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Review

Mitochondria transfer and transplantation in human health and diseases

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ABSTRACT

Mitochondria are dynamic organelles responsible for energy production and cell metabolism. Disorders in mitochondrial function impair tissue integrity and have been implicated in multiple human diseases. Rather than constrained in host cells, mitochondria were recently found to actively travel between cells through nanotubes or extracellular vesicles. Mitochondria transportation represents a key mechanism of intercellular communication implicated in metabolic homeostasis, immune response, and stress signaling. Here we reviewed recent progress in mitochondria transfer under physiological and pathological conditions. Specifically, tumor cells imported mitochondria from adjacent cells in the microenvironment which potentially modulated cancer progression. Intercellular mitochondria trafficking also inspired therapeutic intervention of human diseases with mitochondria transplantation. Artificial mitochondria, generated through mitochondria genome engineering or mitochondria-nucleus hybridization, further advanced our understanding of mitochondrial biology and its therapeutic potential. Innovative tools and animal models of mitochondria transplantation will assist the development of new therapies for mitochondrial dysfunction-related diseases.

1. Introduction

Mitochondria were originally thought to be largely constrained within host cells with few exceptions (Berridge et al., 2016). Rare parasitic flowering plants stole mitochondria from their host, namely horizontal gene transfer (Xi et al., 2013). A pioneering study in mitochondrial transfer dates back to 1969 when intercellular bridges were observed in the developing mouse oocytes. Mitochondria were found in these intercellular tunnels, indicating the active transport or exchange of organelles between adjacent oocytes (Ruby et al., 1969). Phylogenetic studies also suggested that different yeast species exchanged their mitochondria to mediate mitochondrial genome (mtDNA) recombination, which was essential for the evolution of mitochondria (Peris et al., 2017).

Mitochondria transportation has been linked to cellular metabolism, stress response, and cell signaling (Chen et al., 2021; Xu et al., 2020). Correspondingly, mitochondria transfer is involved in the maintenance of physiological function in multiple tissues. Dysregulation of mitochondria transportation has been implicated in multiple human diseases such as cancer, obesity, and cardiovascular diseases. Recent advances in mitochondrial genome editing and mitochondrial transplantation open a new window for the treatment of mitochondria-related diseases. The application of interspecies somatic cell nuclear transfer further boosts the idea of making mitochondria-nucleus hybrid cells from a synthetic biology perspective (Beyhan et al., 2007). Here we reviewed recent advances in mitochondria transfer and the potential application of mitochondria transplantation in human health and diseases.

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2. Discovery and regulation of intercellular mitochondrial transfer

Early studies demonstrated that mitochondria, alongside other organelles, actively traveled between different cells (Rogers and Bhattacharya, 2013; Tadokoro and Takahashi, 2017). Importantly, the direction and efficacy of intercellular mitochondria trafficking were delicately controlled by both the donor and recipient cells. To date, mitochondria transportation has been found to be mediated by intercellular nanotubes, microvesicles, and cell–cell junctions.

2.1. Tunneling nanotubes-mediated mitochondria transfer

Mitochondria could travel to adjacent host cells through tunneling nanotubes (TNTs) (Fig. 1A), which was first discovered in the coculture of human and rat cells (Rustom et al., 2004). The diameter of TNTs ranged from 50 to 700 nm, allowing the transfer of organelles such as mitochondria (Onfelt et al., 2006). TNTs were membranous structures filled with actin bundles that support cargo transfer. Membrane-bound cadherin proteins maintained the tube-like structure of these tunnels (Sartori-Rupp et al., 2019). Microtubules were required for the formation of thicker TNT, allowing for the transfer of mitochondria (Vignais et al., 2017). Different cell lines with the same or various species of origin were capable of forming TNT in coculture system (Koyanagi et al., 2005; Thyssen et al., 2012; Vignais et al., 2017).

TNT-mediated mitochondria trafficking is coordinated by interconnected cells. In the donor cells, nanotube biogenesis and cytoskeleton remodeling are key steps of TNT formation. Mechanistic studies revealed that mammalian target of rapamycin (mTOR) signaling and cell division control protein 42 homolog (CDC42), a cytoskeleton regulatory protein, controlled nanotube protrusion and growth (Walters and Cox, 2021) (Fig. 1A). Ras-related protein Rab-8A and Rab-11A, which are small GTPases, colocalized with F-actin to promote TNT-dependent bridging of adjacent cells (Zhu et al., 2016). Once the TNT was formed, motor proteins including mitochondrial Rho small GTPase (Miro1 and Miro2) assembled with kinesin and other accessory proteins to fulfill cargo transfer (Murray and Krasnodembskaya, 2019; Rogers and Bhattacharya, 2013)(Fig. 1A). Miro was a mitochondrial outer membrane protein that modulated mitochondria movement with its GTPase domain and calcium-binding motifs (Babenko et al., 2018; Nahacka et al., 2021). Of note, TNT connections are controlled by physiological signals. Melatonin, a brain-derived hormone, was shown to facilitate the formation of TNTs in neural cells (Nasoni et al., 2021).

