Perspective

The power and potential of mitochondria transfer

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Mitochondria are believed to have originated through an ancient endosymbiotic process in which proteobacteria were captured and co-opted for energy production and cellular metabolism. Mitochondria segregate during cell division and differentiation, with vertical inheritance of mitochondria and the mitochondrial DNA genome from parent to daughter cells. However, an emerging body of literature indicates that some cell types export their mitochondria for delivery to developmentally unrelated cell types, a process called intercellular mitochondria transfer. In this Review, we describe the mechanisms by which mitochondria are transferred between cells and discuss how intercellular mitochondria transfer regulates the physiology and function of various organ systems in health and disease. In particular, we discuss the role of mitochondria transfer in regulating cellular metabolism, cancer, the immune system, maintenance of tissue homeostasis, mitochondrial quality control, wound healing and adipose tissue function. We also highlight the potential of targeting intercellular mitochondria transfer as a therapeutic strategy to treat human diseases and augment cellular therapies.

Mitochondria are multifunctional organelles essential for the cellular metabolism of nearly all eukaryotic cells. These organelles are believed to have originated through an ancient endosymbiotic process in which proteobacteria were co-opted for host cell function of eukaryotic life forms, ranging from yeast to plants to animals[1]. Although mitochondria are most commonly associated with their metabolic roles in harvesting energy from nutrients and generating essential metabolites, these organelles participate in diverse processes, including but not limited to cell signalling, cytochrome *c*-mediated initiation of apoptosis, antiviral immune responses and regulation of cell proliferation and development[2]. As cells divide post-fertilization, parent cells contribute mitochondria to daughter cells, a process called vertical inheritance of mitochondria (Box 1). Cells then perform mitochondrial biogenesis to increase and retain mitochondrial biomass to support future cell divisions and their cellular functions. It has been widely assumed that cells contain only mitochondria obtained through vertical inheritance during cell division or mitochondrial biogenesis, processes that have been reviewed elsewhere[3].

However, emerging studies in the past two decades have revealed that cells can also export some of their mitochondria and deliver them to recipient cells. This process is called intercellular or horizontal mitochondria transfer. To our knowledge, the first study revealing a functional role of mitochondria transfer was in 2006 and reported that ρ^0 cells that lack mitochondrial DNA (mtDNA) could be rescued by delivery of mitochondria from neighbouring cells in co-culture[4]. A flurry of research in the past decade has revealed that intercellular mitochondria transfer occurs in numerous tissues in vivo using various transfer mechanisms and that this process contributes to both normal physiological processes and disease pathogenesis. In this Review, we describe the mechanisms of intercellular mitochondria transfer reported in vitro and in vivo. We then discuss known functions of intercellular mitochondria transfer in physiological and pathological states and how this process contributes to cellular metabolism, cancer, regulation of immune responses, maintenance of tissue homeostasis, wound healing and other processes. Finally, we discuss emerging concepts of how the biology underlying intercellular mitochondria transfer is being harnessed to treat human diseases.

How and why mitochondria are transferred

Mechanisms of mitochondria transfer

Several distinct mechanisms of intercellular mitochondria transfer have been reported in the literature, with some having been explored in more detail than others. These transfer mechanisms can be divided into three categories: (1) formation of transient cellular connections through which mitochondria can move from one cell to another, (2) ejection of mitochondria in extracellular vesicles for delivery to recipient cells, and (3) release of free mitochondria for capture by recipient cells (Fig. 1).

Transient cellular connections. The most widely reported mechanism is a cell contact-dependent process involving the formation of transient intercellular connections known as tunnelling nanotubes (TNTs) and/or connexin 43 (Cx43)-mediated gap junctional channels (GJCs). Some studies have suggested that connexins such as Cx43 may, in some cases, regulate the formation of TNTs[5–7]. These structures function to exchange cytosolic and plasma membrane components bidirectionally[8], establishing a 'parabiotic' relationship between participating cells. One of the first studies reporting that these structures transport mitochondria used scanning electron microscopy of human mesenchymal stem cells and rat cardiomyocytes in culture[9]. Since then, TNTs have been reported as a mechanism of intercellular mitochondria

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Box 1

Key definitions

Vertical inheritance of mitochondria: mitochondria passed on to daughter cells during cell division.

Horizontal or intercellular transfer of mitochondria: the delivery of mitochondria from one cell type to another, not through vertical inheritance.

Mitochondria transfer axis: a defined cell of origin and a defined recipient cell type establish a mitochondria transfer axis.

Free mitochondria: mitochondria that have been released from a cell but are not enveloped by an additional membrane structure, such as an extracellular vesicle.

Extracellular vesicle-associated mitochondria: mitochondria that have been released from a cell and are contained within an extracellular vesicle.

transfer in the cardiovascular system[9–17], immune system[18–20], respiratory system[6,21–24], corneal epithelium[25], tumours[8,26–35], and central nervous system in both neuronal injury[36–39] and neurodegeneration[40]. The formation of TNTs depends on growth-associated protein 43 (GAP43)[41] and perhaps also Cx43 (refs. 5–7), and mitochondria are shuttled along an actin–microtubule highway using the Rho-GTPase Miro1 to enter the cytoplasm of the recipient cell[23].

Given that TNTs enable sharing of multiple cellular components, it remains a challenge to determine whether phenotypes ascribed to contact-dependent intercellular mitochondria transfer are correlative or directly mediated by the exchange of mitochondria between cells. It will be useful to determine the molecular mechanisms that cells use to transfer mitochondria via TNTs or GJCs compared with other cargo. This may allow for selective disruption of mitochondria transfer while allowing other cellular cargo to be transferred. There are also open questions about whether the donor or recipient cell calls for mitochondria transfer via a TNT or GJC or whether it is a cooperative process involving signals from both participating cell types.

