

REVIEW

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Inter- and intracellular mitochondrial communication: signaling hubs in aging and age-related diseases

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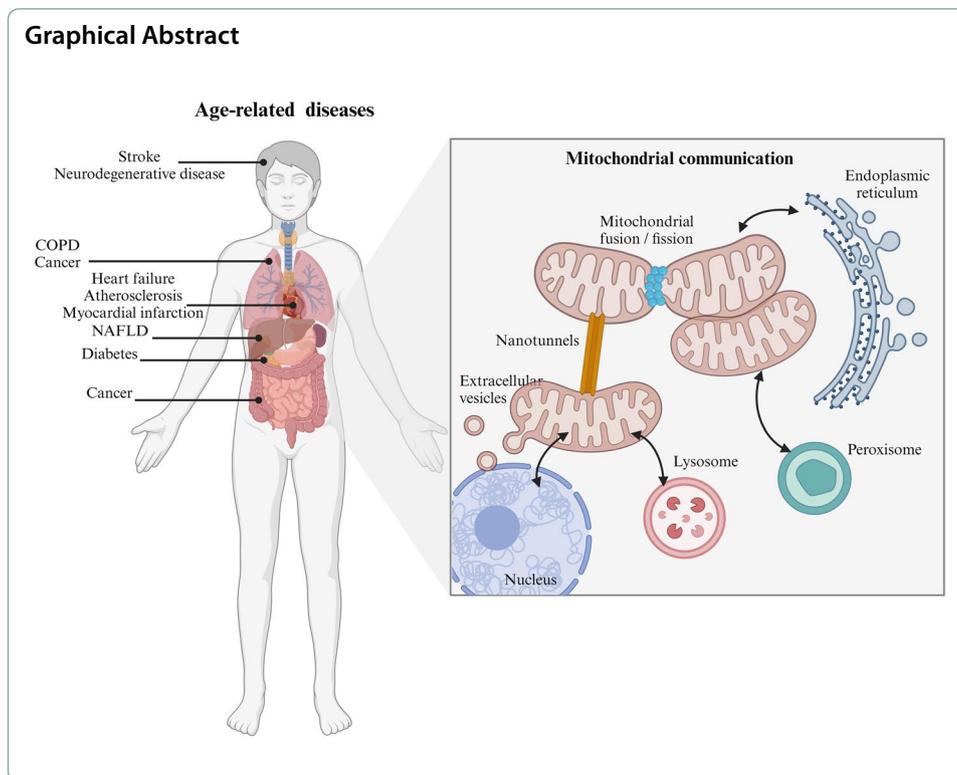
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Abstract

Mitochondria are versatile and complex organelles that can continuously communicate and interact with the cellular milieu. Deregulated communication between mitochondria and host cells/organelles has significant consequences and is an underlying factor of many pathophysiological conditions, including the process of aging. During aging, mitochondria lose function, and mitocellular communication pathways break down; mitochondrial dysfunction interacts with mitochondrial dyscommunication, forming a vicious circle. Therefore, strategies to protect mitochondrial function and promote effective communication of mitochondria can increase healthy lifespan and longevity, which might be a new treatment paradigm for age-related disorders. In this review, we comprehensively discuss the signal transduction mechanisms of inter- and intracellular mitochondrial communication, as well as the interactions between mitochondrial communication and the hallmarks of aging. This review emphasizes the indispensable position of inter- and intracellular mitochondrial communication in the aging process of organisms, which is crucial as the cellular signaling hubs. In addition, we also specifically focus on the status of mitochondria-targeted interventions to provide potential therapeutic targets for age-related diseases.

Keywords: Mitochondrial communication, Mitochondrial dysfunction, Aging, Age-related diseases, Signaling hubs





Introduction

Although commonly called the cell's powerhouse, mitochondria have roles beyond energy generation. They are essential for pathways within cells and organisms that control immunity, stress reactions, metabolism, and cellular fate [1–3]. To carry out these duties, mitochondria have formed intricate inter- and intracellular communication systems. Within cells, communication pathways consist of direct connections between mitochondria and other subcellular structures and indirect transportation of ions, metabolites, and other intracellular messengers through vesicles. Mitochondria can trigger stress reactions or other cellular alterations that release mitochondrial cytokine factors outside of cells. These factors can move between different tissues and react to immunological challenges originating from outside of cells. Mitochondrial communication refers to the processes by which mitochondria share information and energy capacity with neighboring mitochondria. Additionally, it encompasses the physical interactions and exchange of chemicals and metabolites between mitochondria and other organelles [4]. Nevertheless, the process of mitochondrial communication relies on the synchronized effort of numerous elements, and as a result, it is not infallible. The deregulation of communication between mitochondria and host cells has significant implications and serves as a fundamental element in various pathological diseases, including the aging process.

Aging is an intricate process characterized by a decrease in biological and metabolic functioning, leading to the onset of various age-related illnesses, such as neurological disorders, cardiovascular disorders, metabolic disorders, immune system disorders, and cancer [5]. Over the past 20 years, there has been a significant amount of research

on age-related aspects that have provided valuable insights into the aging process. This research has also identified interventions that can potentially extend human lifespan and enhance overall well-being [6–8]. The relationship between cellular and mitochondrial health in the aging process is well recognized as highly interconnected. In addition, it has been shown that affecting the condition of mitochondrial health and communication processes can affect the rate of senescence in a number of experimental organisms. Observations have revealed deficiencies in many molecular components involved in mitochondrial signaling pathways in aging and diseases associated with aging. This suggests that molecular deterioration may occur as a result of disruptions in mitochondrial communication.

