integrated to support energy production and cellular metabolism [1,2]. Mitochondria are widely acknowledged as biosynthetic hubs crucial for generating nucleotides, fatty acids, amino acids, cholesterol, heme, etc., while also maintaining redox homeostasis [3]. Beyond energy production and cellular metabolism, these organelles are critically involved in cell signaling, aging, differentiation, immune responses, and cancer progression [4,5]. To fulfill diverse functions, mitochondria exhibit dynamic behavior characterized by continuous processes such as fission, fusion, mitophagy, and interactions with other organelles. This dynamic nature is essential for maintaining optimal mitochondrial efficiency and enabling cellular adaptation to ever-changing metabolic demands.

Mitochondria provide the capacity for aerobic respiration, the creation of the eukaryotic cell, and eventually complex multicellular organisms [2]. During mammalian evolution, mitochondria adapted to meet the diverse energy demands of different species. Notably, endothermic species developed specialized mitochondrial functions to support high metabolic rates required for thermoregulation and sustained activity [6]. These adaptations were crucial for the metabolic flexibility that allowed mammals to thrive in various environmental conditions. Since cells cannot survive without an energy supply, the replacement of their engines, mitochondria, seems to be the most efficient way to revitalize exhausted cells [7,8]. Indeed, researchers first observed the transport of organelles between mammalian cells in 2004 [9]. In 2006, researchers presented *in vitro* evidence of **mitochondrial transfer** from **mesenchymal stem cells (MSCs)** to mammalian

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somatic cells [2], and in 2015 researchers provided *in vivo* evidence for this phenomenon using syngeneic mouse models of cancer [10]. Since then, a growing body of evidence has revealed that mitochondrial function can transcend cellular boundaries through the intercellular trafficking of intact mitochondria and/or mitochondrial DNA (mtDNA). Nowadays, mitochondrial transfer has represented one of the most fascinating discoveries in relevant fields, which can be achieved through various modes and routes (Box 1). Researchers have realized that intercellular mitochondrial trafficking is implicated in plenty of scenarios, including maintaining mitochondrial quality and quantity [11], thereby supporting cell survival and tissue homeostasis under various physiological and pathological conditions [1,7,8]. Additionally, the outcomes of mitochondrial transfer vary considerably, depending on donor cell types and their surrounding milieu. Among different donors, stem cells – especially MSCs – have been studied most extensively and have emerged as key players in mitochondrial transfer [7,8].

In this review, we aim to integrate the latest biological insights and findings on the mechanisms and functions of intercellular mitochondrial transfer from the perspective of various donor cells (see Table S1 in the supplemental information online), underscoring its potential as a promising therapeutic strategy for tissue regeneration and the treatment of various diseases. This review

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Box 1. Modes and routes of mitochondrial transfer

Common modes and routes are outlined in Figure I.

Extracellular vesicles

EVs facilitate mitochondrial transfer between various cells or even different tissues [110] and serve as an alternative approach for maintaining mitochondrial quality control when lysosomal function is impaired [111]. Specifically, different types of mitochondria-containing EVs, collectively termed 'mitoEVs' [98], are generated and released through different mechanisms. For instance, mitochondria-containing microvesicles are formed by budding and shedding from the plasma membrane, motivated by the interaction between ARRDC1 [24], while mitochondria-containing apoptotic vesicles are generated during apoptosis, with phosphatidylserine externalization and annexin V positivity [112].

Gap junctions

Gap junctions are channels joining the cytoplasm of adjacent cells, formed by transmembrane proteins called 'connexins' (CXs), with CX43 being a major participant in mitochondrial transfer [104,113–118]. Gap junction-mediated mitochondrial transfer contributes to regenerative effects in various disease models. Researchers have shown interactions between mitochondria and gap junction plaques or annular gap junction vesicles, one of the most prominent cytoplasmic CX43-containing structures [116]. Using 3D electron microscopy and immunogold labeling of CX43, researchers have observed mitochondrial transfer processes mediated by CX43 *in vivo* [115].

Tunneling nanotubes

As one of the most popular routes of mitochondrial transfer, TNTs can be generated by multiple cells, including neurons, epithelial cells, and most immune cells [7,8,20,29,105,119]. To date, two mechanisms for TNT formation have been proposed: cell dislodgement and filopodial interplay. In the former, a membrane thread remains when two connected cells begin to separate, eventually developing into a TNT structure. In the latter, cells extend filopodia toward neighboring cells, which are subsequently transformed into TNTs. Several regulators of TNT formation have been identified, including mitochondrial Rho GTPase 1 (MIRO1) [31,120], melatonin [93,121,122], and growth-associated protein 43 [83]; however, none of them are specifically targeted for intercellular mitochondria transportation [1,121].

Others

Cell fusion and free mitochondria release are less common but notable forms of mitochondrial transfer [1]. Cell fusion involves merging plasma membranes and sharing cytosolic components, often triggered by injury, inflammation, or malignancy. Recently, we found that mitochondrial transfer through cell fusion could fuel cancer progression [20]. Besides, free mitochondria have been detected in mouse and human blood, relying on mitochondrial fission proteins [1,123], which are later captured via endocytosis or micropinocytosis [124], although they are sometimes nonfunctional [125]. Additionally, studies have shown that mitochondria can be transferred through synaptosomes and dendritic networks [16,126–129].