2.2. Microvesicles-dependent mitochondria transportation

In addition to TNT-mediated transportation, mitochondria can be encapsulated in microvesicles (0.1–1 μm in diameter) and secreted outside of the host cells (Amari and Germain, 2021; Nawaz and Fatima, 2017). Mitochondria-carrying microvesicles typically expressed the endosomal sorting complex required for transport (ESCRT) related proteins, such as tumor susceptibility gene 101 (TSG101) and arrestin domain containing 1 (ARRDC1) (Phinney et al., 2015). Release of mitochondria into the tissue microenvironment or the blood vessels allowed for long-distance travel (Murray and Krasnodembskaya, 2019). After being endocytosed by the target cells, imported mitochondria could escape from the lysosomal degradation pathway and coexist with the new host cell.

The export of microvesicles is initiated by cytoskeleton reorganization. In astrocytes, cluster of differentiation 38 (CD38) and cyclic ADP ribose signaling controlled the release of mitochondria-containing microvesicles. Microvesicles were formed in a calcium-dependent manner and further transported mitochondria to neurons, where integrin-induced Src/Syk signaling regulated the entry of foreign mitochondria (Hayakawa et al., 2016) (Fig. 1B).

2.3. Cell junction and fusion-mediated mitochondria transfer

Although TNTs and microvesicles are the major routes for mitochondria transfer, intercellular junctions formed with connexins and cytoskeleton proteins also played a role in intercellular mitochondria translocation (Berridge and Neuzil, 2017). Mitochondria could be transferred through gap junction internalization or engulfment of cellular contents from neighboring cells (Norris, 2021; Qin et al., 2021). Interestingly, cell fusion was also reported to mediate the exchange of mitochondria and other cellular contents (Zampieri et al., 2021).

3. Biological functions of mitochondria transfer

Mitochondria transfer potentially maintains metabolic homeostasis and intercellular communication in the tissue microenvironment to cope with metabolic, oxidative, or genotoxic stresses. Correspondingly, aberrant mitochondria trafficking is linked to multiple human diseases such as cancer and cardiovascular diseases.

3.1. Metabolic communication and stress response

Ultraviolet light (UV) treatment mediated apoptosis of pheochromocytoma-derived PC12 cells. Unexpectedly, when cocultured

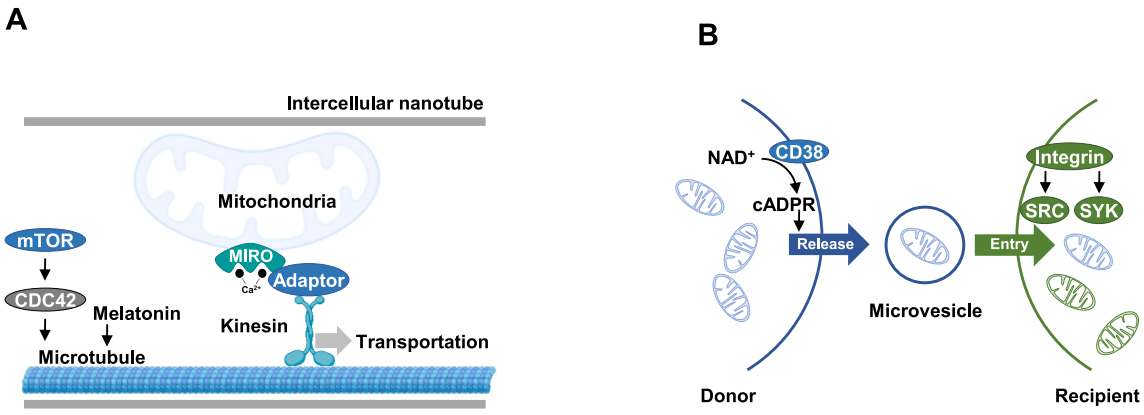

Fig. 1. Intercellular nanotubes or microvesicles mediate mitochondria transfer A. Intercellular nanotube mediates mitochondria transfer. mTOR/CDC42 signaling controls nanotube formation, which can be activated by melatonin. Mitochondria are loaded on kinesin and motor proteins by MIRO and adaptor proteins, a process dependent on calcium. B. Microvesicle formation is regulated by CD38 signaling, which converts NAD^+ to cyclic ADP ribose. Mitochondria-carrying microvesicle enters recipient cells under the control of integrin/SRC/SYK signaling.