However, the precise regulatory mechanism governing mitochondrial communication in aging process is still unknown, which could impede the progress of mitochondria-targeted therapeutics. In this review, we present an up-to-date analysis of the processes and physiological effects of communication in mitochondrial signaling, including the interactions with the hallmarks of aging. In addition, we evaluate the age-related diseases linked to malfunctions in mitochondrial communication. Gaining knowledge about the role of mitochondrial communication in regulating cellular homeostasis will provide a deeper understanding of how impaired mitochondria impact health during disease and the aging process.

Mitochondrial communication

To coordinate cellular processes such as metabolism, stress response, and adaptive nuclear gene expression, mitochondria employ a variety of communication mechanisms. It has been demonstrated that mitochondrial communication is implicated in crucial intracellular and intercellular processes, the nature and extent of which are continually being uncovered. In a dynamic cellular environment, mitochondrial communication

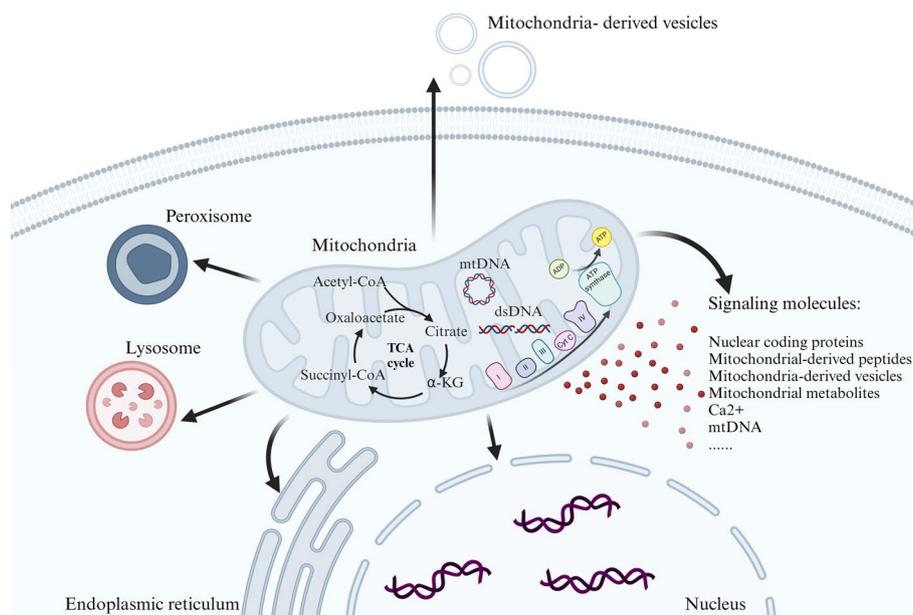


Fig. 1 Mitochondrial communication modes The figure was created with Biorender.com

transmits signals such as inflammation and metabolic stress to all cells and regions of the body to maintain cellular homeostasis (Fig. 1) [9].

Intracellular mitochondrial communication

Mitochondria are vital for multiple fundamental biological activities and establish a dynamic functional network to uphold cell homeostasis by interacting with cellular components, including the nucleus, endoplasmic reticulum (ER), peroxisome, lysosome, and other mitochondria. Cells can effectively respond to different environmental changes through the functional network of mitochondrial communication. Disruption in mitochondrial communication can result in the disruption of cell homeostasis and trigger a range of illnesses.

Mitoendoplasmic reticulum

In 1959, Copeland et al. discovered for the first time that there were many highly ordered tubular ER structures around mitochondria by transmission electron microscopy [10]. Vance first put forward the concept of mitochondrial-associated endoplasmic reticulum (MAMs) in 1990. MAMs are a lipid raft domain closely related to ER and mitochondria, participating in the control of diverse cellular biological processes and mediating mitochondria and ER [11]. Subsequently, Csordas et al. carried out 3D modeling of transmission electron microscope images, which further confirmed the relationship between the mitochondrial membrane and ER, which is similar but not overlapping, and the distance is between 5 and 25 nm [12]. The communication between mitochondria and ER is accomplished by many protein structures on MAMs. MAMs regulate calcium homeostasis and lipid synthesis and transport, as well as mitochondrial dynamics, mitophagy, and cell apoptosis. The abnormality of quantity, structure or function of MAMs is related to the occurrence of many age-related diseases [13–15].

MAMs are an essential platform for the ER and mitochondrial Ca^{2+} transporter [16]. Many studies have shown that the IP3R–GRP75VDAC complex formed by IP3R, GRP75, and VDAC as classical MAMs proteins is the main structure of Ca^{2+} transport from the ER to mitochondria [17, 18]. Stoica et al. found that ER-resident protein VAPB can bind to mitochondrial protein PTPIP51, affect the interaction between mitochondria and ER, and regulate intracellular Ca^{2+} homeostasis [19]. Studies have shown that the upregulation of Nogo-B protein expression in smooth muscle cells increases the distance between the ER and mitochondria, thereby reducing the calcium transfer from the ER to mitochondria, damaging mitochondrial function and, ultimately, unbalanced the proliferation and apoptosis of smooth muscle cells, thus promoting the occurrence and development of pulmonary arterial hypertension (PAH) [20]. Mfn1/2, which mediates mitochondrial fusion, and Drp1, which mediates mitochondrial division, play essential roles in mitochondrial dynamics [21]. Mfn2 is enriched in the MAMs region and connects the two organelles by forming homologous or heterologous complexes with Mfn1 or Mfn2 on the mitochondrial surface to regulate mitochondrial fusion and mitochondrial uptake of Ca^{2+} [22]. In mouse embryonic fibroblasts, knocking down Mfn2 makes contact between ER and mitochondria closer, resulting in increased Ca^{2+}