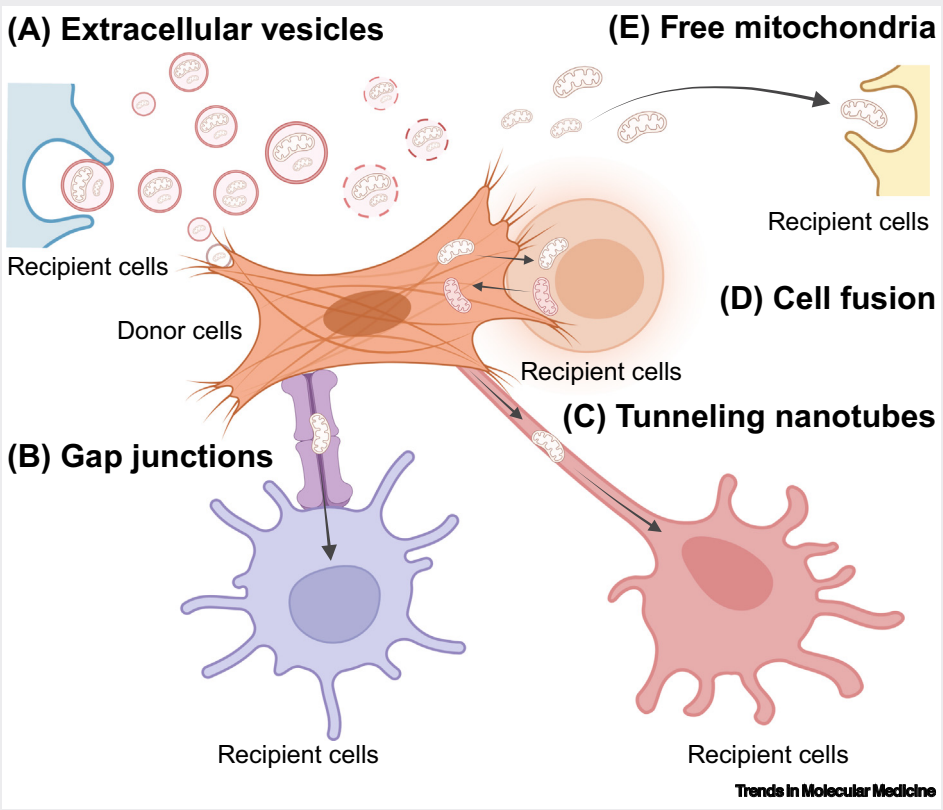

Figure I. Common modes and routes of mitochondrial transfer. Mitochondria can be packaged into extracellular vesicles and transported to other cells (A). Also, mitochondrial transfer can be achieved through transient direct cell–cell contact, such as gap junctions (B) and tunneling nanotubes (C). Moreover, cell fusion (D), free mitochondria release (E), synaptosomes, and dendritic networks are also employed for mitochondrial trafficking, although less commonly. Figure created using BioRender.

is timely and important because mitochondrial dysfunction is implicated in many pathological conditions. An in-depth understanding of intercellular mitochondrial transfer will shed light on innovative treatment approaches. As such, this review contributes to advancing regenerative medicine and mitochondria-based therapies.

Potential triggers leading to mitochondrial transfer

Mitochondrial transfer is usually initiated by distress signals from injured recipient cells, typically characterized by their intracellular reactive oxygen species (ROS) overload or mitochondrial dysfunction within these cells [7,12–15]. Recent studies also have shown that ADP released from stressed cells triggers mitochondrial transfer [16]. Because of limited experimental evidence, only highly potential triggers are discussed below, including ROS, dysfunctional mitochondria and their components, and ADP.

ROS

ROS are highly reactive chemicals formed as by-products during mitochondrial electron transport when diatomic oxygen (O_2) undergoes partial reduction. During mitochondrial respiration, electron leakage in the electron transport chain, particularly at complexes I and III, can reduce O_2 to produce a superoxide anion ($O_2^{\bullet-}$). Under pathological conditions, injured cells produce

Glossary

Alveolar macrophages: also known as dust cells, located in the lumens of airways and the lung alveoli, playing a role in pathogen defense and inflammatory responses.
Endosymbiosis: the incorporation and residence of one organism, the endosymbiont, inside the other, the host, recognized as a primary force in eukaryotic cell evolution. Here, it refers to the original internalization of prokaryotes by an ancestral eukaryotic cell, resulting in the formation of mitochondria. Another well-known example is chloroplasts in plant cells.
Extracellular vesicles (EVs): lipid-bilayer enclosed vesicles, typically ranging in size from 30 to 3000 nm, including exosomes, microvesicles, migrasomes, exophers, apoptotic bodies, and others. EVs carry proteins, lipids, nucleic acids, metabolites, and organelles.
Mesenchymal stem cells (MSCs): also referred to as 'mesenchymal stromal cells,' representing a highly heterogeneous population of stem cells located within the perivascular niche of various tissues such as the bone marrow, contributing to tissue development and homeostasis. MSCs are characterized by colony-forming ability, capacity for self-renewal, and multilineage differentiation potential.
Mitochondrial fragmentation: a hallmark of mitochondrial stress that isolates damaged mitochondria for removal via mitophagy.
Mitochondrial transfer: mitochondria usually segregate during cell division and differentiation, passing directly from parent to daughter cells along with their mitochondrial DNA (mtDNA) through a process known as 'vertical inheritance.' However, some cells can transfer their mitochondria to developmentally unrelated cells, a phenomenon termed 'intercellular or horizontal mitochondrial transfer.' In this review, mitochondrial transfer explicitly refers to intercellular or horizontal mitochondrial transfer.
Neutrophil extracellular traps: weblike structures composed of extracellular DNA and antimicrobial proteins, formed by neutrophils as a defense mechanism.
ROS-induced ROS release: an initial burst of ROS triggers further mitochondrial dysfunction, resulting in increased ROS production and even spreading damage to neighboring mitochondria.

excessive ROS that cannot be effectively neutralized by intracellular antioxidant systems, resulting in ROS overload and oxidative damage. Stress-induced ROS tend to trigger intercellular mitochondrial transfer [7,13–15]. For instance, the accumulation of ROS in hematopoietic stem cells (HSCs) induced by bacterial infection activated phosphoinositide 3-kinase (PI3K) signaling and facilitated horizontal mitochondrial transfer from MSCs to HSCs [15].

Besides, excessive ROS usually lead to mitochondrial dysfunction, representing another trigger of mitochondrial transfer. First, superoxide anion may trigger the opening of the mitochondrial permeability transition pore (mPTP). The prolonged opening of mPTP disrupts mitochondrial membrane potential and alters intra- and intermitochondrial redox states, causing a positive feedback loop known as '**ROS-induced ROS release**' [17]. Second, high ROS levels reduce mitochondrial complex I activity and stimulate the ubiquitination of mitofusins such as MFN1 and MFN2, leading to **mitochondrial fragmentation** [4]. Third, ROS overload suppresses the transcription of mitochondrial transcription factor A (TFAM) and promotes its degradation, causing mtDNA instability and damage, which exacerbates mitochondrial dysfunction [4,18]. The following section discusses dysfunctional mitochondria and their components as potential triggers for mitochondrial transfer.

ADP

Recently, researchers uncovered that ADP, when released from stressed cells, acts as a signaling molecule that facilitates mitochondrial transfer to the recipient cells [16,19]. Specifically, within the osteocyte dendritic network, osteocytes respond to distress signals in the form of ADP, subsequently triggering horizontal mitochondrial transfer through dendrites [16,19]. The recipient cell receiving the mitochondria detects the ADP molecules via purinergic P2Y2 and P2Y6 receptors on its plasma membrane [16,19]. This process helps osteocytes undergoing bioenergetic crisis restore their mitochondrial dysfunction, leading to the normalization of mitochondrial respiration and the recovery of physiological status [16,19]. Notably, the mechanism is further validated as the absence of these receptors blocks intercellular mitochondrial trafficking [16,19]. Thus, ADP has unequivocally been documented as a molecular trigger of horizontal mitochondrial transfer.