with healthy PC12 cells, apoptotic PC12 cells formed nanotubes with them to import functional mitochondria and reverse early apoptosis (Wang and Gerdes, 2015). Mitochondria are actively transported among cells from the energy-consuming neural system to rescue new host cells from energy stress. Schwann cells and astrocytes are critical glial cells supporting neuron functions. Serum starvation boosted the formation of tunneling nanotubes (TNTs) between Schwann cells. The consequent exchange of mitochondria and other cellular components promoted cell migration and prevented apoptosis (Zhu et al., 2016). Besides, astrocytes were prone to ischemic mimicking damage during oxygen-glucose deprivation. Mesenchymal stem cells (MSCs) transferred mitochondria to damaged astrocytes and, as a result, restored their energy production and cell proliferation (Babenko et al., 2018). Of note, astrocytes were reported to maintain neuron viability by microvesicle-dependent mitochondria transfer (Hayakawa et al., 2016).

3.2. *Remodeling the tumor microenvironment*

Mitochondria transfer potentially contributes to the metabolic reprogramming of cancer (Ge et al., 2022). Cancer cells took advantage of mitochondria trafficking during the reconstruction of tumor microenvironment. Acute myeloid leukemia (AML) is a malignant form of blood cancer and is highly dependent on oxidative phosphorylation (Wang et al., 2021). Strikingly, leukemia cells formed more TNT connections with mesenchymal stem cells upon exposure to oxidative phosphorylation inhibitors. MSCs transferred their mitochondria to AML cells to restore leukemic respiration and proliferation (Saito et al., 2021).

Mitochondria transfer is possibly coupled with chemoresistance (Hekmatshoar et al., 2018; Yan et al., 2018). A co-culture model of breast or ovarian cancer cells revealed mitochondria-trafficking nanotubes between cancer cells and endothelial cells or BM-MSCs (Fig. 2). Mitochondria mainly traveled from endothelial cells to tumor cells and enhanced their resistance to doxorubicin, a DNA damaging agent (Pasquier et al., 2013). In the leukemic bone marrow microenvironment (Man et al., 2021), cancer cells replenished mitochondria mass by forcing bone marrow stromal cells to donate their mitochondria (Fig. 2). Imported mitochondria reduced the cytotoxic effect of cytosine arabinoside, a nucleoside analog widely used in leukemia chemotherapy (Moschoi et al., 2016). Additionally, chemotherapy boosted mitochondria export from stromal cells and the endocytosis by leukemia cells. Leukemia-driving mutations may reprogram the signaling pathways of mitochondria transfer, as AML cells showed more active mitochondrial transfer than normal hematopoietic cells (Moschoi et al., 2016). Besides, cell differentiation state potentially modulates mitochondria transportation because more active mitochondria transfer was observed in leukemia-initiating cells and hematopoietic progenitor cells (Moschoi et al., 2016).

Mitochondria transportation was shown to mediate immune-metabolic crosstalk in the cancer microenvironment (Shangguan et al., 2021; Tang et al., 2020). Breast cancer cells imported mitochondria from surrounding immune cells through nanotubes to suppress their tumor-eliminating activity (Fig. 2). Chemical inhibition of Ras/Rho GTPase signaling repressed TNT formation and improved the effect of immune-checkpoint inhibitor in a breast cancer model (Saha et al., 2022).