transfer between the two organelles and increased sensitivity of cells to mitochondrial Ca^{2+} overload [23]. When the mitochondria are divided, the tubular ER is close to the mitochondria, wrapping the contraction sites of the mitochondria and anchoring Drp1 to the mitochondrial membrane to form a Drp1 oligomer contraction ring, which leads to mitochondrial fission [24]. The synthesis of phospholipids mainly relies on the transport of phosphatidic acid between the ER and mitochondrial membranes. PSS1/2 can catalyze the conversion of phosphatidic acid (PA) into phosphatidylserine (PS), which is then transferred to the inner mitochondrial membrane to generate phosphatidylethanolamine (PE) under the action of phosphatidylserine decarboxylase (PSD), CHO-K1. Western blotting results of cells and mouse liver tissue showed that PSS1/2 was highly enriched in MAMs [25]. Studies have shown that the expression of Mfn2 is significantly reduced in liver tissues of patients with nonalcoholic fatty liver disease and mouse models, and specific knockout of Mfn2 from liver cells, the levels of inflammatory factors, and triglycerides in mice increased significantly, promoting the occurrence and development of liver fibrosis and liver cancer. The specific mechanism is that Mfn2 can bind to PS and promote the transfer of PS into the mitochondrial membrane structure, thereby promoting PE synthesis in mitochondria, elucidating the effect of Mfn2 on phospholipid metabolism in maintaining MAMs morphology and function, lipid metabolism, and ER homeostasis [26]. During the process of mitophagy, PINK1, which is localized in the MAMs region, can directly interact with BECN1 to promote the contact between mitochondria and ER and the formation of autophagosome precursor. Silencing PINK1 will reduce the enrichment of BECN1 on MAMs and inhibit the mitophagy process, suggesting that PINK1 is significantly involved in regulating mitophagy [27, 28]. MAMs can not only provide a platform for the occurrence of apoptosis but also recruit apoptosis-related regulatory factors. When the mitochondria divide, the tubular ER is close to the mitochondria and wraps the mitochondria at the fission site. When cells are exposed to apoptosis stress, BAX in the cytoplasm is activated and recruited to the fission site of mitochondria wrapped in ER, which promotes the permeability of mitochondrial outer membrane (MOMP) and the release of cytochrome C, thus inducing apoptosis [24].

Mitonucleus

Mitochondria serve as the central hub for cellular energy metabolism. However, most of the mitochondrial proteins are encoded by nuclear genes, and only 13 subunits of the electron transport chain complex (ETC) encode genes. Recent studies have confirmed the physiological function of CYTB-187AA, the 14th protein encoded by mitochondrial DNA (mtDNA) [29]. Therefore, mitochondria must communicate with the nucleus continuously to coordinate the expression and assembly of oxidative phosphorylation complexes to maintain mitochondrial function (Fig. 2). The metabolic state of cells not only changes during aging but also responds to environmental stimuli. Stress signals convey the functional status of mitochondria to the nucleus to promote gene transcription that adapts to the environment. Impaired mitochondrial function can lead to mtDNA loss, mtDNA mutation accumulation, respiratory impairment, mitochondrial protein homeostasis and reactive oxygen species (ROS) production. These signals promote communication between mitochondria and nuclei (mitonucleus) to change gene expression,

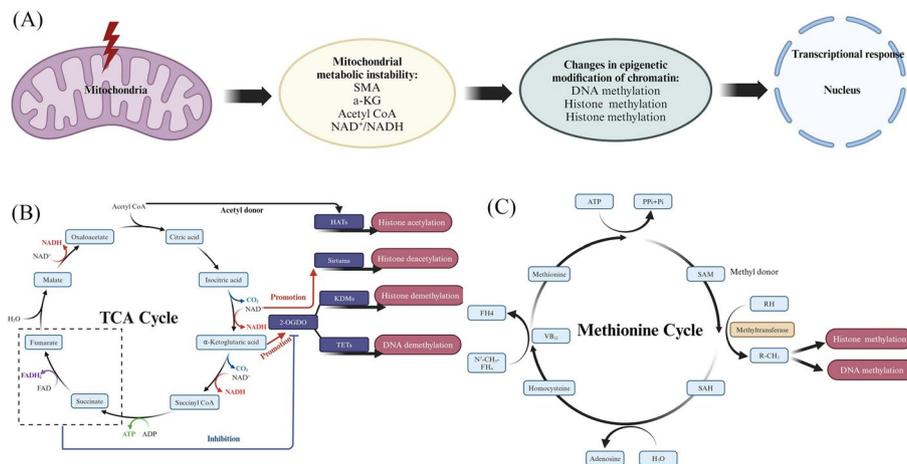


Fig. 2 Mitochondrion–nuclear communication and mitochondrial metabolites for epigenetic modifications
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thereby affecting metabolic adaptation and lifespan. Studies have shown that chromatin changes in response to mitochondrial disturbance promote the communication between mitochondria and nuclei and leave epigenetic memories that may affect the aging process [30].

Precise and strict coordination between the mitochondria and the nucleus is essential for maintaining cellular homeostasis. This process happens through two-way communication via anterograde signaling, where the nucleus regulates the expression of mitochondrial genes and makes posttranslational modifications, and retrograde signaling, where the mitochondria regulate the expression of nuclear genes [30, 31]. Mitochondrial function mainly consists of nuclear coding genes to mitochondrial signals, such as PCG1 α , nuclear respiratory factor 1 (NRF1), and other coregulatory factors, which regulate the process of mitochondrial biogenesis or enhance mitochondrial activity to meet cellular requirements [32, 33]. On the contrary, in the process of senescence, mitochondrial function decreases due to internal disturbance of mitochondria or accumulation of mtDNA mutations, resulting in decreased OXPHOS activity, changes in tricarboxylic acid (TCA) cycle-related enzymes, increase of ROS, and imbalance of mitochondrial protein homeostasis [34, 35]. This mitochondrial dysfunction will regulate the expression of related nuclear genes, leading to changes in the expression of age-related genes and metabolic reediting. For a long time, the intermediate metabolites of mitochondria have been regarded as byproducts of cell metabolism. However, more and more studies have pointed out that these intermediate metabolites can be used as signals to regulate epigenetic modification in the nucleus and further regulate nuclear gene expression. This affects cell homeostasis and senescence. It includes acetyl-coenzyme A (acetyl-CoA), α -ketoglutaric acid (α -KG), nicotinamide adenine dinucleotide (NAD⁺), and methionine [30, 36, 37]. As potential longevity regulators, they form a dynamic regulatory network with the nucleus, promote cell homeostasis and regulate the expression of age-related metabolic genes, and make cells respond to different metabolic conditions and aging stress.