Dysfunctional mitochondria and their components

Researchers have found that mitochondrial dysfunction in recipient cells acts as a prerequisite for mitochondrial transfer [20], attributed to several potential mechanisms. First, injured cells release damaged mitochondria as 'rescue me' signals to alert nearby donor cells [7,12]. For instance, in a coculture system of MSCs and distressed somatic cells, mitochondria from injured somatic cells are engulfed and degraded by MSCs [12]. This process, known as **transmitophagy**, triggers heme release and the production of heme oxygenase-1 (HO-1) in mitochondrial donor cells [12]. HO-1 overexpression can promote the expression of nuclear respiratory factor 1 (NRF1) and its coactivator, peroxisome proliferator-activated receptor γ coactivator 1 (PGC1α), which induces TFAM expression and initiates mitochondrial biogenesis and the restoration of mitochondrial function [12]. Moreover, HO-1 has been shown to inhibit the expression of the translocase of outer mitochondrial membrane 20, a protein critically involved in mitochondrial fission and quality control [21]. Thus, damaged mitochondria stimulate mitochondrial biogenesis in donor cells, after which the newly generated functional mitochondria are transferred to rescue stressed cells.

Second, mitochondria and their components, such as mtDNA, can act as damage-associated molecular patterns (DAMPs) [4,7] because of their bacterial ancestry [1,2], contributing to transmitting distress signals and inducing mitochondrial transfer [8]. When released into the cytoplasm or extracellular space, these DAMPs can provoke proinflammatory responses by interacting with pattern recognition receptors, including Toll-like receptors (TLRs) and cyclic GMP-AMP synthase

Transmitophagy: a process whereby damaged mitochondria are transferred from one cell to another, typically from neurons to neighboring astrocytes for degradation via mitophagy. Transmitophagy is crucial in preventing mitochondrial dysfunction.
Tunneling nanotubes (TNTs): F-actin-based membranous protrusions that connect distant cells, supporting the exchange of cytoplasmic factors and organelles. TNTs range from 0.05 to 1.5 μm in diameter.
Warburg effect: the observation that most cancers use aerobic glycolysis for energy production, even in the presence of oxygen, rather than oxidative phosphorylation.

(cGAS)-stimulator of interferon genes (STING) pathway, triggering proinflammatory immune responses, thereby transferring and further amplifying the injury response. Innate immune cells, such as natural killer and dendritic cells, can target cells containing allogeneic mtDNA [22]. Such mitochondria-dependent inflammatory responses are closely associated with intercellular mitochondrial transfer [23,24]. Supporting this idea, MSCs under oxidative stress secrete arrestin domain-containing protein 1 (ARRDC1)-mediated **extracellular vesicles (EVs)** containing defective mitochondria, then are engulfed by macrophages; meanwhile, MSCs release microRNA-containing EVs that inhibit macrophage activation and modulate TLR signaling, fostering immune tolerance toward the transferred mitochondria [24]. Besides, mitochondria transferred from osteocytes to metastatic cancer cells have been found to activate the antitumor response via the cGAS-STING pathway. Inhibition of mitochondrial transfer, achieved by osteocyte-specific depletion of mitochondrial Rho GTPase 1 or MFN2, reduces tumor immunogenicity and promotes malignant progression, highlighting the role of mitochondrial transfer in immune responses.

Therapeutic potential of mitochondrial transfer from different cells

Dissecting mitochondrial transfer by cell type is vital for understanding how different cells influence tissue repair, immune responses, and disease progression (Table S1 in the supplemental information online). Here, we introduced common donor cells, including MSCs, cancer-associated fibroblasts (CAFs), T cells, macrophages, astrocytes, and others (Box 2). This perspective facilitates the development of targeted therapies for specific conditions, enhancing both precision and treatment outcomes.

Versatile functions of mitochondrial transfer from MSCs

MSCs, because of their multifaceted functions and easy accessibility [25], are the most extensively investigated donor cells capable of transferring mitochondria to various recipient cells [7,26,27] (Figure 1). Increasing evidence unravels the therapeutic potential of MSC-mediated mitochondrial transfer in various diseases [26,27], including neurological, cardiovascular, respiratory, and autoimmune diseases.

Neurological diseases often involve mitochondrial dysfunction, with MSC-derived mitochondrial transfer emerging as a promising approach to restore neural functions via metabolic rewiring and immune modulation. For example, in ischemic stroke, MSC transplant enhanced angiogenesis and reduced brain lesions and neurological deficits, with mitochondrial transfer observed both *in vitro* and *in vivo* [28–30]. Notably, pre-coculturing MSCs with neurons enhanced neuroprotection compared with native MSCs, implying that cytosol transfer may initiate or amplify mitochondrial transfer [28,31]. Additionally, MSC-derived mitochondrial transfer plays an important role in spinal cord injury recovery, reducing oxygen and glucose deprivation injury, promoting neural regeneration, and restoring locomotor function in rats [32,33].

Mitochondrial transfer also holds potential in cardiovascular diseases. In ischemic myocardium models, MSCs improve cardiac function, such as ejection fraction, by transferring mitochondria to cardiomyocytes [34]. In a preclinical study, mitochondria-rich EVs from stem cell-derived cardiomyocytes restored ATP production and cardiac function more effectively than free through PGC1α, using a murine myocardial infarction model, highlighting their role in cellular bioenergetics and regeneration [35].

In ophthalmic diseases, such as retinal ischemia and ganglion cell degeneration, MSC transplant could restore mitochondrial function, promoting cell survival and regeneration, potentially through mitochondrial transfer [36–39]. These findings suggest that leveraging mitochondrial transfer from

Box 2. Other donor cells of mitochondrial transfer

Intercellular mitochondrial transfer has been observed across various tissues. Other cell types also engage in this process, highlighting its widespread physiological and therapeutic significance [1,7,8].

Adipocytes

Under steady states, adipocytes transfer mitochondria to neighboring macrophages in white adipose tissue, a process disrupted in obesity [130]. Impairing this transfer through genetic deletion of *Ext1*, the heparan sulfate biosynthetic gene, in myeloid cells leads to fat accumulation and reduced energy expenditure [130]. Under energetic stress, such as chronic obesity, adipocytes package damaged mitochondria into EVs and release them into the circulation, where they integrate into cardiomyocytes, causing ROS bursts but also preconditioning the heart against ischemia-reperfusion injury [110]. Furthermore, dietary factors can shift adipocyte-derived mitochondrial transfer from macrophages to the circulation, with long-chain fatty acids inhibiting local transfer [131]. In brown adipose tissue, adipocytes eject damaged mitochondria via EVs for macrophage clearance, ensuring thermogenesis efficiency [132].

Bone-related cells

Mitochondrial transfer between osteolineage cells and other cells contributes to maintaining skeletal homeostasis. Most recently, researchers found that osteolineage cells transfer mitochondria to myeloid cells, inhibiting their commitment toward osteoclasts and activating ferroptosis, a process mediated by MIRO1 in osteolineage [120]. Besides, disruption of this transfer leads to osteoporosis in animal models, highlighting its role in skeletal health [120]. Moreover, mitochondria can transfer within osteocytes or from osteocytes to ECs [128,133], improving transcortical angiogenesis and reducing ROS stress, potentially via the sphingolipid pathway [133]. Notably, in the context of bone metastasis, osteocytes transfer mitochondria to metastatic cancer cells, activating the cGAS-STING pathway to enhance antitumor response [23].