Extracellular vesicle-associated mitochondria. Another commonly reported mechanism of intercellular mitochondria transfer is the release and capture of extracellular vesicle-containing mitochondria (EVMs) as cargo. EVMs can be categorized based on size and their mitochondrial cargo. Small extracellular vesicles approximately 100–200 nm in diameter often contain oxidatively damaged mitochondrial components, as has been shown for EVMs released by white and brown adipocytes[42,43]. These extracellular vesicles are marked with the tetraspanins CD63, CD9 and CD81. In brown adipose tissue, brown adipocytes experiencing thermogenic stress accumulate damaged mitochondrial components, which are then removed via the formation of mitochondria-derived vesicles (MDVs)[43]. These structures are formed in a PINK1-dependent manner and are packaged into extracellular vesicles approximately 100 nm in size before being ejected from the cell, probably via multivesicular bodies. However, this ejection process is impaired without parkin, an E3-ubiquitin ligase that binds to PINK1 and labels damaged mitochondrial components to target them for degradation via mitophagy[42]. Therefore, PINK1–parkin interactions are essential for both mitophagy and exportation of MDVs, and there must be factors downstream of parkin that determine which pathway is used to eliminate damaged mitochondrial components.

Like brown adipocytes, osteoblasts release mitochondria in extracellular vesicles but do so through various export mechanisms, including release of fragmented mitochondria and MDVs formed from mitochondrial donuts[44]. This process is mediated by a CD38-dependent process and is inhibited by OPA1. In this context, the released EVMs promote osteoprogenitor cell differentiation into osteoblasts in a positive-feedback loop that promotes bone formation. As osteoblasts and bone marrow adipocytes are derived from a common lineage, it will be interesting to determine whether mitochondria transfer might contribute to cell-type specification.

Cardiomyocytes also export damaged mitochondria in extracellular vesicles in two types of EVMs. First, they release large, damaged mitochondria in LC3-studded extracellular vesicles called exophers, which are 3–4 μm in diameter[45]. The presence of LC3 on these extracellular vesicles implies that they are derived from the autophagolysosomal system. These exophers are generated preferentially in the setting of impaired autophagy in cardiomyocytes and captured by heart-resident macrophages, where the cardiomyocyte mitochondria are degraded. Second, cardiomyocytes release mitochondria 300–600 nm in size in extracellular vesicles via multivesicular bodies[46]. The small GTPase Rab7, which is involved in lysosomal fusion[47], determines whether these EVMs are released from the cell[46]. Activated Rab7–GTP favours lysosomal degradation of mitochondria within the cell, whereas inactivated Rab7–GDP leads to the exportation of these mitochondria in extracellular vesicles.

Although most reports have suggested that mitochondria contained within extracellular vesicles are damaged, this is not always the case. Several reports indicate that intact, functional mitochondria can be released from cells in approximately 1-μm-sized extracellular vesicles, which may also be released from cells via the multivesicular body or bud off from the plasma membrane. For example, platelets release respiratory-competent mitochondria in extracellular vesicles (as well as free mitochondria) after activation by thrombin, and this process appears to be mediated via a plasma membrane budding mechanism rather than multivesicular body packaging[48]. Furthermore, in the brain following ischaemic stroke, astrocytes release EVMs containing mitochondria for delivery to hypoxic neurons to support neuronal mitochondrial metabolism and survival[49]. CD38 mediates this process, and impairing it leads to more severe stroke pathology and worse outcomes in mice. In addition, macrophages release CD200R-studded EVMs in the dorsal root ganglia for delivery to neurons via iSec1, dampening the propagation of inflammatory pain signals to the brain[50]. These studies indicate that mitochondria transfer via EVMs is not purely utilized to maintain mitochondria quality control of the donor cell and can regulate recipient cell functions.

Further supporting this idea are studies involving neural stem cells, which release intact, functional mitochondria in extracellular vesicles[51]. Placing these EVMs on mtDNA-depleted ρ^0 cells restores normal metabolic characteristics, including reversion of their dependence on uridine for cell survival. Neural stem cell-derived EVMs are endocytosed and then integrated into the mitochondrial network of bone marrow-derived macrophages. This process blocked the metabolic reprogramming that occurs in macrophages following lipopolysaccharide stimulation. It is unclear how the mitochondria in extracellular vesicles enter the cytoplasm of bone marrow-derived macrophages or ρ^0 cells. It is possible that the extracellular vesicle fuses with the endosome membrane, releasing the mitochondrial contents into the cytoplasm of the recipient cell. Additional studies are needed to understand the mechanisms by which EVMs dock on their target cells, how they are processed once internalized and their localization in the cell.