However, our comprehension of the relationship between mitochondrial–nuclear stress signals remains restricted, despite these advancements. It is crucial to ascertain the impact of mitochondrial metabolites on the regulation of specific sites of epigenetic modifications in a manner that is specific to a particular tissue. Future studies will aid in the development of therapies targeting mitochondrial–nuclear communication to induce advantageous epigenetic modifications that can delay the aging process or alleviate age-related illnesses.

Mitolysosome

Lysosomes are mainly responsible for clearing inactivated biological macromolecules or damaged organelles. There is direct physical contact between mitochondria and lysosomes, which differs from the contact formed by lysosomes targeting damaged mitochondria. Mitochondrial–lysosomal (mitolysosome) contact is continuously formed and dissociated in normal cells. Functionally, it allows two-way regulation of mitochondrial and lysosomal dynamics [38]. In the contact formation stage, Ras-associated GTP binding protein 7 (Rab7) promotes contact by binding to GTP on the lysosomal membrane. The member of the Tbc1 domain family 15 (TBC1D15) is recruited to the mitochondria by the mitochondrial fission 1 protein (FIS1). TBC1D15 binds to the RAB7 at the contact site and hydrolyzes guanosine triphosphate (GTP) to guanosine diphosphate (GDP), which drives the hydrolysis of RAB7–GTP, thus relieving contact [39]. Mitochondrial–lysosome contact is significant in cardiac dysfunction induced by acute myocardial infarction. Three days after myocardial infarction in adult rats, mitochondrial–lysosome contact is abnormal, the lysosome is enlarged, and damaged mitochondria can not be cleared. This abnormal function is related to the downregulation of TBC1D15 levels. TBC1D15 relieves mitochondrial–lysosomal contact through the FIS1/Rab7 pathway, and then, it depends on the lysosome for mitochondrial autophagy. Overexpression of TBC1D15 can restore myocardial contractile function and reduce myocardial infarction size and myocardial interstitial fibrosis [40].

Mitoperoxisome

Peroxisomes and mitochondria (mitoperoxisome) are linked both physiologically and functionally [41], and effective metabolic intermediate transfer requires this intimate contact. Together, these two organelles facilitate essential biological functions, including peroxisomal growth, lipid metabolism, redox balancing, and antiviral signaling. β -Oxidation in mammals necessitates the presence of both mitochondria and peroxisomes, and there is a requirement for the transfer of metabolites between peroxisomes and mitochondria in both directions. Due to the limited ability of peroxisomes in mammals to metabolize fatty acids with long chains, it is necessary to transport intermediate products to mitochondria in the form of acylcarnitine ester or free acids to assure their complete oxidation. In addition, these coordinated metabolic processes generate ROS, and changes in the metabolism of peroxisomal ROS have an effect on the mitochondrial redox balance [42]. Additionally, to sustain peroxisomal β -oxidation, NADH produced within peroxisomes must be directed to the mitochondria for effective energy regeneration of NADH into NAD^+ [43]. The SLC25A17 gene encodes peroxisomal membrane protein 34 (PMP34), the only transporter found in human peroxisomes that exhibits

substrate selectivity toward NAD^+ [44]. In the presence of pyrimidine deprivation, peroxisomes-derived ether lipids are responsible for driving the assembly of mitochondrial respiratory supercomplexes, which is an additional metabolic link between peroxisomes and mitochondria [45]. Peroxisomes mainly undergo proliferation through the expansion and asymmetric division of existing organelles. The peroxisomal fission machinery consists of Pex11b, Fis1, MFF, and DRP1. With the exception of Pex11b, these components are also found in mitochondria, indicating a coordinated division process in specific circumstances [46].

It has been observed that peroxisomes and mitochondria are in contact with one another in mammalian cells [47]. However, the components responsible for tethering are still challenging to find or understand. The ACBD2 protein, which is found in both peroxisomes and mitochondria, has been suggested as a biological mechanism that brings peroxisomes and mitochondria closer together, hence enhancing steroid production in Leydig cells [48]. Peroxisomal malfunction is known for triggering mitochondrial abnormalities, demonstrating the significance of peroxisomes for proper mitochondrial activity [49].

Intercellular mitochondrial communication

Intercellular communication and the transfer of cellular components are crucial for maintaining the balance of multicellular organisms, and the transcellular transport of mitochondria serves as a prominent example of this exchange. In physiological contexts, the process of mitochondrial transfer is associated with biological growth, energy regulation, and removal of detrimental substances, playing crucial roles in preserving the quality of mitochondria. Mitochondria are indispensable for a multitude of vital biological processes, such as oxidative metabolism and biomolecular synthesis, and are particularly susceptible to dysfunction in pathological conditions. Significantly, extensive mitochondrial damage will intensify the deficiencies in the system responsible for maintaining mitochondrial quality. This will stimulate increased transfer of active mitochondria, restore healthy mitochondria from external sources, and eliminate damaged mitochondria from within the body to promote disease outcomes [50].