Other cells

Various other cell types participate in mitochondrial transfer. Airway smooth muscle cells can exchange mitochondria partially via EVs as a homeostatic mechanism for modulating bioenergetics and cellular function within the airways [134]. Cardiomyocytes and erythroblasts eject dysfunctional mitochondria to macrophages as an alternative mitochondrial clearance mechanism [117,135]. Moreover, platelets transfer functional mitochondria to cancer cells, leading to their metabolic reprogramming to a metastatic state [136]. In bone marrow transplants following irradiation, HSCs and hematopoietic progenitors transfer mitochondria to the host's stromal cells via CX43, aiding bone marrow regeneration and hematopoietic engraftment [118]. Most recently, researchers have observed some transfer events occurring within cancer cells, such as glioblastoma and hepatocellular carcinoma [137,138]. Overall, mitochondrial transfer across different cells underscores the universality and therapeutic potential of this phenomenon in various pathophysiological processes.

MSCs could enhance recovery in tissues with limited regenerative capacity, such as neural and cardiac tissues [30,32–37,40].

MSC-mediated mitochondrial transfer is essential for immunomodulation, particularly in respiratory diseases such as acute lung injury (ALI) and asthma. In ALI models, MSCs transfer mitochondria to alveolar epithelial cells through connexin 43 (CX43)-containing gap junctions, EVs, and **tunneling nanotubes (TNTs)**, restoring cellular energy metabolism and modulating inflammatory responses, whereas inhibiting CX43 in MSCs abolishes these treatment effects [41]. Similar mechanisms are seen in asthma, where MSC-derived mitochondrial transfer to bronchial epithelial cells alleviated airway inflammation through CX43-mediated TNT formation [42]. More recently, mitochondrial transfer from MSCs was shown to mitigate pulmonary fibrosis in mice through CX43-containing gap junctions, which can be augmented by iron oxide nanoparticles (IONPs) [43,44]. Furthermore, MSC-mediated mitochondrial transfer through EVs could alter **alveolar macrophage** phenotypes, enhancing their anti-inflammatory and phagocytic functions, and promoting tissue regeneration [45,46]. In autoimmune diseases, mitochondrial transfer from MSCs is associated with enhanced regulatory T cell activation, inducing higher expression of FOXP3, IL2RA, CTLA4, and TGF-β1, thus contributing to suppressing immune responses and maintaining immune tolerance [47]. MSC-mediated immune suppression also involves repressing T helper type 1 (Th1) and Th17 cells [48,49].

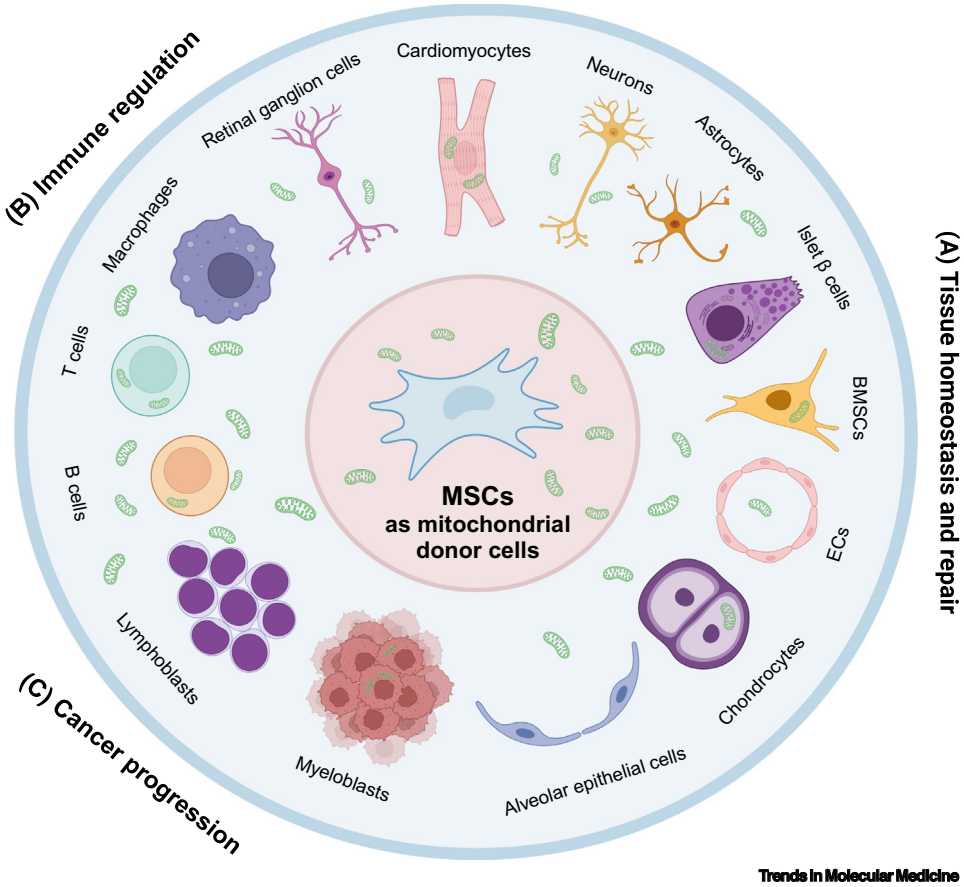

Figure 1. Different recipient cells and versatile functions of MSC-mediated mitochondrial transfer. Mitochondrial transfer from MSCs exhibits versatile functions due to different recipient cell types, such as facilitating tissue homeostasis and repair, immune regulation, and cancer progression. (A) MSCs facilitate tissue homeostasis and repair and resistance to oxidative stress by transferring mitochondria to injured cells such as cardiomyocytes, neurons, and alveolar epithelial cells. (B) Mitochondrial transfer from MSCs to immune cells displays immunoregulatory effects and is implicated in autoimmune diseases. (C) In cancers, malignant cells hijack mitochondria from MSCs to relieve oxidative stress caused by chemotherapy and boost cancer progression. Abbreviations: BMSCs, bone marrow stromal cells; ECs, endothelial cells; MSCs, mesenchymal stem cells. Figure created using BioRender.

In response to acute bacterial infection, mitochondria are transferred from MSCs to HSCs, inducing a metabolic shift from glycolysis to oxidative phosphorylation (OXPHOS), supporting rapid HSC activation and leukocyte expansion [15]. This intercellular mitochondrial transfer is mediated by ROS-induced oxidative stress and activation of PI3K signaling [15]. Intriguingly, mitochondria trafficking from MSCs happens even before HSCs initiate their own mitochondrial biogenesis program [15]. Taken together, these findings indicate that MSC-mediated mitochondrial transfer is an efficient strategy for regulating immune homeostasis under inflammatory and autoimmune conditions.