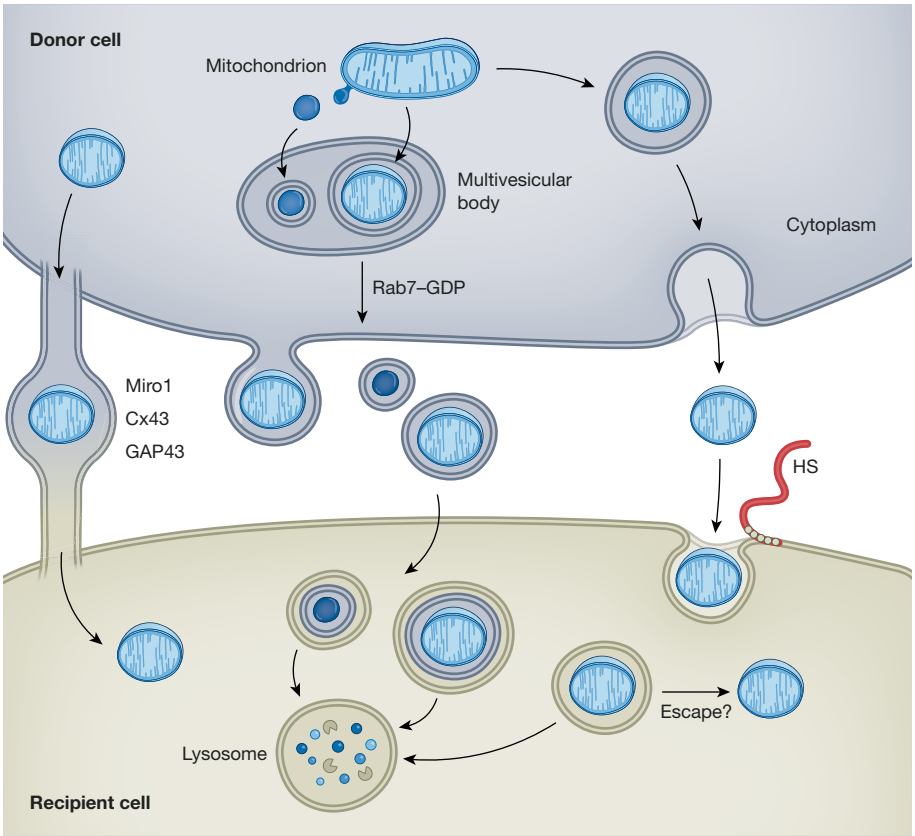

Fig. 1 | Mechanisms of mitochondria transfer. Cells transfer mitochondria through transient cellular connections, such as tunnelling nanotubes, that depend on Cx43, GAP43 and the Rho-GTPase Miro1 shuttle. In addition, mitochondria are exported from cells via multivesicular bodies. Mitochondria-derived vesicles and whole mitochondria are packaged in vesicles studded with CD9, CD63, CD81 and/or LC3, which are released as extracellular vesicles in a Rab7–GDP-dependent manner for capture by recipient cells. Mitochondria are also released in extracellular vesicles via budding off the plasma membrane. The recipient cell degrades mitochondria captured in extracellular vesicles via the lysosome. Finally, free mitochondria are released from cells and then captured by recipient cells in a heparan sulfate (HS)-dependent manner. Captured mitochondria can then be degraded via the lysosome, with some evidence suggesting that they might escape into the cytoplasm.

Release and capture of free mitochondria. The third major mechanism of intercellular mitochondria transfer is the release of free or naked mitochondria, which are then captured by recipient cells. This form of extracellular mitochondria was, to our knowledge, first identified in the blood of mice and humans, with one source being activated platelets, which release both EVMs and free mitochondria upon activation in an approximately 2:1 ratio[48]. In the blood, free mitochondria lacking an extracellular vesicle are approximately 0.5–1 µm in diameter and contain a full-length mtDNA genome[52,53]. Cell-free mitochondria in mouse and human blood can be stained with TMRE, a membrane potential-dependent mitochondria dye, suggesting that cell-free mitochondria in the blood are polarized[54]. Consistent with this polarized state, fresh human plasma can consume oxygen but not after mitochondria are removed[48], an observation that was confirmed by one group[52] but not another[55]. The cellular sources of free mitochondria in blood are not well described but are probably heterogeneous. Platelets are one source[48], and adipocytes are another[53]. Evidence that these mitochondria are not in extracellular vesicles are the surface expression of the outer mitochondrial membrane protein TOM22; the lack of extracellular vesicle markers such as CD9, CD63 and CD81; and electron micrographs showing cell-free mitochondria without an extracellular vesicle membrane[48,52,53]. However, there are probably many sources of mitochondria in circulation.

Cells release free mitochondria in a manner that depends on mitochondrial fission proteins, such as dynamin-related protein 1 (DRP1) and mitochondrial fission 1 protein (FIS1)[56]. We lack a detailed understanding of how these mitochondria are then packaged for exportation, but the cell of origin probably contains these mitochondria in vesicles that fuse with the plasma membrane to release the free mitochondria into the extracellular space. The free mitochondria are then captured via a phagocytic mechanism, which some have suggested to be macropinocytosis[57]. A genome-wide CRISPR knockout screen identified that free mitochondria are captured by recipient cells using a heparan sulfate-dependent process[58], perhaps reflecting an ancient origin of intercellular mitochondria transfer. Heparan sulfate is complex, varying in length, sulfation pattern, epimerization, attached core protein and other features that contribute to diverse structures and specificities[59]. Sulfation of the heparan sulfate chain at the 6-O position is essential for mitochondrial capture. Furthermore, heparan sulfate does not mediate the capture of latex beads of a similar size as free mitochondria[58]. These observations suggest that the biochemical features of heparan sulfate can confer some degree of specificity to bind to free mitochondria and are not simply due to the negative charge of heparan sulfate, as heparan sulfate lacking 6-O sulfation still retains other sulfate groups[58]. Treating mice with the anticoagulant heparin, a highly sulfated form of heparan sulfate, is sufficient to partially impair mitochondria transfer from adipocytes to macrophages[58], suggesting that this mitochondria transfer pathway is operative in vivo and may be affected by this commonly used class of anticoagulant.