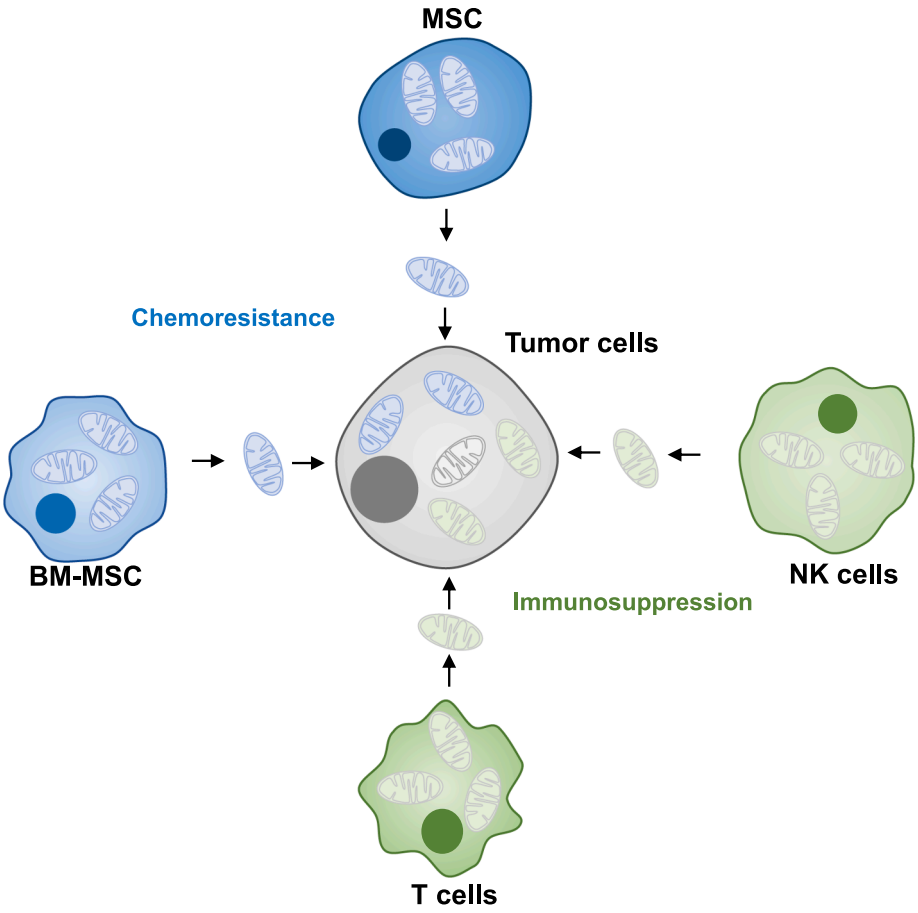

Fig. 2. Mitochondria transfer in tumor microenvironment Tumor cells reprogram the microenvironment and steal mitochondria from mesenchymal stem cells (MSC), bone marrow-derived mesenchymal stem cells (BM-MSC), T cells, and natural killer (NK) cells.

3.3. Tissue metabolism and injury repair

Mitochondria transfer plays a protective role in the vascular system (Fig. 3). When rat cardiomyocytes were cocultured with human endothelial progenitor cells or mesenchymal stem cells, TNTs promoted the onset of cardiomyogenic phenotype (Koyanagi et al., 2005; Plotnikov et al., 2008). Oxygen deprivation and reoxygenation mimicked ischemia–reperfusion and caused vascular injury. Impaired vascular endothelial cells were shown to connect to mesenchymal stem cells with TNTs and imported their mitochondria to prevent oxidative damage and apoptosis (Liu et al., 2014). Interestingly, macrophages internalized and degraded depolarized mitochondria from cardiomyocytes and bone marrow mesenchymal stem cells to maintain cardiovascular function (Pang et al., 2021).

Intercellular mitochondria trafficking is correlated to lung homeostasis. In a mouse model of rotenone-induced lung injury, TNTs promoted mitochondria transfer from MSCs to lung epithelial cells to repair airway injury and improve lung inflammation (Ahmad et al., 2014). In an LPS-induced lung injury model, lung alveoli cells took up mitochondria from mouse bone marrow-derived stromal cells to avoid acute lung damage (Islam et al., 2012) (Fig. 3).

Mitochondria transportation was reported to be involved in neural integrity maintenance (Fig. 3). TNTs participated in axon repairment in a rat model of peripheral nerve transection. Axonal outgrowth was enhanced by the mitochondria imported from adjacent cells (Zhu et al., 2016). Interestingly, mitochondria transfer potentially contributed to neuronal metabolism. Retinal ganglion cells transferred their mitochondria at the optic nerve head to adjacent astrocytes. These morphologically healthy mitochondria were further degraded in astrocytes, namely transmitophagy (Davis et al., 2014). Unknown defects in transmitophagy might cause neuronal degeneration (Davis et al., 2014). The exact role of mitochondrial transfer in this process requires further investigation.