Intercellular mitochondrial transfer

For a considerable period of time, it has been widely believed that mitochondria persist within cells throughout an organism's lifespan and are passed down only from the mother [51]. However, under some circumstances, mitochondria have the ability to be released from the cell and moved across different cells [52]. Various cell types, such as lymphocytes, neurons, and heart muscle cells, can transfer or receive mitochondria from one another [53]. Organelle exchange is a special form of intercellular communication, which allows one-way or two-way transport of small molecules or ions and intracellular structures, including mitochondria, lysosomes, endosomal vesicles, and plasma membrane modules [54]. Research has indicated that the transmission of mitochondria between cells serves as a protective mechanism, preventing mitochondrial dysfunction that may occur in stressed cells [55].

There are many methods to replace damaged mitochondria in recipient cells. Coincubation is the simplest method, and the transfer efficiency differs in different cell lines. Microinjection and other invasive techniques, such as nanomaterials, can also inject mitochondria into human cells and quickly replace their endogenous intrinsic mtDNA but with lower efficiency than coincubation methods [56, 57]. To facilitate mitochondrial internalization into recipient cells, other techniques have been developed, such as binding mitochondria to the cell-penetrating peptide Pep-1, labeling mitochondria with magnetic beads of mitochondrial outer membrane translocation enzymes, and increasing mitochondrial uptake by MitoCeption [58]. A number of age-related disorders, including Parkinson's disease (PD), stroke, diabetes, and metabolic syndrome, have shown that mitochondrial activity in damaged cells can be preserved through endogenous or exogenous mitochondrial transfer. This has been demonstrated in a string of cases, highlighting the effectiveness of mitochondrial transfer as a new model of regenerative therapy in aging [59]. Because the effectiveness of mitochondrial internalization into diseased tissues depends on the number and quality of mitochondrial organelles and their appropriate mode of transport, the efficacy of mitochondrial therapy may vary between patients. If mitochondrial transfer is to be applied to the clinic, a better understanding of the mechanisms of mitochondrial transfer and cellular uptake is needed.

Mechanisms of mitochondrial transfer

Mechanisms of mediating intercellular mitochondrial transfer include the formation of intercellular tunnelling nanotubes (TNT) or extracellular vesicles (EVs), connexin-43 (Cx43), cell fusion, and mitochondrial extrusion (Fig. 3) [50, 60, 61]. TNT and Cx43

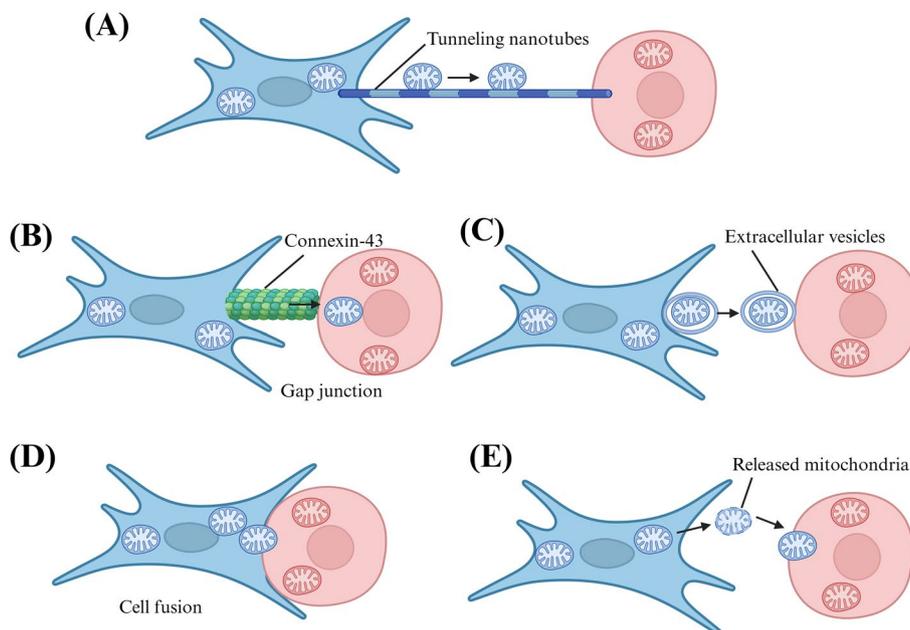


Fig. 3 Mechanisms of mitochondrial transfer. **A** Tunneling-nanotubes-mediated mitochondrial transfer. **B** Gap-junction-mediated mitochondrial transfer. **C** Microvesicle-mediated mitochondrial transfer. **D** Cell-fusion-mediated mitochondrial transfer. **E** Endocytosis-mediated mitochondrial transfer. The figure was created with Biorender.com

maintain communication between the two connected cells through the membrane tube structure, while EV allows information transfer between the two separated cells, ensuring long-distance communication [62]. In fact, intercellular mitochondrial transfer provides a new mode of intercellular signaling that can occur in vivo and function under a number of unhealthy circumstances to restore damaged cell function [63].