After being captured by a recipient cell, the fate of naked mitochondria is unclear. One study has suggested that some naked mitochondria can escape the endosomal compartment after being captured[60]. This controversial observation requires verification and a detailed understanding of the underlying mechanism. However, it is supported by

studies indicating that cells can capture purified mitochondria and use them for aerobic respiration in vitro[61] and in vivo[53]. For this to occur, the exogenous mitochondria must be able to respire in endosomes or escape into the cytoplasm of the recipient cell. As bacteria and viruses can escape the endolysosomal compartment, it is not inconceivable that mitochondria may also possess this ability, especially given their proteobacterial ancestral origins. If mitochondria escape mechanisms do exist, this process is very likely mediated by genes in the nuclear genome.

Functions of mitochondria transfer

Recently, our understanding of the functional roles of intercellular mitochondria transfer has expanded. Although several observations have indicated that mitochondria transfer supports the energy metabolism of recipient cells, recent studies have indicated that this process contributes to maintaining the function of various organ systems.

Support of recipient cell metabolism. To our knowledge, the first evidence that intercellular mitochondria transfer supports the energetic demands of recipient cells was the demonstration that ρ^0 cells, which cannot perform oxidative phosphorylation and thus require uridine and pyruvate to grow, can obtain mitochondria from co-cultured cells in vitro to restore their ability to produce ATP and resume cell division[4]. Exposing ρ^0 cells to purified mitochondria can also rescue aerobic respiration in vitro[61]. Similar results have also been observed in human breast cancer cells exposed to purified mitochondria in vitro[62]. Furthermore, administering purified wild-type mitochondria to mice lacking NDUFS4, a nuclear genome-encoded protein essential for mitochondrial complex I activity, can completely restore mitochondrial metabolism in peritoneal macrophages in vivo[53]. Although wild-type and NDUFS4-deficient cells capture exogenous mitochondria with similar efficiencies, macrophages lacking NDUFS4 appear to retain exogenous mitochondria for longer, suggesting that healthy exogenous mitochondria may be selectively retained in metabolically compromised cells. Interestingly, exogenous mitochondria do not appear to substantially affect the mitochondrial metabolism of wild-type or healthy macrophages in vitro or in vivo, suggesting that cells may only utilize exogenous mitochondria for aerobic respiration when they are experiencing a metabolic crisis or surpass their metabolic capacity. Consistent with this idea, BV2 cells do not appear to use purified mitochondria in normal culture conditions to boost aerobic respiration but can utilize them to overcome pharmacologically induced mitochondrial failure[53].

These findings lead us to speculate that cells preferentially use their own mitochondria for nutrient metabolism but can import and utilize cell-free mitochondria if the demand arises in response to a metabolic emergency. We refer to this concept as the 'generator hypothesis', reflecting that many buildings rely on an electric grid for power but can use energy supplied by generators to overcome grid failures. In this metaphor, mitochondria delivered by other cells serve in a generator capacity until mitochondrial metabolism of the cell is restored.

Several in vivo studies support this notion. In particular, ischaemic neurons and cardiomyocytes can receive and use mitochondria from other cell types to support their survival[49,63–65]. In the ischaemic brain, astrocytes release EVMs in response to CD38 signalling, leading to the transfer of mitochondria to neighbouring neurons[49] (Fig. 2a). Inhibiting this process with an anti-CD38 monoclonal antibody was associated with worse outcomes in mice subjected to an ischaemic stroke model. Another group has shown that intra-arterial administration of purified mitochondria shortly after ischaemic stroke leads to accumulation of exogenous mitochondria in the infarct zone, restores adenosine triphosphate concentrations locally and reduces the volume of the infarct[66]. Interestingly, the levels of extracellular mitochondria are also increased in the cerebrospinal fluid of rats and humans after subarachnoid haemorrhage, and a higher membrane potential of cell-free mitochondria in cerebrospinal fluid is associated with better clinical outcomes in patients three months after subarachnoid haemorrhage[67]. These studies suggest that cell-free mitochondria may support the metabolism of neurons in both ischaemic stroke and subarachnoid haemorrhage.

Mitochondria transfer-mediated support of cellular energetic demands can also have pathogenic outcomes, at least in cancer (Fig. 2b). Initially, it was shown that ρ^0 tumour cells divide slowly but can acquire respiratory function by obtaining whole mitochondria and associated mtDNA from neighbouring cells, thereby enabling faster cell division and restoring their tumorigenic potential[68,69]. The mechanisms by which exogenous mitochondria drive cancer cell proliferation are not well understood but may relate to the generation of reactive oxygen species that stimulate delivery of mitochondria to cancer cells[30] and that lead to activation of mitogenic signalling pathways, such as extracellular signal-regulated kinases[70]. The role of mitochondria transfer in cancer is complex, as this process has been reported to increase neoplastic cell proliferation[30,32,68,70,71], invasiveness[72], immune evasion[73] and resistance to therapy[26,73–75].

Cancer cells are known to obtain mitochondria from other cells via TNTs and EVMs; however, the mechanisms of transfer and functional implications may depend on the cell of origin and recipient cancer cell type. Indeed, tumour cells can obtain mitochondria from different cell types in the tumour microenvironment, including mesenchymal stem cells/stromal cells[30,62,71], cancer-associated fibroblasts[32], T cells[73], macrophages[70], astrocytes[41] and other cell types, and these distinct mitochondria transfer axes may differentially affect the recipient cancer cell. For example, breast cancer cells can acquire mitochondria from macrophages to promote cell proliferation and from T cells to support cancer cell aerobic respiration and immune evasion[70,73]. Given the multitude of intercellular mitochondria transfer axes reported in cancer, there is a need to understand how these various mitochondria transfer axes intersect to regulate tumour growth and resistance to therapy. Developing a better understanding of these pathways may lead to novel therapeutic strategies against cancer.