Mitochondria transfer has been implicated in liver metabolism (Fig. 3). Bone marrow-derived mesenchymal stem cells (BM-MSCs) transferred mitochondria to steatotic cells and enhanced their respiration activity in fatty liver. The fatty liver was alleviated after BM-MSC implantation in the acute disease model (Bi et al., 2021). Whether mitochondria transfer affects the steady-state liver metabolism needs further elucidation.

In addition, damage repair of skin cells is potentially linked to mitochondria transportation. Platelets functioned as the sensors of skin injury and released intact mitochondria into the microenvironment. These signaling mitochondria were internalized by mesenchymal stem cells and resulted in the activation of lipid metabolism and proangiogenic signaling pathways to promote damage repair. Citrate, a glucose-derived metabolite that fueled mitochondria metabolism, remarkably improved the re-vascularization of wounded cells (Levoux et al., 2021) (Fig. 3). Interestingly, mesenchymal stem cells emerged as major mitochondria donors that coordinated different cell types to respond to external stress or injury (Rodriguez et al., 2018).

Adipose tissue is also a hotspot for mitochondria transportation. In obese animals, stressed adipocytes released extracellular vesicles that delivered damaged mitochondria to cardiac tissue to increase oxidative stress. The consequent activation of antioxidant signaling was protective against acute oxidative stress in the heart (Crewe et al., 2021). Adipocytes also transported their mitochondria to macrophages, which was suppressed in obese conditions. Genetic ablation of mitochondria transportation increased adipose deposit and promoted obesity in high fat diet-induced animal models. This immunometabolic crosstalk was critical for maintaining metabolic fitness (Brestoff et al., 2021).

Renal cell differentiation is also accompanied by intercellular mitochondria trafficking. Human mesenchymal multipotent stromal cells (MMSC) formed tunneling nanotubes with rat renal tubular cells in a co-culture system. Renal tubular cells transported mitochondria to MMSC and promoted renal-specific marker expression. This observation suggests that mitochondria trafficking possibly contributes to MMSC-to-tubular differentiation (Plotnikov et al., 2010). It is thus reasonable to speculate that loading MMSC with tubular cell-derived mitochondria might enhance the efficacy of renal repairment.

Noteworthy, long-distance mitochondria trafficking may have unanticipated biological significance (Al Amir Dache et al., 2020). This is at least partially supported by the existence of intact mitochondria in circulation. Although the origin of these cell-free mitochondria remains