In in vitro and in vivo experiments, TNT is formed between different cell types and promotes the selective exchange of organelles, membrane vesicles, small soluble cytoplasm, and membrane molecules. The establishment of nanotubes begins with the formation of a membrane-like process that shrinks upon arrival at the recipient cell, leaving an ultrafine structure separated from the substrate. TNT is essential for effective mitochondrial transfer, and if the formation of TNT is inhibited by chemical inhibitors or mechanical stress, the mitochondrial exchange can be reduced [64]. Mitochondrial transfer via TNT is usually unidirectional, from the cell initiating TNT formation to the recipient cell [65]. However, there have been a few reports of two-way transfers [66]. Mitochondrial damage is the main trigger of mitochondrial transfer based on TNT. Complete loss of mitochondrial function (including mtDNA depletion or addition of mitochondrial inhibitors) activates mitochondrial transfer. During ischemia–reperfusion injury, mesenchymal stem cells (MSCs) transport mitochondria to damaged endothelial cells using TNT-like structures. This transfer helps prevent endothelial cell death by restoring normal aerobic respiration [67]. Similarly, MSCs can transfer mitochondria to myocardial cells after I/R injury through TNT structure and improve cell survival [68]. In a model of *Escherichia coli* pneumonia, mitochondrial transfer between TNT MSCs and innate immune cells enhances the ability of alveolar macrophages to phagocytic invading bacteria [69]. Other favorable conditions for TNT formation are the induction and stimulation of P53 and nanotube formation in hippocampal astrocytes and neurons by serum starvation or hydrogen peroxide [70]. Similarly, hyperglycemic or acidified media and cytokines that stimulate epithelial–mesenchymal transformation increase mitochondrial transfer through TNT formation [71]. EV is a membrane-containing vesicle shed by cells, which contains protein, lipids, and nucleotides, and plays an important role in intercellular communication. According to its origin, size, and molecular composition, EV can be divided into microbubbles, exosomes, and apoptotic bodies. EV is a tool of intercellular communication, which exists in many physiological and pathological processes and can be used as a biomarker of health and disease [72]. Mitochondrial proteins and mtDNA loaded in different EVs are not clear, but mitochondrial components have been detected in them. Larger EVs can contain complete mitochondrial particles and mtDNA, which can be seen in MSC and participate in its intercellular mitochondrial transfer. It is found that MSC can shed EV, including exosomes (50–100 nm in diameter) and vesicles (0.1–1 μm in diameter), and enter the extracellular space for mitochondrial phagocytosis and delivery of microRNA (miRNA) [73]. Up to now, the mechanism of cell-to-cell transfer of free mtDNA across the mitochondrial inner membrane and outer membrane is still unclear, and in the process of cell-to-cell mitochondrial transfer, EV is most likely to mediate the transfer of the whole mitochondrial particle and restore mitochondrial function. Cell fusion is a process in which two independent cells share organelles and cytoplasmic compounds through the fusion cell membrane. Permanent cell fusion allows cells to share cytoplasm and have unique karyotypes. In contrast, some

cell fusion allows short and direct intercellular communication and exchange of a variety of protein complexes and organelles (including mitochondria). It is reported that mature stem cells and embryonic stem cells can fuse with cardiomyocytes, hepatocytes, and neurons, helping to maintain cell differentiation and plasticity [74]. Injury and inflammation can promote cell fusion of target organs, and myeloid cells and lymphocytes can fuse with different tissues in the event of injury or inflammation [75]. When stem cells are used to treat myocardial infarction, partial or whole cell fusion can occur between stem cells and cardiomyocytes, restoring mitochondrial function and promoting cardiomyocyte regeneration [76]. Human adipose stem cells were cocultured with mouse cardiomyocytes, and it was found that F-actin connections were formed between the cells, indicating that mitochondria can participate in the process of cell function recovery through partial cell fusion [77]. When MSC was cocultured with skin fibroblasts from patients with mitochondrial diseases, it was observed that the abnormal mitochondrial morphology of skin fibroblasts was saved from the fission state to the fusion state, and mitochondrial function was restored [78]. Connexins form gap junctions after oligomerization, allowing cells to connect and transfer small molecular cellular components. Cx43 plays an important role in regulating intercellular mitochondrial transfer. In a Ca^{2+} -dependent manner, connexins regulate intercellular mitochondrial transfer from MSC to alveolar epithelial cells damaged by lipopolysaccharide through the formation of TNT and EV to restore alveolar biological energy, thus protecting acute lung injury [79]. In addition, the gap junction can connect the mesosome particles to the plasma membrane to form a channel, and the small molecules can spread into the damaged neurons through the connexin half channel composed of Cx43 [80]. Mitochondrial squeeze is another mechanism of mitochondrial transfer, which can release mitochondria or mitochondrial components in cells under certain conditions. For example, when a large amount of ROS is produced, HeLa cells can squeeze and release mitochondrial fragments [81]. Mitochondrial compression occurs not only *in vitro* but also *in vivo*, such as platelets squeeze functional mitochondria wrapped in particles and free organelles, thus enhancing the inflammatory response [82]. In addition, when mouse hepatocytes were treated with an anti-FAST antibody, mitochondria were detected in perisinus space and serum, indicating that mitochondrial compression occurred [83].

The mediators of mitochondrial communication

Nuclear coding proteins

The regulation of communication between mitochondria and nuclei is very complex, which can be simply summarized as forward regulation from nucleus to mitochondria and reverse regulation from mitochondria to nucleus [30]. In forward regulation, different stimuli regulate mitochondrial function by producing nuclear transcription factors to ensure the normal expression of proteins in mitochondria and the normal progress of various physiological functions. Forward regulation completes the instruction transmission from the nucleus to mitochondria through a variety of signal molecules, regulates mitochondrial biogenesis and mitochondrial function, and responds to different environmental stimuli. The loss of forward regulation will lead to the destruction of mitochondrial homeostasis, leading to various cell dysfunction and age-related diseases.

Nuclear respiratory factor 1 (NRF1) activates the expression of mitochondrial transcription factor A (TFAM). TFAM enters the mitochondria and binds to mtDNA and recruits mitochondrial RNA polymerase and mitochondrial transcription factor B2 (TFB2M) at the promoter to start transcription, promoting mitochondrial biogenesis [84–86]. For example, overexpression of NRF1 can activate the transcriptional process of myocardial regeneration and induce the regeneration of damaged cardiac myocytes in newborn mice. Overexpression of NRF1 in adult mouse hearts can reduce myocardial ischemia–reperfusion injury (MIRI) [61].