Donor cell mitochondria quality control. Although many studies have indicated that intercellular mitochondria transfer is involved in supporting the metabolism of recipient cells, a series of recent studies indicate that this process also serves to support the mitochondrial health of the donor cell. As described in detail above, brown adipocytes and cardiomyocytes release damaged mitochondrial components in extracellular vesicles, which are then captured and degraded by tissue-resident macrophages (Fig. 2c). Impairing the degradation of ejected mitochondria by macrophages is associated with impaired cardiac function[45] and brown adipose tissue thermogenesis[43], indicating that this process preserves normal tissue function. Cardiomyocytes from mice and humans with loss-of-function mutations in the lysosomal protein LAMP2 release more EVMs[46], suggesting that ejection of damaged mitochondria may be a compensatory mechanism to prevent accumulation of damaged mitochondria when cells cannot successfully recycle them via mitophagy. Consistent with this idea, a recent study has found that mitochondrial oxidative stress is sufficient to promote the exportation of damaged mitochondria in zebrafish retinas to Müller glia, where they are degraded[76]. These data suggest that irreplaceable or difficult-to-replace cells eject damaged mitochondria for elimination by macrophages or other support cells as a mechanism of mitochondria quality control that is conserved from fish to mammals. As one cell type is borrowing the mitophagy function of another, we refer to this process as 'licensed mitophagy'.

Regulation of wound healing. One of the first clues that intercellular mitochondria transfer pathways are important outside of metabolic support of the donor and recipient cells is the role of this process in wound healing. Physical damage to epithelial cells leads to a complex,