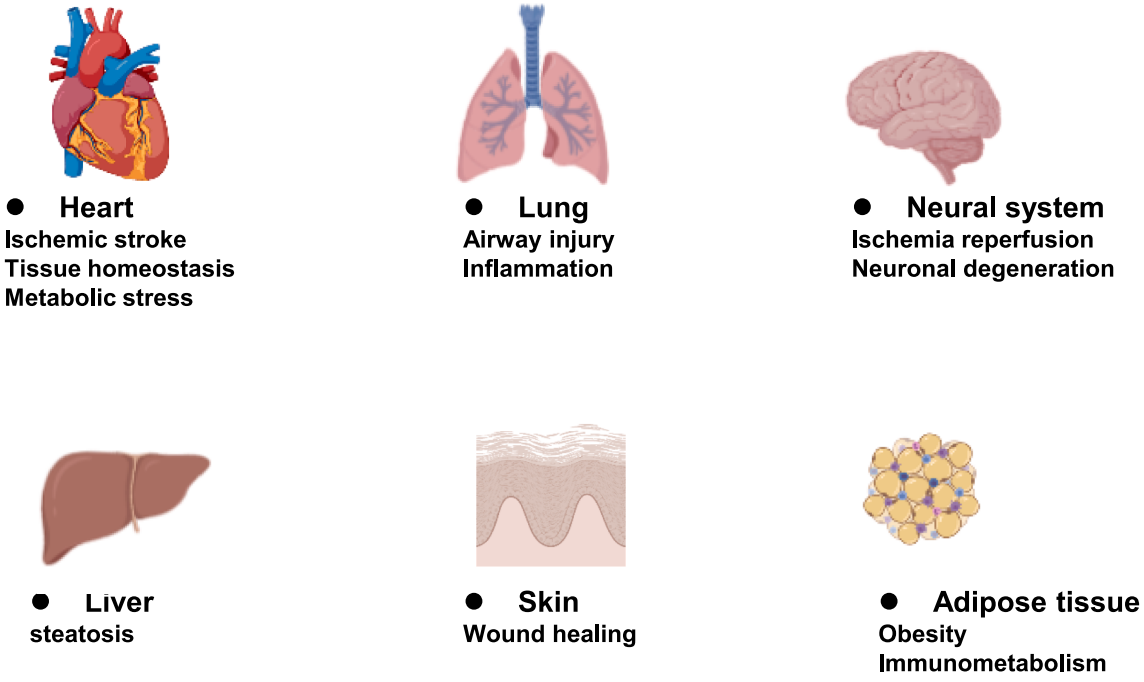

Fig. 3. Mitochondria transfer is involved in tissue homeostasis Mitochondria transfer between different cell types is involved in tissue homeostasis in the heart, lung, neural system, liver, skin, and adipose tissue.

controversial (Stier, 2021), circulating mitochondria hold the potential to mediate long-distance cell-to-cell communication.

4. Mitochondria transplantation in preclinical studies

The transferable nature of mitochondria sparks the concept of mitochondria transplantation in the treatment of mitochondrial disorder-related diseases. Of note, techniques of mitochondria transplantation had been successfully established in the lower organisms in the mid-1970 s. The development of microinjection allowed mitochondria transplantation across different paramecium species (Beale and Knowles, 1976). In 1982, free mitochondria isolated from donor mammalian cells were found to enter into different host cells by direct co-incubation (Clark and Shay, 1982), a process potentially mediated by micropinocytosis but not endocytosis (Kesner et al., 2016; Kitani et al., 2014). Although the early efforts of mitochondria transplantation in paramecium pointed out mitochondria-nuclear incompatibility in some unsuccessful trials (Beale and Knowles, 1976), mitochondria transplantation has been vividly tested in animal and human models. Vascular or aerosol delivery-mediated mitochondria transplantation reduced lung tissue injury in a mouse model of ischemia–reperfusion (Moskowitzova et al., 2020). Autologous mitochondria transplantation showed cardioprotective effects in an ischemia–reperfusion porcine model (Blitzer et al., 2020). Moreover, blood cells-derived mitochondria were transplanted into hematopoietic stem cells, aiming for the treatment of bone marrow disorders in a human clinical trial (NCT03384420) (Almannai et al., 2020). Of note, the clinical outcome of mitochondria transplantation requires further validation to ensure its safety and efficacy.

Mitochondria transplantation shows neuroprotective effects against ischemic stroke. Mouse astrocyte-derived mitochondria were introduced into neurons through direct cortex injection and decreased apoptosis-related gene expression (Hayakawa et al., 2016). Allogenic or autologous transplantation of mitochondria played a cardioprotective role in mouse and pig models of ischemia and diabetes (Ali Pour et al., 2021; Doulamis et al., 2020; Kaza et al., 2017; Moskowitzova et al., 2019). Interestingly, xenograft transplantation of mitochondria had also seen success in animal studies (Hayashida et al., 2021). An ex vivo study suggested that microvesicles efficiently delivered human mitochondria into mouse endothelial cells and neural cells, resulting in an increase in cell survival under ischemic conditions (D'Souza et al., 2021). Transplantation of respiration active mitochondria, isolated from mouse cell lines, enhanced mitochondrial metabolism and reduced tissue injury in a rat model of cerebral ischemia–reperfusion (Xie et al., 2021).

Deficient mitochondrial function in cardiomyocytes is responsible for heart failure. Mitochondria transplantation also holds potential in the treatment of heart diseases. Autologous mitochondria transplantation, from rat skeletal muscle cells to cardiomyocytes, mediated a short-term improvement of cellular respiration and energy production (Ali Pour et al., 2020). Besides, mitochondrial dysfunction is a key feature of cancer metabolism (Guo et al., 2020; Morita et al., 2018; Wang et al., 2014; Xu et al., 2016; Yan et al., 2018; Zhang et al., 2021). Transplantation of normal epithelium-derived mitochondria into breast cancer cells exaggerated respiration and sensitized cancer cells to chemotherapy (Elliott et al., 2012).

5. Future perspectives in mitochondria transfer and transplantation

Mitochondria transfer and transplantation is a rapidly evolving field. In contrast to the tremendous attention on its therapeutic capabilities, mechanisms governing mitochondria transfer remain poorly understood. Specifically, the signaling pathways and cell skeleton dynamics controlling mitochondria transplantation require systemic in-depth illustration. Previous studies using cell lines had identified donor-recipient pairs that allowed mitochondria transportation (Qin et al., 2021). Subsequent investigations into general mechanisms or context-dependent regulation of mitochondria transfer are essential to improving our knowledge in this field. Besides, the majority of recent studies is performed with implanted cells or acute disease models. The in vivo relevance of mitochondria transfer in steady-state metabolism and health maintenance remains an unsettled biological question. Therefore, it is important to develop new animal models and tools to elucidate the exact roles of transferred mitochondria in the maintenance of health under baseline conditions and in the development of chronic diseases.