Nuclear factor erythroid 2-related factor 2 (NRF2) is a multifunctional transcription factor regulating antioxidant stress, which can bind to Kelch-like epichlorohydrin-related protein 1 (Keap1). Under steady-state conditions, Keap1 binds to NRF2 to cause its ubiquitin degradation and inhibit the activity of NRF2. In the stress response, Keap1 activity decreases or binding to NRF2 decreases, and NRF2 escapes ubiquitin and accumulates in cells. After the accumulated NRF2 is transported to the nucleus, it activates the antioxidant responsive element (ARE) and promotes the antioxidant process [87]. Keap1/NRF2 is an important antioxidant signal pathway in the human body. Targeting the Keap1/NRF2 pathway can improve the symptoms of many cardiovascular diseases. For example, phosphoglycerate mutase family 5 reduces ROS-induced oxidative stress and ferroptosis in mice with heart failure through Keap1/Nrf2 signal pathway [88]. Targeting the Keap1/NRF2 signal pathway can reduce mitochondrial apoptosis and oxidative stress, which can improve the therapeutic effect of lung injury [89].

The activities of various transcription factors are affected by transcription coactivators, and the most studied one is peroxisome proliferator-activated receptor- γ -coactivator 1 α (PGC-1 α), which regulates mitochondrial energy metabolism by regulating the activity of transcription factors [30]. In the state of exercise, excessive ATP consumption, decreased ATP level or increased AMP/ATP ratio will activate the energy receptor AMPK [adenosine-5'-monophosphate (AMP)-activated protein kinase], activation of AMPK increases the level of PGC-1 α [90], and PGC-1 α activates its downstream NRF1 and NRF2 nuclear genes, thereby promoting mitochondrial biosynthesis and energy metabolism to meet the energy consumption during exercise [91]. In vascular smooth muscle cells, PGC-1 α regulates small noncoding RNA miR-378a by binding to NRF1, and the PGC1 α /NRF1/miR-378a axis can protect blood vessels from smooth muscle cell proliferation, migration, and inflammation induced by free fatty acids [92]. The high expression of miR-378a has the function of preventing atherosclerosis, and PGC-1 α in human aortic endothelial cells incubated with oxidized low-density lipoprotein is significantly decreased [93], resulting in the inhibition of miR-378a, which is a possible cause of atherosclerosis.

Mitochondrial-derived peptides

Mitochondrial-derived peptides (MDP) is a new peptide, which is a mitochondrial genome encoded by a small open reading frame. Although MDP can be detected in a variety of tissues and plasma, the mechanism of its secretion and release is still unclear. It has been found that it can regulate mitochondrial bioenergetics and mitochondrial metabolism and has a variety of biological effects, such as helping to maintain mitochondrial function and cell viability under stress, giving full play to cytoprotection, improving

metabolic markers and so on. In recent years, MDP has been found in vascular endothelium, cardiomyocytes and islet cells, and its therapeutic value in glucose and lipid metabolic diseases, cardiovascular diseases, Alzheimer's disease (AD), and other diseases has been proved and affirmed [34, 94–96].

Humanin (HN) is the first member of the MDP family and the most studied peptide in the family. HN is an autopsy of patients with AD performed by Japanese scholar Hashimoto in 2001. A copy DNA library containing an open reading frame was extracted from the undamaged brain region of the occipital cortex. A linear peptide encoding 24 amino acids was found after functional testing. HN can effectively inhibit a variety of familial AD gene mutations and β -amyloid protein-induced neuronal apoptosis, which is considered to be a specific neuroprotective peptide for AD [97]. Cell surface receptors that can activate HN signaling pathways have been identified, including signal transducers and activators of transcription and extracellular regulated protein kinases (ERK) 1 and 2, which are related to cell proliferation and survival [98]. With the deepening of research, it has been found that HN exists in the pathological process of diabetes, myocardial ischemia, atherosclerosis, and other diseases [99–101]. It is secreted by cellular stress and has extensive cytoprotective and neuroprotective effects in these diseases. Now, studies have confirmed that it has the functions of anti-apoptosis, reducing inflammatory reactions and antioxidative stress and improving insulin sensitivity [102–105]. MOST-c is a linear peptide that encodes 16 amino acids in the open reading frame of mitochondrial 12SrRNA. It is a newly found bioactive MDP encoded in mtDNA. The main target of MOST-c is skeletal muscle, which is considered the first peptide in MDP that regulates gene expression in the nucleus by interacting with transcription factors, producing retrograde signal molecules. In the nucleus, MOST-c interacts with antioxidant regulatory transcription factors, such as transcription factor 1 and transcription factor 2, to stimulate the transcription of target genes involved in mitochondrial protection. The cytoprotective effect of MOST-c may be related to this new mechanism. Modern studies have proved that MOST-c can improve muscle metabolism, increase insulin sensitivity, and regulate fat metabolism by increasing glucose utilization and fatty acid oxidation and changing mitochondrial function and nucleotide metabolism [106–110]. SHLP1–6 is another of six small HN-like peptides found in HN's 16SrRNA gene, all of which are encoded by a small open reading frame. Studies have found that a single SHLP exists in the kidney, spleen, heart, brain, and other organs, with different biological effects. SHLP is a bioactive peptide that regulates cell function. At present, related studies are mainly focused on SHLP2 and SHLP3, which have similar cytoprotective effects to HN and have effects on apoptosis and metabolism [94, 95]. For example, SHLP2 has the effect of antioxidant stress, which can improve insulin sensitivity in the central and peripheral system [94]. The level of SHLP2 in the cycle decreased with age. In addition, similar to HN, SHLP2, and SHLP3 can induce phosphorylation of ERK and activator of transcription 3 [111].