While MSC-mediated mitochondrial transfer benefits tissue regeneration and immune modulation, it also implicates cancer progression [50–56]. MSCs can transfer mitochondria to tumor cells, supporting their high metabolic demands and chemotherapy resistance. For instance, in B-cell acute lymphoblastic leukemia (B-ALL), chemotherapy-induced oxidative stress activates MSCs into a CAF phenotype, prompting them to donate mitochondria to B-ALL cells and rescue cancer cells from apoptosis [51]. In acute myeloid leukemia (AML), mitochondrial transfer from

MSCs through TNTs enables tumor cells to sustain OXPHOS, a primary metabolic process for ATP generation in AML [52], albeit that such metabolism is less common than the '**Warburg effect**' seen in most cancers. This transfer can be enhanced by oxidation phosphorylation inhibitors or certain chemotherapeutics, such as cytarabine, and reduced by daratumumab, an anti-CD38 monoclonal antibody [52,57,58]. Similarly, mitochondrial transfer via TNTs is associated with CD38 expression in multiple myeloma, which may contribute to tumor survival and sustained growth [53].

Collectively, these findings indicate that MSC-mediated mitochondrial transfer, while supporting tissue homeostasis, regeneration, and immunomodulation, can also enhance cancer cell survival, proliferation, and invasion, representing a double-edged sword in therapeutic applications.

Mitochondria transferred from CAFs boost cancer progression

CAFs are pivotal components of the tumor stroma, facilitating cancer progression through reciprocal interactions with cancer cells. Fibroblasts or CAFs undergo metabolic alterations in response to oxidative stress induced by cancer cells, leading to mitochondrial dysfunction and enhanced glycolysis [20,51,59–61]. In turn, fibroblasts or CAFs provide cancer cells with metabolites that fuel their progression. Furthermore, CAFs transfer intact mitochondria or mtDNA to cancer cells, a process linked to increased tumor invasion and resistance to chemotherapy [51,61–63] (Figure 2).

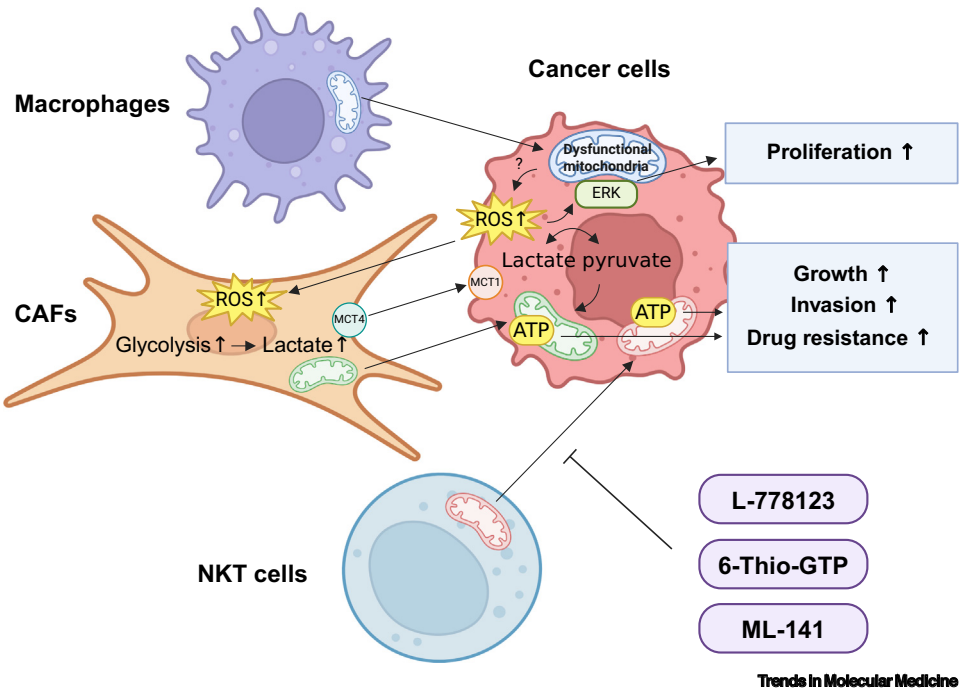

Figure 2. Mitochondria transferred from CAFs and immune cells boost cancer progression. Cancer cells hijack mitochondria from CAFs and immune cells to support their high metabolic demand for growth, proliferation, invasion, and chemotherapy resistance. Macrophages transfer dysfunctional mitochondria to cancer cells, causing ROS accumulation and activating ERK signaling for cell proliferation. Cancer cells induce oxidative stress in CAFs, causing mitochondrial dysfunction and increased aerobic glycolysis; in return, lactate transported from CAFs to cancer cells to MCT fuels energy production in cancer cells. Meanwhile, mitochondrial transfer from CAFs to cancer cells further supports mitochondrial respiration and boosts cancer progression. Besides, cancer cells acquire mitochondria from NKT cells through TNTs, supporting their metabolism. Pharmacological inhibitors, such as ML-141 (inhibits CDC42), 6-thio-GTP (inhibits RAC1), and L-778123 (inhibits FPTase and GGPTase-I), reduce TNT formation and mitochondrial transfer from NKT to cancer cells. Abbreviations: CAFs, cancer-associated fibroblasts; MCT, monocarboxylate transporter; NKT cells, natural killer T cells; ROS, reactive oxygen species. Figure created using BioRender.

In prostate cancer, mitochondrial transfer from CAFs fosters cancer cell respiration and invasiveness in a lactate-dependent manner [61]. Blocking the lactate transporter monocarboxylate transporter 1 (MCT1) hinders this transfer, highlighting its critical role in cancer progression [61]. Similarly, in breast cancer, CAFs transfer free mtDNA through EVs or TNTs, promoting cancer cell metabolic activities and resistance to hormone therapies [62,64]. CAF-mediated mitochondrial transfer has also been observed in other cancers, such as B-ALL and lung cancer, contributing to cancer metastasis and chemotherapy resistance [51,63]. These findings underscore the potential of targeting CAF-medicated mitochondrial transfer in tumor growth, metastasis, and therapy resistance, although the underlying molecular mechanisms await further investigation.

Mitochondrial transfer from innate and adaptive immune cells

Both innate and adaptive immune cells, such as macrophages and T cells, engage in intercellular mitochondrial transfer, affecting cellular metabolism, tissue homeostasis, and disease outcomes.