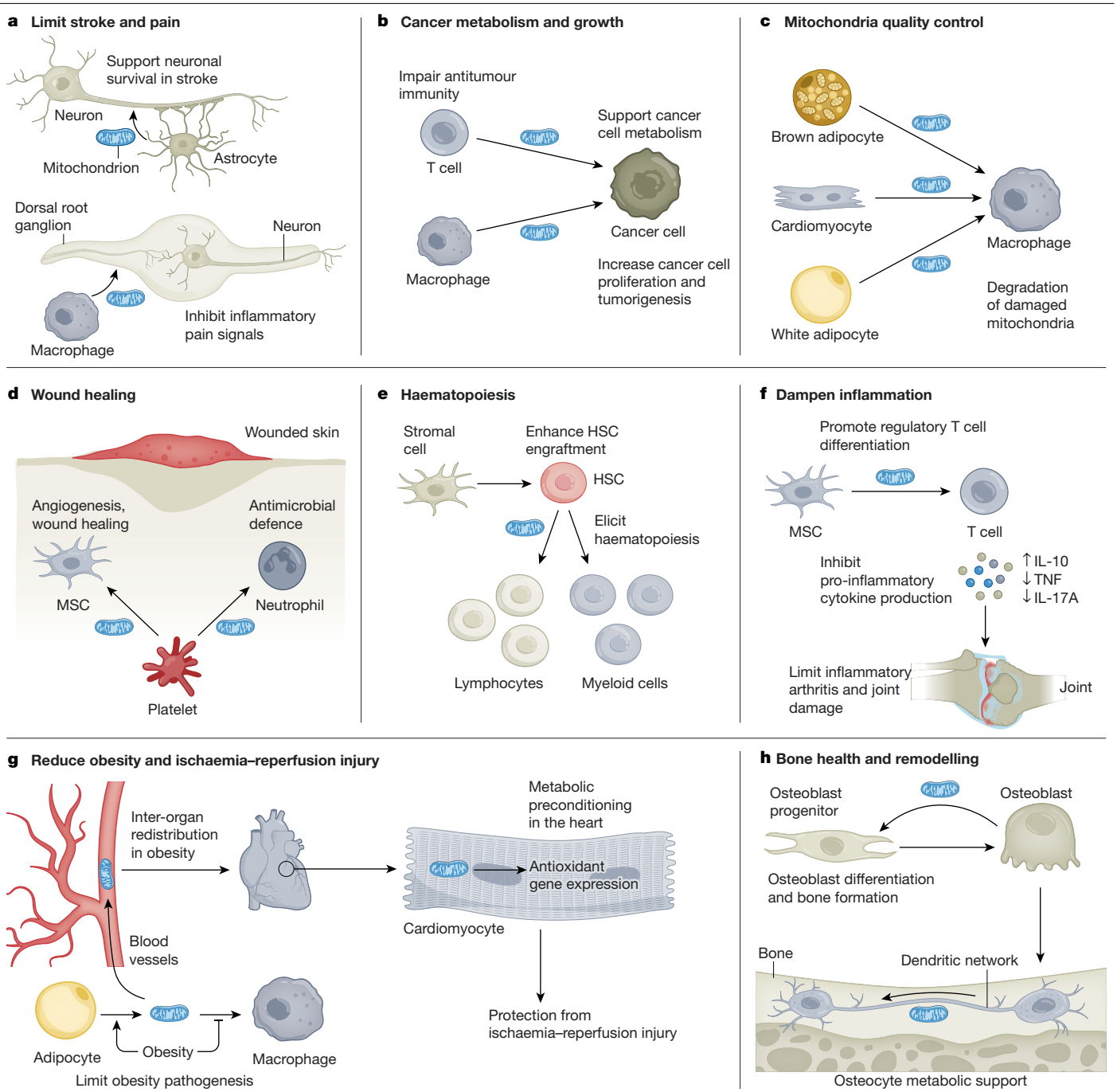

Fig. 2 | Functional roles of mitochondria transfer. Mitochondria are transferred between cells in tissue-specific and cell-type-specific mechanisms and have been linked to various physiological and pathological processes in diverse tissues. **a**, In the central nervous system, astrocytes deliver mitochondria to neurons to support their survival in ischaemic stroke, whereas in the peripheral nervous system, macrophages deliver mitochondria to neurons in the dorsal root ganglia to limit inflammatory pain signal propagation. **b**, Cancer cells obtain mitochondria from immune cells such T cells and macrophages, impairing antitumour immunity while also supporting the cellular metabolic demands of cancer cells and driving their proliferation. **c**, Adipocytes and cardiomyocytes transfer damaged mitochondria to macrophages for elimination and preservation of mitochondrial quality of the donor cell. **d**, In wounded skin, activated platelets seal the damaged vessel and deliver their mitochondria to mesenchymal stem cells (MSCs) to promote angiogenesis and wound healing, as well as to neutrophils to promote antimicrobial defence. **e**, Mitochondria transfer enhances haematopoietic stem cell (HSC) engraftment and contributes to eliciting haematopoiesis. **f**, MSCs also transfer mitochondria to T cells to promote regulatory T cell differentiation and inhibit pro-inflammatory cytokine production, limiting joint damage in arthritis. **g**, In white adipose tissue, adipocytes transfer mitochondria to macrophages to support maintenance of tissue homeostasis, a process that is impaired in obesity to divert adipocyte mitochondria into the blood for inter-organ transport to the heart, where cell-free mitochondria elicit an antioxidant response that protects the heart from ischaemia–reperfusion injury. **h**, In the bone, osteoblasts transfer mitochondria to their progenitors to reinforce osteoblast differentiation and promote bone formation, and osteocytes transfer mitochondria along dendritic networks to support their metabolism and bone mineral homeostasis.

intricate wound-healing response that limits bleeding, defends against invading microorganisms and repairs the barrier surface. As platelets are recruited to the site of injury to seal the vessel surface, their mitochondria move from the centre of the platelet to the inner surface of the plasma membrane[48]. As the platelets degranulate, their mitochondria are released in the extracellular space as EVMs and free mitochondria[48].

These platelet-derived mitochondria have been reported to have distinct, complementary functions. It was first shown that platelet-derived mitochondria bind to the surface of neutrophils, driving an antimicrobial inflammatory response[48]. Subsequently, it has been shown that platelet-derived mitochondria are also captured by subendothelial mesenchymal stem cells, leading to the secretion of pro-angiogenic factors into the vessel microenvironment to promote a wound-healing response[57]. These findings suggest that platelets participate in coordinated mitochondria transfer axes: one to neutrophils that elicits a local innate immune response at the injury site and a second that promotes wound healing to restore the broken barrier surface (Fig. 2d).

Mitochondria transfer from cell types other than platelets might also contribute to wound healing. For example, endothelial cell progenitors can release mitochondria that are captured by mature endothelial cells in the brain, a process that is associated with increased angiogenesis and enhanced endothelial barrier function[77]. As another example, mesenchymal stem cell-derived mitochondria can be captured by endothelial cells in vitro and in vivo, increasing antioxidant defence systems, decreasing cellular senescence and reducing myocardial infarction severity[78]. In vitro exposure of human umbilical vein endothelial cells to mesenchymal stem cell-derived mitochondria increases the formation of tubal structures[78]. These studies suggest that intercellular mitochondria transfer to endothelial cells can enhance angiogenesis, which is essential for the revascularization of wounded tissue.

Regulation of the immune system. Several features of mitochondria are thought to be relics of their bacterial ancestry, including their circular genomic DNA with hypomethylated CpG residues and the presence of formylated N-terminal methionine peptides in mtDNA-encoded proteins. The unmethylated CpG residues and formylated N-terminal methionine peptides are recognized by the immune system as damage-associated molecular patterns by Toll-like receptor 9 (TLR9) and formyl peptide receptors 1–3 (FPR1–3), respectively, and drive pro-inflammatory immune responses[79,80]. Because of the presence of these mitochondria-associated damage-associated molecular patterns, it has been widely assumed that cell-free mitochondria are intrinsically pro-inflammatory. However, intercellular mitochondria transfer to immune cells has been reported to have both pro-inflammatory and anti-inflammatory effects.

The best-described example of mitochondria transfer being pro-inflammatory is when neutrophils are the recipient. As noted above, platelet-derived mitochondria transfer to neutrophils elicits a pro-inflammatory process that may facilitate the clearance of foreign material from wounds[48]. Similarly, in the setting of lung transplantation, allografts experiencing rejection release mitochondria and/or particles containing mitochondrial components into the alveolar space and blood[81,82]. The released mitochondrial components trigger an FPR1-dependent neutrophil response that potentiates rejection of the engrafted organ in mice[81]. The abundance of cell-free mitochondria or mtDNA in bronchoalveolar lavage fluid or blood from patients with a lung transplant directly correlates with early rejection, the severity of lung allograft dysfunction, and concentrations of IL-6, IL-8, IFNγ and IL1-RA in circulation[81,82]. These data suggest that tissue damage-associated release of mitochondria appears to be pro-inflammatory and may relate to formylated N-terminal methionine peptides or released mtDNA; however, mitochondria transfer probably regulates the activation state of the immune system in a more complex manner. For example, in the bone marrow, stromal cell-derived mitochondria are delivered to progenitor cells to induce a leukocyte proliferative response that defends against acute bacterial infection in distant sites[20] (Fig. 2e). This observation suggests that mitochondria transfer pathways may contribute to mobilizing host-protective immune responses.