5.1. Animal models of mitochondria transfer

Animal models of mitochondria transfer are powerful tools in mitochondrial biology and translational studies. A synthetic mitochondria-nuclear hybrid mouse model was first reported in 2013, in which the mitochondria from C3H/HeN mice were transplanted into C57/BL6 nuclear background. Reciprocal transplantation was also performed to generate two complementary strains of mitochondria-nuclear exchange (MNX) mice (Fetterman et al., 2013). The MNX model became a powerful tool in elucidating the role of mitochondria in cardiac stress, metabolic syndrome, cancer, and immune response (Betancourt et al., 2014; Brinker et al., 2020; Brinker et al., 2017; Fetterman et al., 2013; Sammy et al., 2021). The development of new mitochondria-nucleus hybrid animal models will help to address the biological function of mitochondria transfer in health and diseases.

5.2. De novo synthesis of artificial mitochondria

The availability of healthy and respiration-active mitochondria is a limiting factor for mitochondria transplantation. The source of mitochondria could be expanded by de novo synthesis of artificial mitochondria using synthetic biology approaches. Importantly, new metabolic traits may be genetically incorporated into mitochondria when they are assembled in vitro. Although de novo synthesis of mitochondria remains an impossible mission, exosome-based assembly of soluble metabolic enzyme mix and membrane-bound electron transport chain successfully created a simplified version of mitochondria in vitro (Fig. 4) (Kumar et al., 2021). These artificial powerhouses produced energy for hours after being transplanted to tissue spheroids. The roadmap of making artificial mitochondria in a bottom-up approach was under intensive investigation (Biner et al., 2018).

5.3. Breaking boundaries of mitochondria-nucleus incompatibility

Mitochondria transplantation is bottlenecked by mitochondria-nucleus incompatibility, which has been observed in yeast and mouse studies (Lee et al., 2008; Ma et al., 2016; Sharpley et al., 2012). This also raised the concern about the safety of mitochondria transplantation in clinical translation (Bertero et al., 2018; Lightowlers et al., 2020; McCully et al., 2017; Yamada et al., 2020). Mitochondria-nucleus incompatibility was at least in part caused by the malfunctioning of mtDNA in the genetic background of the new host, a phenomenon similar to graft versus host disease observed in stem cell or organ transplantation (Jiang et al., 2011). Additionally, foreign mitochondria may be eliminated by the competitive pressure from original mitochondria in the host. Despite these depressing observations, transplantation of mouse or buffalo mitochondria into bovine oocytes supported embryonic development till the blastocyst stage (Takeda et al., 2012). Successful replacement of mitochondria between mouse strains also sheds light on the future of the clinical application of mitochondria therapy (Ma et al., 2016).

5.4. New biology tools aiding mitochondria transplantation

Mitochondria transplantation allows visualization of recipient cells or detection of small molecules in vivo. Specifically, sensors for small