Macrophages, typically responsible for digesting dysfunctional mitochondria to maintain homeostasis, can also donate mitochondria in pathological contexts. In osteoporosis, macrophages with an M1-like phenotype transfer mitochondria to MSCs, inducing ROS bursts that impair the osteogenic differentiation of MSCs [65]. Conversely, M2-like macrophages facilitate the resolution of inflammatory pain through transferring mitochondria to sensory neurons, mediated by the CD200 receptor (CD200R) on macrophages and its noncanonical ligand iSEC on sensory neurons [66]. In chronic heart failure and hypertension, macrophages are recruited to the heart and deliver mitochondria to cardiomyocytes, causing injury through ferroptosis via glutathione metabolism dysregulation and lipid peroxidation [67]. In the tumor microenvironment, tumor-associated macrophages transfer dysfunctional mitochondria to cancer cells, triggering ROS production, activating extracellular signal-regulated kinase signaling, and promoting cancer proliferation [68] (Figure 2). Besides, conditioned media from macrophages stimulate TNT formation and mitochondrial transfer *in vitro*, enhancing motility and epithelial-mesenchymal transition of pancreatic cancer cells [69].

T cells also transfer mitochondria to cancer cells, facilitating immune evasion. For example, natural killer T cells transfer mitochondria via TNTs, enhancing cancer cell basal respiration, spare respiratory capacity, and growth [70]. Recently, researchers developed a statistical deconvolution method called 'MERCI' to track and measure mitochondrial transfer between cancer and T cells, linking this process to increased cancer cell cycle activity and poor clinical outcomes in various cancers [71]. Hence, targeting mitochondrial hijacking might offer new avenues for developing next-generation immunotherapies.

Supportive roles of mitochondrial transfer from astrocytes

Astrocytes maintain neuronal health by promoting synaptogenesis, axonal growth, and metabolism in the central nervous system [72]. Mitochondrial transfer between astrocytes and neurons is bidirectional. When stimulated by acidosis, excitotoxicity, or oxidative stress, neurons release injured mitochondria into the extracellular space, signaling astrocytes for help [73]; in turn, astrocytes deliver healthy mitochondria to neurons, supporting their survival and plasticity [72,74,75]. Astrocyte-mediated mitochondrial transfer has been shown to ameliorate oxidative stress-damaged neurons in animal models of ischemic stroke [76].

This transfer depends primarily on CD38 [7,74,77–80]. For instance, ginsenoside RB1 can preserve astrocytic mitochondria and enhance their delivery to ROS-injured neurons via CD38 against ischemic insult [77]. Suppression of CD38 signaling reduced extracellular mitochondria transfer and worsened neurological outcomes [74]. Beyond neurons, astrocytes also support

microglia by transferring mitochondria and humanin, an mtDNA-encoded peptide, improving microglial phagocytosis and reducing inflammation, potentially beneficial for treating intracerebral hemorrhage [81]. Moreover, astrocytes transfer mitochondria to endothelial cells (ECs) to maintain the blood–brain barrier integrity during aging [82]. In glioblastoma, astrocytes transfer mitochondria to cancer cells via TNTs, upregulating metabolic pathways related to proliferation and tumorigenicity [83]. This process is regulated by the growth-associated protein 43, which facilitates intercellular connections. Astrocytes also receive mitochondria from glioblastoma cells, adopting a tumor-like metabolic profile and increasing resistance to hypoxia [84]. Notably, it was recently reported that microglia also play a supportive role by delivering healthy mitochondria to neurons, restoring neuronal dysfunction by reducing oxidative stress and normalizing gene expression [85].

Mitochondrial transfer-targeted strategies and therapies

Recent advances have highlighted the potential of artificial mitochondrial transfer/transplant (AMT/T) and stem cell-mediated mitochondrial transfer, focusing on replacing dysfunctional mitochondria to achieve functional tissue repair [86]. These strategies and therapies deliver healthy mitochondria to damaged cells, aiding recovery across various diseases (see Clinician's corner).

Artificial mitochondrial transfer/transplantation

AMT/T, pioneered by researchers in 1982 [87], involves extracting healthy mitochondria from tissues and then transplanting and replenishing them into damaged tissues, offering therapeutic effects by restoring cellular metabolism. The liver and skeletal muscle are vital sources of mitochondria because of their high metabolic activity [35,88,89]; meanwhile, platelets offer another abundant and easily accessible supply [90] (Figure 3).

Preclinical research has shown that AMT/T can significantly alleviate ischemia-reperfusion injuries in various tissues, including the brain, heart, liver, and kidney [18,35,91–95]. A proof-of-concept preclinical study has demonstrated that intramyocardial injection of mitochondria-rich EVs enhanced post-myocardial infarction cardiac function *in vivo* using murine models [35]. Moreover, AMT/T has shown beneficial effects in ischemia-reperfusion-injured peripheral muscles *in vivo* in mouse models [94]. A systematic review of animal and human studies confirmed the effects of AMT/T in treating such injuries, with improvements observed in tissue function and survival [96].

Beyond repairing ischemia-reperfusion injuries, AMT/T holds promise for treating cognitive impairments. Mitochondria acquired from human MSCs, administered nasally, improved cognitive deficits in mice with cisplatin-induced memory impairment, restoring white matter integrity and synaptic damage *in vivo* [92]. Similarly, platelet-derived mitochondria injected into the brain mitigated diabetes-related cognitive decline, with attenuated neuronal apoptosis and oxidative stress and decreased accumulation of amyloid-β and Tau in the hippocampus *in vivo* in diabetic mice [90].

However, there are significant differences among mitochondrial isolation, dosage, and administration methods. Recent preclinical research has shown MSC-derived EVs as an ideal AMT/T delivery system whose safety has been confirmed in animals and healthy volunteers [35,97,98]. EVs maintain mitochondrial stability and have shown better therapeutic effects in animal models of myocardial infarction, liver ischemia, and acute respiratory distress syndrome (ARDS) [35,95,98,99]. For example, mitochondria-containing EVs demonstrated superior recovery of myocardial bioenergetics compared with isolated mitochondria in a mouse model of myocardial infarction [35]. Additionally, MSC-derived EVs were shown to reduce **neutrophil extracellular trap** formation in liver tissue by transferring mitochondria to intrahepatic neutrophils, thereby alleviating ischemia-reperfusion injury *in vivo* in mice [95].