Conversely, there are several examples in which mitochondria transfer is anti-inflammatory. Early reports indicated that mitochondria transfer reduces inflammation in lung epithelial cells in asthma and acute lung injury[6,21]. Later studies have reported anti-inflammatory effects of intercellular mitochondria transfer in the adaptive immune system, especially with the delivery of mitochondria to T cells. It appears that mitochondria transfer preferentially occurs to $CD4^+$ T cells and induces a regulatory T cell phenotype with enhanced IL-10 expression and immunosuppressive capacities in graft-versus-host disease and arthritis models[83,84]. Similarly, transfer of mitochondria delivers citric acid cycle intermediary metabolites, such as aspartate, that inhibit $CD4^+$ T helper type 1 cell pro-inflammatory cytokine expression and can be used to limit joint damage in a humanized mouse model of rheumatoid arthritis[85,86]. Together, these studies suggest that mitochondria transfer can also have anti-inflammatory effects (Fig. 2f). An exciting area for further research is to understand how intercellular mitochondria transfer affects immune cell activation, differentiation and function throughout the course of the normal immune response, and how dysregulation of this process might contribute to inflammation.

Maintenance of metabolic homeostasis. Several recent papers have demonstrated that intercellular mitochondria transfer regulates local and systemic metabolic homeostasis, especially in adipose tissues. Using bone marrow transplants and adipocyte-specific mitochondria reporter mice, we found that adipocytes transfer mitochondria to macrophages in white adipose tissue under steady-state (that is, healthy) conditions[58]. This process is partially mediated by heparan sulfate on the surface of macrophages, which facilitate the capture of adipocyte-derived mitochondria. In diet-induced obesity, macrophages exhibit downregulated heparan sulfate levels on their surface and decreased mitochondria transfer, despite their increased phagocytic efficiency[58]. Deleting *Ext1* in macrophages to ablate heparan sulfate synthesis leads to reduced mitochondria transfer in vivo and is associated with metabolic dysfunction, weight gain and increased susceptibility to high-fat-diet-induced obesity[58]. These studies suggest that intercellular mitochondria transfer from adipocytes to macrophages supports normal energy homeostasis (Fig. 2g), although the underlying mechanisms of this effect are not yet clear.

In the setting of high-fat-diet-induced obesity in mice, energetically stressed adipocytes release some of their mitochondria into the blood in at least two major forms: small extracellular vesicles containing oxidatively damaged mitochondria[42] and large, free mitochondria approximately 1 μm in diameter[53]. Adipocytes exposed to palmitic acid or that are undergoing lipolysis release more adipocyte-derived extracellular vesicles, many of which contain mitochondrial proteins[42,87]. The adipocyte-derived mitochondria are then distributed to other organs, such as the heart[42,53], where they promote an antioxidant response that preconditions the heart to defend against metabolic stress and ischaemia–reperfusion injury[42]. Mitochondria from other organs, such as skeletal muscle, also protect against ischaemia–reperfusion injury of the heart, improving post-reperfusion ventricular pressures and reducing humoral evidence of heart damage[63–65]. The underlying mechanisms of the cardiac benefits from obtaining cell-free mitochondria from other organs are not well defined but may involve induction of antioxidant enzymes in the heart[42]. In humans with metabolically unhealthy obesity, there are more EVMs in blood than in metabolically normal controls, suggesting that this biological pathway also might be operative in human obesity[42].

Later, we demonstrated that dietary long-chain fatty acids (LCFAs) directly inhibit mitochondria capture by macrophages in white adipose tissue, diverting adipocyte-derived mitochondria into the blood for

delivery to the heart[53]. Other models of obesity with low dietary LCFA exposure, including ageing, a corn-starch diet or a high-fat diet enriched with medium-chain fatty acids instead of LCFAs, do not exhibit alterations in adipocyte-to-macrophage mitochondria transfer in white adipose tissue and are not characterized by increased adipocyte-derived mitochondria in blood. Together, these studies suggest that macrophages sense dietary factors such as LCFAs and determine whether adipocyte-derived mitochondria are captured locally for elimination or released into the blood for delivery to distant organs, where they support systemic metabolic adaptation to nutrient stress.

Brown adipocytes can also release mitochondria in small extracellular vesicles and transfer them to macrophages in vivo[43]. Damaged mitochondrial membranes are removed as MDVs and ejected from brown adipocytes in extracellular vesicles. Macrophages capture these brown adipocyte-derived extracellular vesicles and degrade them. Depleting macrophages leads to the accumulation of brown adipose tissue extracellular vesicles in the tissue, which can either be recaptured by brown adipocytes or stimulate signalling pathways that downregulate the expression of thermogenic genes, leading to impaired brown adipose tissue function and an inability to properly defend core body temperature in response to cold environmental temperatures[43]. Although adipocytes transfer some of their mitochondria to macrophages to support the maintenance of mitochondria quality control, they also deliver numerous metabolites, proteins and signalling molecules in the process that may influence the function of the recipient cell type. This raises the possibility that mitochondria transfer pathways may enable cells to efficiently communicate a great deal of metabolic information to each other locally and between distant organs. We speculate that maintaining the correct mitochondria transfer axes is essential to tissue homeostasis and that these transfer axes can be altered locally or systemically to influence organ function.