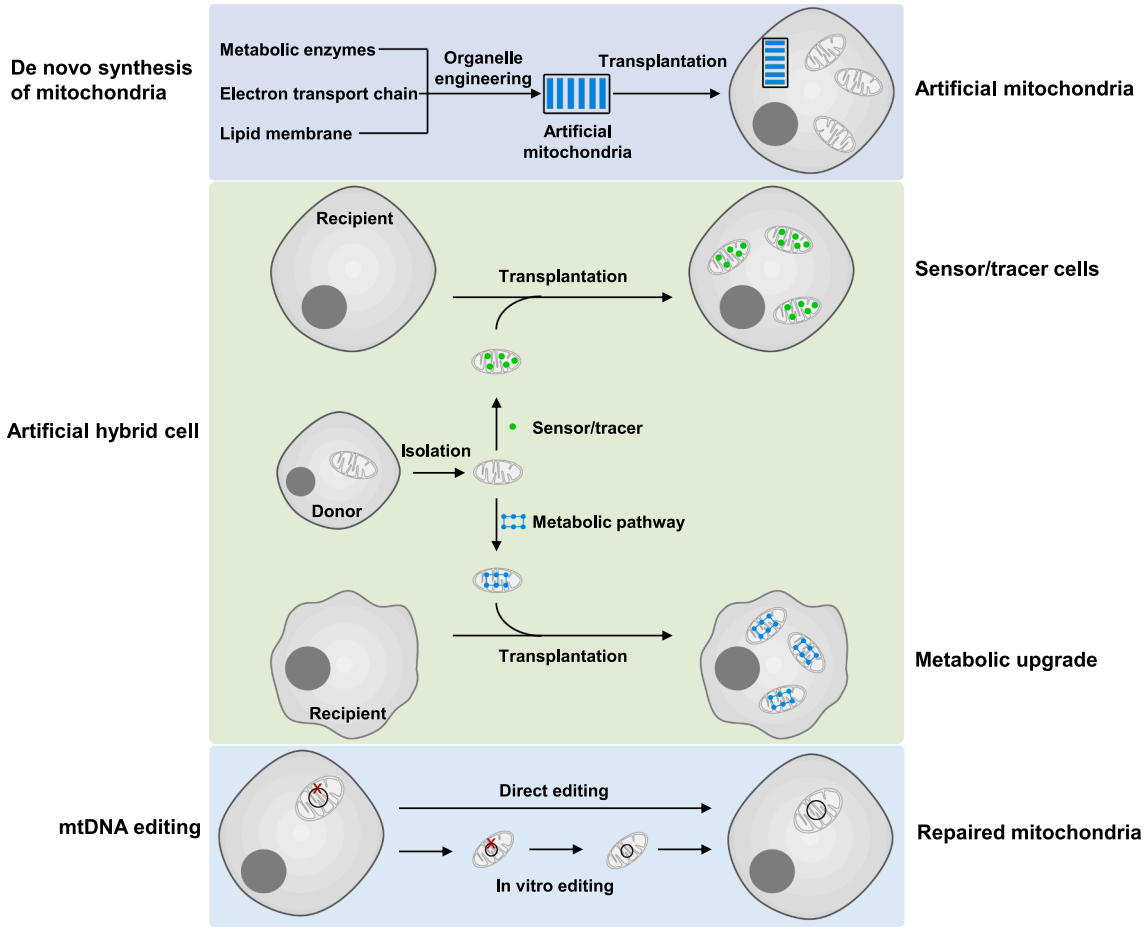

Fig. 4. Strategies of mitochondria engineering and transplantation Schematic overview of manipulating mitochondria transfer. Upper: mitochondria are assembled in vitro with metabolic and structural components through organelle engineering. Artificial mitochondria are further transplanted to target cells for metabolic upgrade. Middle: allogeneic or xenogeneic transplantation of mitochondria confers new metabolic or genetic traits to recipient cells. Lower: the mitochondrial genome is edited in vivo or in vitro. Repaired mitochondria restore the biological activity of host cells.

molecules or fluorescent tracers can be loaded into mitochondria to generate reporter cells, allowing for in vivo tracking of recipient cells and real-time detection of their metabolic activity (Pendin et al., 2019; Spees et al., 2006). Alternatively, metabolic genes or pathways could be genetically incorporated into mitochondria to restore metabolic activity or confer new genetic traits to new hosts (Buren et al., 2019; Xiang et al., 2020) (Fig. 4).

mtDNA mutations cause incurable inborn disorders. New tools for mitochondrial genome editing, such as mitoTALEN (Bacman et al., 2018) or CRISPR-free base editing (Mok et al., 2020), corrected mitochondria genomes with inborn deficiencies in vivo or ex vivo (Tang, 2015). Hence, mitochondria transplantation remains a promising strategy in the treatment of mtDNA diseases (Fig. 4).

Targeted mitochondria transplantation is a challenging task as a low delivery rate was observed after direct injection of mitochondria into circulation or corresponding tissue. While microinjection is technically demanding, mitochondria transplantation by coincubation has relatively low efficacy. Magnetic force or pressure-driven techniques were developed to enhance the efficiency of transplantation (Sercel et al., 2021). The application of optical tweezers was reported to fulfill automatic mitochondria transplantation (Shakoor et al., 2021). Moreover, specific markers or receptor proteins may be inserted on mitochondria outer membrane or microvesicles membrane to guide precise engraftment of mitochondria. Of note, Coronavirus disease 2019 (COVID-19) led to systemic mitochondria dysfunction (Valenti et al., 2021). Mitochondria therapy has unprecedented potential in the treatment of human diseases including infection.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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