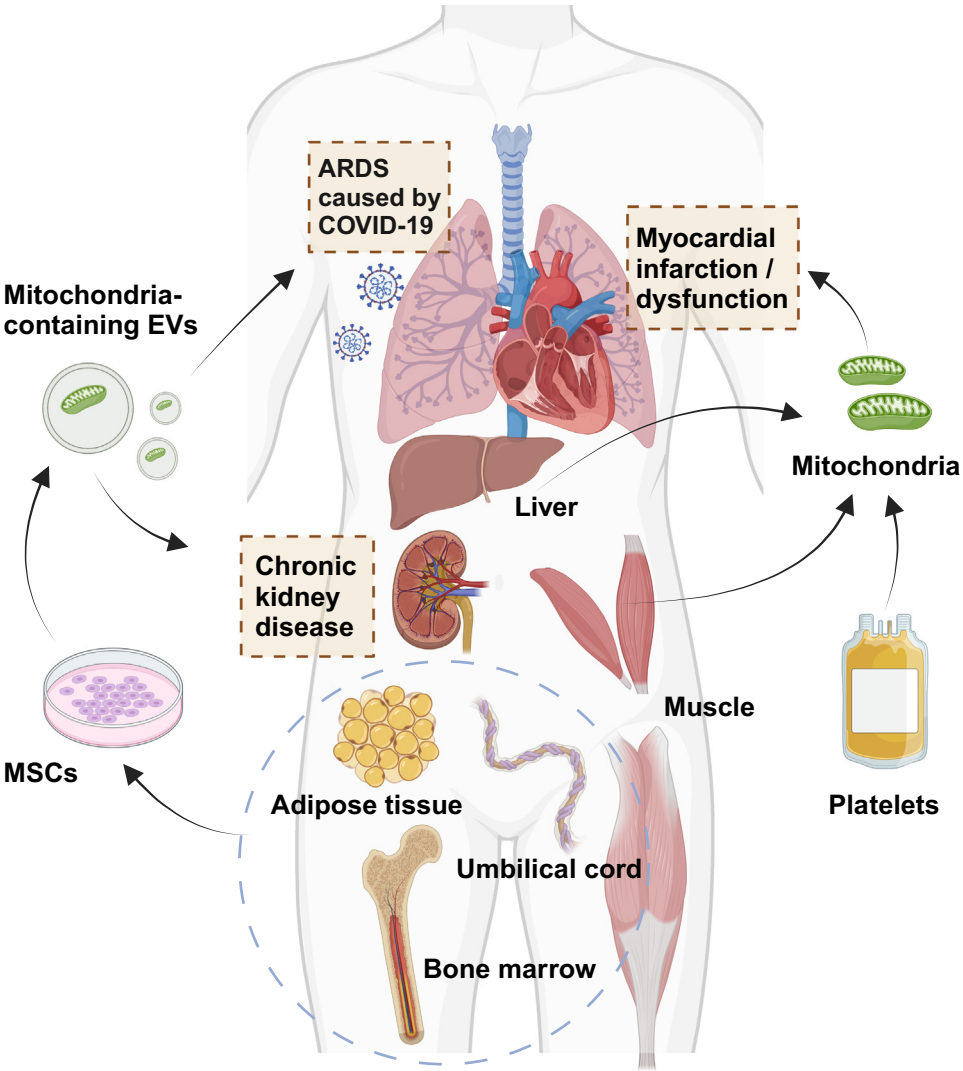

Figure 3. Artificial mitochondrial transfer/transplantation in clinical trials. Mitochondria-containing EVs are isolated from cultured MSCs, which are usually harvested from bone marrow, umbilical cord, platelets, and adipose tissue. The safety of MSC-derived EVs has been confirmed in animals and healthy volunteers. In addition, healthy mitochondria for AMT/T can be isolated from the liver and skeletal muscle due to their high metabolic activity. Clinical trials have investigated the therapeutic effects of AMT/T in various diseases, such as ARDS caused by COVID-19, chronic kidney disease, and myocardial infarction/dysfunction. Abbreviations: AMT/T, artificial mitochondrial transfer/transplant; ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; EVs, extracellular vesicles; MSCs, mesenchymal stem cells. Figure created using BioRender.

Several clinical trials have explored mitochondrial transfer due to beneficial effects observed in preclinical models (Figure 3). In 2017, the first-in-human clinical application of autologous mitochondrial transplant was performed in pediatric patients who required extracorporeal membrane oxygenation support for ischemia-reperfusion injury after cardiac surgery, showing promising outcomes [100]. Healthy mitochondria were isolated from the rectus abdominis muscle and directly injected into the ischemic myocardium, leading to rapid recovery of ventricular function [100,101]. In another phase 2 clinical trial, MSC-derived EVs were found to significantly reduce

Clinician's corner

Mitochondrial transfer has emerged as a cutting-edge therapeutic approach with the potential to restore cellular function across various diseases, especially those marked by mitochondrial dysfunction [7,86]. By harnessing the capacity of donor cells, particularly MSCs, to deliver healthy mitochondria to stressed cells, mitochondrial transfer shows promise in preclinical models for treating conditions such as neurodegenerative diseases, cardiac injury, and ischemia-reperfusion injury.

In addition to the transfer of competent mitochondria from healthy donor cells, such as MSCs, to stressed cells, recent studies also uncovered the essential role of trafficking damaged mitochondria from diseased cells to healthy neighboring recipient cells in cellular homeostasis [119,139]. This intercellular trafficking allows stressed cells to share the burden of degrading defective mitochondria, thus preventing the accumulation of cellular damage. Such findings highlight the versatile nature of mitochondrial transfer, suggesting its significant therapeutic implications in broader pathophysiological settings.

For clinicians, the implications of mitochondrial transfer therapies are profound. These treatments could offer novel strategies to improve recovery in patients where traditional therapies may fall short, especially for those with chronic conditions that exacerbate cellular energy production. Notably, the role of mitochondrial transfer differs significantly between cancerous and noncancerous diseases. In cancer, inhibiting mitochondrial transfer is generally considered beneficial, because it may limit tumor growth, progression, and metastasis by preventing cancer cells from hijacking functional mitochondria from healthy cells. By contrast, promoting mitochondrial transfer in noncancerous diseases can enhance tissue repair and regeneration by supplying damaged cells with healthy mitochondria. This distinction is critical when considering the therapeutic potential of mitochondrial transfer in clinical applications. Therefore, it is important to keep in mind that mitochondrial transfer can lead to diverse outcomes, depending on the disease context.

the 60-day mortality in patients of all ages with severe ARDS caused by COVID-19 [102]. Furthermore, clinical trials are investigating the therapeutic effects of AMT/T in conditions such as repeated *in vitro* fertilization failure (NCT06020742[i]; ongoing), myocardial ischemia (NCT02851758[ii]; recruiting), cerebral ischemia (NCT04998357[iii]; recruiting), and coronary artery bypass graft surgery (NCT05669144[iv]; unknown status).

As this field moves closer to clinical application, relevant novel therapies may soon expand the clinician's toolkit, such as AMT/T and stem cell-mediated mitochondrial transfer. To this end, future research should focus on large-scale, multicenter, randomized controlled clinical trials to evaluate the safety, efficacy, and feasibility of mitochondrial transfer-related treatments. Such clinical trials should address challenges such as efficient mitochondrial delivery, minimizing immune rejection, and ensuring targeted therapy. Hopefully, mitochondrial transfer will offer a targeted and innovative approach to address cellular dysfunction and related diseases at its core organelle, transforming outcomes into conditions once believed untreatable.

Stem cell-mediated mitochondrial transfer

Stem cell-mediated mitochondrial transfer has emerged as a promising strategy leveraging stem cells' ability to deliver mitochondria to damaged tissues. This approach enhances the therapeutic effects of stem cells by combining their regenerative properties with AMT/T. Mitochondria are well-preserved within stem cells, and injury signals from recipient cells and bidirectional communication between stem cells and injured tissues facilitate this transfer [12].