Beyond adipose tissues, mitochondria transfer also appears to be essential for maintaining bone metabolic homeostasis (Fig. 2h). Osteoblasts transfer mitochondria to osteoblast progenitors, a process that stimulates their differentiation into mature osteoblasts[44]. This feed-forward mechanism promotes bone matrix formation. In addition, specialized bone cells called osteocytes, which are embedded within mineralized bone, transfer mitochondria to each other via an interconnected dendritic network[88]. Donated mitochondria support the metabolic demands of the receiving osteocytes, thereby optimizing bone mineral homeostasis and health.

Mitochondria transfer therapeutics

The realization that cells can import mitochondria from their environment or obtain them from other cell types has stimulated interest in tapping into this biology for therapeutic purposes. It could be argued that the first clinical application involving artificially enforced mitochondria transfer is ooplasmic transplantation, an early form of mitochondria replacement therapy in which cytoplasm containing mitochondria and mtDNA from a healthy donor oocyte is microinjected directly into another oocyte with a pathogenic mtDNA mutation. The resulting cells contain both donor and recipient mtDNA and are used for in vitro fertilization. Although ooplasmic transplantation is not currently used clinically and has been replaced by other forms of mitochondria replacement therapy[89], donor mtDNA has been detected in children born following this procedure[90]. Therefore, ooplasmic transplantation is an example in which exogenous mitochondria that gain entry into the cytoplasm can be incorporated at least partially into the mitochondrial network in humans in vivo.

Outside of mitochondria replacement therapy, there are considerable efforts to harness the biology of mitochondria transfer to develop new therapies for patients. Two promising postnatal mitochondria transplantation strategies have emerged. One involves exposing a cellular product to purified mitochondria during cell manufacturing or processing before transfusion to the patient. In preclinical studies, this approach has been used to enhance engraftment of haematopoietic stem cells in mice[91]. Subsequently, an exciting clinical trial has been performed in which autologous haematopoietic stem cells from patients with large-scale mtDNA deletion syndromes were loaded with healthy maternally derived mitochondria before haematopoietic stem cell transplantation[92]. This treatment was associated with improved clinical features and quality of life. Although there are several possible explanations for how mitochondrial augmentation of haematopoietic stem cell transplantation might ameliorate inherited mitochondrial diseases, one possibility is that the engrafted cells deliver wild-type mitochondria to recipient cells. Another is that the exogenous mitochondria metabolically rewire the cells ex vivo before administration and that this process functionally alters their functional state. This idea is particularly interesting in the era of engineered cells (for example, chimeric antigen receptor T cells), as mitochondrial treatment of cells during manufacturing might improve cell product performance.

The second postnatal mitochondria transplantation strategy is the administration of purified mitochondria or EVMs directly to patients. Several therapeutic indications for administering exogenous mitochondria have been explored, including but not limited to preventing ischaemia–reperfusion injury in the heart[63,64,93] or central nervous system[66,94,95]. There has been speculation about the therapeutic potential of postnatal mitochondria transplantation to treat inherited mitochondrial diseases, such as Leigh syndrome. Although exogenous mitochondria can rescue cell-intrinsic defects in NDUFS4-deficient cells from mice that model Leigh syndrome[53], there is not yet direct evidence that mitochondria transplantation ameliorates this disease. Overall, these data suggest that administering cell-free mitochondria may have potential as a novel class of subcellular therapy. Translational studies furthering this type of therapy should investigate the relevance of the mitonuclear conflict with postnatal mitochondria transplantation, the degree of mtDNA heteroplasmy achieved and the possibility of reversion to pathogenic variants after treatment. In addition, it will be important to consider that the source of mitochondria may substantially impact the safety or efficacy of mitochondria transplantation therapy.

Three lines of evidence suggest that cell-free mitochondria are likely to be tolerated relatively well by humans. First, an early clinical study of autologous mitochondria transplantation in paediatric patients on extracorporeal membrane oxygenation found no short-term complications from mitochondria transplantation[65]. Second, cell-free mitochondria are an abundant, normal component of blood[48,52], suggesting human physiology is permissive of cell-free mitochondria. Third, quantities of free and extracellular vesicle-associated mitochondria are high in some blood products, especially stored platelets[48], that are regularly administered to patients without complications. These observations suggest that administering cell-free mitochondria from autologous or heterologous sources might be well tolerated; however, it will be necessary to carefully evaluate the safety and efficacy of emerging mitochondria transplantation modalities.

Outlook

The intracellular mitochondria transfer field is growing rapidly, fuelled by improved tools and techniques to measure mitochondria transfer in vivo and observations that intercellular mitochondria transfer is functionally important in both healthy and pathological states. Many organ systems, cell types and diseases remain to be studied through the lens of intercellular mitochondria transfer biology. Although progress has been made, we still know relatively little about the molecular mechanisms that underlie the different intercellular mitochondria transfer axes known to occur. Several major future questions warrant detailed investigation, including whether mitochondria transfer occurs in humans in vivo and in what physiological and pathophysiological

contexts; what signals determine whether cells deliver or accept mitochondria; which genes are required for each mitochondria transfer mechanism to occur; and how intercellular mitochondria transfer affects the function of both the donor cell and the recipient cell. Answers to these questions will probably be cell type, tissue and context specific but have the potential to fundamentally alter our understanding of mitochondrial biology and may reveal biological pathways that can be tapped for therapeutic or diagnostic purposes.

Data availability

Data sharing is not applicable because no new data were created or analysed in this Review article.

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