Preclinical research has explored various methods to enhance mitochondrial transfer in stem cell therapy. Highly purified MSCs, such as the rapidly expanding clones, display superior ability for mitochondrial transfer *in vitro*, using EVs and CX43 gap junctions as primary routes [103,104]. Genetic modifications such as overexpressing MIRO1 or CD157, and treatments such as melatonin preconditioning, can further boost mitochondrial transfer *in vitro* and *in vivo* [31,32,93]. In pulmonary fibrosis animal models, combining pioglitazone with IONPs significantly increased mitochondrial biogenesis in MSCs via PGC1α/ NRF1/TFAM signaling and enhanced their transfer by promoting CX43 gap junction formation *in vitro* and *in vivo* [44].

Most recently, stem cell-mediated mitochondrial transfer has been studied in EC transplants *in vivo* [29]. Researchers found that preloading ECs with mitochondria from MSCs enhanced EC engraftment and angiogenesis, while blocking this transfer impairs EC engraftment, albeit that exogenous mitochondria did not integrate into the EC mitochondrial pool [29]. Likewise, in T-cell based immunotherapies, MSC-mediated mitochondrial transfer could supercharge $CD8^+$ T cells by supplying exogenous mitochondria to them via TNTs, which required Talin 2 on donor and recipient cells [105]. Consequently, mitochondria-empowered T cells expanded more robustly and showed superior antitumor effects in tumor-bearing animals, extending their survival [105]. Although no clinical trials have specifically tested stem cell-mediated mitochondrial transfer, stem cell therapies for ischemic stroke, multiple sclerosis, and other diseases have been studied widely [106–108]. These clinical trials have demonstrated the safety and efficacy of stem cell therapies. However, further research is required to directly assess the potential of mitochondrial transfer mediated by stem cells during patient treatment.

Concluding remarks

Mitochondrial transfer introduces a paradigm shift in intercellular communication, primarily through EVs, gap junctions, and TNTs. Mitochondrial transfer occurs in both physiological and pathological contexts, especially under oxidative stress driven by excessive ROS, but the precise triggers and regulatory mechanisms remain to be explored. Moreover, evidence of mitochondrial transfer in humans *in vivo* remains scarce because of technical limitations, such as the difficulty in accurately tracking and visualizing mitochondrial transfer within living tissues (see Outstanding questions). This review highlights significant progress in understanding mitochondrial transfer across various donor cells and their potential applications (Table S1 in the supplemental information online).

MSC-derived mitochondria have attracted widespread attention for their versatile roles in tissue regeneration, immune regulation, and cancer progression. Selectively enhancing mitochondrial transfer from MSCs could optimize stem cell therapies for injury repair. Plus, CAFs and immune

cells participate in mitochondrial transfer, especially within the tumor microenvironment, where cancer cells hijack mitochondria to gain metabolic support for malignant progression. Thus, inhibiting mitochondrial transfer offers a promising antitumor strategy [109]. However, despite promising results in preclinical settings, the pathway to clinical applications is complicated. Standardizing protocols for mitochondrial isolation, optimizing delivery mechanisms, and tailoring protocols to individual patient needs are all critical steps before clinical implementation. We advocate that as research progresses toward human trials, clinicians should stay updated on the developments, especially regarding safety, efficacy, delivery methods, and long-term outcomes data, that will shape the future landscape of mitochondrial transfer therapies.

Besides, it is crucial to understand the precise role of intercellular mitochondrial transfer in different disease settings. In cancer, suppressing mitochondrial transfer usually reduces tumor growth, albeit that some contradictory findings exist, whereas promoting mitochondrial transfer can enhance tissue repair in noncancerous diseases (see Clinician's corner). Although ongoing clinical trials hold promise, their success is uncertain because of difficulties in controlling transfer and the need for disease-specific approaches. Further research into the mechanism of mitochondrial transfer and developing selective inhibitors or agonists is required. Here, we recommend that future studies focus on mechanisms behind selective mitochondrial transfer and harness their therapeutic power, overcoming the complexity of mitochondrial dynamics and potential immune responses and off-target effects. Overall, targeting mitochondrial transfer is a promising therapeutic strategy, representing a revolutionized prototype of organelle therapy in regenerative medicine, oncology, and beyond.

Outstanding questions

What are the precise cellular and molecular mechanisms initiating and regulating mitochondrial transfer between cells? Specifically, what are the shared mechanisms that trigger different modes/routes of mitochondrial transfer? What are the unique mechanisms of various forms of mitochondrial transfer?

How can we harness the power of mitochondrial transfer *in vitro* and *in vivo*? Furthermore, how can we enhance mitochondrial transfer in therapeutic settings to maximize its efficacy while avoiding potential side effects?

Can selective inhibition of mitochondrial transfer in tumors provide a viable anticancer strategy? In what ways might targeting the mechanisms of mitochondrial transfer alter tumor microenvironments and influence tumor growth or metastasis? What are the implications of such strategies for the surrounding healthy tissues, and how can we balance the therapeutic benefits against potential risks in cancer treatment?

What are the potential applications of mitochondrial transfer in other diseases and physiological processes? For instance, how might mitochondrial transfer be leveraged to address conditions such as neurodegenerative diseases, cardiovascular diseases, metabolic disorders, or autoimmune diseases? What challenges do researchers face in translating these findings from bench to bedside?

What are the long-term effects and safety considerations of mitochondrial transfer-targeted therapies in humans? Especially, how do these therapies impact cellular function over extended periods, and what are the potential risks associated with unintended consequences of mitochondrial transfer? Besides, what measures can be taken to monitor and mitigate potential adverse effects in clinical settings, ensuring the safety and efficacy of these innovative treatments?

Author contributions

B.L., B.Z.L., X.Q., and L.L. drafted the manuscript. B.Z.L., W.M., X.Q., Y.X., J.G., Y.F., and B.L. edited the manuscript. B.Z.L., W.M., and B.L. prepared the figures. B.L. and L.L. critically reviewed the manuscript. B.L., B.Z.L., and X.Q. contributed equally and are co-first authors. All authors approved the final version of the manuscript.

Acknowledgments

This work was supported by research funding from the National Natural Science Foundation of China (82401070, 82372735, 82141130), the Sichuan Province Science and Technology Support Program (2023NSFSC1519, 2024NSFSC0545), the China Postdoctoral Science Foundation (2022M712240, 2024M752978), and the Henan Province Scientific and Technological Project (242102311007).

Declaration of interests

The authors declare no competing interests.

Resources

[i]https://clinicaltrials.gov/study/NCT06020742

[ii]https://clinicaltrials.gov/study/NCT02851758

[iii]https://clinicaltrials.gov/study/NCT04998357

[iv]https://clinicaltrials.gov/study/NCT05669144

Supplemental information

Supplemental information associated with this article can be found online at https://doi.org/10.1016/j.molmed.2025.04.002.

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