Studies have found that MDP affects the process of cell aging by regulating the transformation of senescence-related secretory phenotype (SASP), inhibiting oxidative stress and antiapoptosis of aging cells, and interferes with the outcome of age-related diseases [112]. Cell senescence is accompanied by the production of SASP, which can continuously block the progress of the cell cycle and induce adjacent cell senescence

or carcinogenesis by paracrine. When senescent cells are not removed by the immune system, SASP will cause chronic inflammation, change tissue structure and function, and, eventually, enter an irreversible aging state of stagnation of growth and proliferation [113, 114]. Some studies have found that the bioenergetics of senescent cells play a key role in the expression of some specific SASP, and MDP plays a cytoprotective role in age-related diseases by regulating mitochondrial energy metabolism and then affecting the transformation of SASP in the process of cell aging, so as to reduce the symptoms of aging, reduce the harm caused by aging, and prolong the healthy period [115]. In senescent cells, the levels of HN and MOST-c increased, and MDP moderately increased mitochondrial respiration and a certain part of SASP expression. At the same time, it was found that MDP enhanced energy metabolism but did not cause senescence, indicating that MDP has a therapeutic regulatory effect on mitochondrial energetics and SASP transformation and is a factor to help senescent cells maintain senescence and prevent deterioration and partial SASP expression [112]. Under stress conditions, MDP helps maintain mitochondrial function and cell viability, plays a cytoprotective role, and may become a candidate for various age-related diseases. The effects of MDP on senescent cells are not only related to SASP, but also delay cell senescence by inhibiting oxidative stress, reducing inflammatory response and apoptosis [116]. Further exploration of the specific mechanism and function of MDP will help to clarify the pathogenesis of diseases related to mitochondria and aging, and provide new ideas and targets for the treatment of diseases.

Mitochondria-derived vesicles

Extracellular vesicles (EVs) are tiny vesicles produced by cells that can transport biologically active substances across cells or organs [117, 118]. Recent data indicate that specific EV subpopulations include a variety of mitochondrial contents. These mitoEVs have the ability to transfer mitochondrial components to target cells, hence influencing their functioning in various contexts [119]. These intracellular vesicles that contain components of mitochondria are known as mitochondrial-derived vesicles (MDVs) [120]. The creation of MDVs has been suggested as the ancient homeostatic mechanism in live cells at the mitochondrial level, occurring under physiological and mild stress situations [121, 122]. One new MDVs biogenesis pathway involves PINK1/Parkin, an E3 ubiquitin protein ligase with a ubiquitin-like domain at the N-terminus but does not require DRP1 [123–126]. Under conditions of mild stress or little damage to the mitochondria, the curvature of the mitochondrial membrane is initiated, which is then followed by the accumulation of PINK1 [93, 127, 128]. Parkin is subsequently enlisted at the outer mitochondrial membrane (OMM), and the MDVs are severed and liberated through an ambiguous process [128, 129]. The participation of DRP1 in the formation of MDVs has been ruled out due to the fact that MDVs can still form even in the absence of DRP1 [128].

The nanoscale vesicles, ranging from ~70 to 150 nm in diameter, are enveloped by either a single or double membrane. These membranes are known as the outer mitochondrial membrane (OMM) and/or the inner mitochondrial membrane (IMM) [130–132]. MDVs are also the particular carriers for mitochondrial nucleic acids [101,

133–136], proteins [133, 137, 138], lipids [121, 139], fragmented mitochondria [140], and/or other mitochondrial components [141, 142]. At present, intracellular MDVs may be distinguished from other intracellular vesicles by utilizing their distinctive markers, such as OMM, IMM, mitochondrial matrix proteins, and mtDNA [143, 144]. Prior research has demonstrated that MDVs are important in intracellular interactions of the parental mitochondria with lysosomes [129, 136], endosomes [136], and peroxisomes [145, 146]. Further investigations have shown the intercellular involvement of MDVs in immune response regulation [147, 148], in eliminating malfunctioning parts of mitochondria [149], and in transporting functional MDVs to target cells that demand more energy for communication [150].

MDVs are recognized as the primary element of the initial secure process in the mitochondrial quality control (MQC) system, and their potential functions are completely distinct from mitochondrial dynamics and mitophagy [151, 152]. In addition, the quantity of MDVs is augmented by mild stress or the initial phase of mitochondrial malfunction [128]. The MQC system has identified two primary categories of MDVs: steady-state MDVs and stress-induced MDVs [153], both of which can be distinguished by their distinct indicators. Translocase of outer mitochondrial membrane 20 (TOMM20), which is a protein located in the OMM, is primarily present in steady-state MDVs [121]. In contrast, pyruvate dehydrogenase (PDH) is mostly present in MDVs that are induced by oxidative stress [123]. Revealing the creation of MDVs and their functional activities will enhance our understanding of the communication that occurs within and between cells related to mitochondria.

Mitochondrial metabolites

The disorder of mitochondrial energy metabolism leads to abnormal levels of oxidative phosphorylation and respiratory chain intermediate molecules, thus regulating the activity of related epigenetic modifying enzymes, affecting the epigenetic modification status of the genome and changing the expression of related genes. At the initial stage of injury, protective mechanisms such as mitochondrial unfolded protein response (UPR^{mt}) are activated to increase the expression of chaperone molecules, proteases and other related genes to maintain mitochondrial homeostasis; with the aggravation of injury, the overactivation of protective mechanisms leads to genomic instability, increases the expression of aging-related genes, and, finally, leads to apoptosis and senescence. Therefore, the abnormal epigenetic regulation of gene expression mediated by mitochondrial metabolic disorders is an important reason for the initiation and progress of the aging phenotype [30].

The TCA cycle is traditionally recognized for generating essential metabolites necessary to ensure cellular proliferation and survival, in addition to generating bioenergetic intermediates that contribute to the ETC [154]. Several of these metabolites also engage in mitochondria-to-nucleus signaling, where they are utilized as secondary messengers, and their levels serve as a direct indicator of mitochondrial health and metabolic condition [155]. Changes in the quantities and accessibility of these metabolites

are incorporated into epigenetic regulation techniques that induce transcriptional modifications in response to different stress conditions and physiological states because they frequently function as substrates or regulators of enzymes involved in chromatin remodeling [3]. Two common changes that affect how mitochondrial metabolites work are acetylation and methylation. These are caused by enzymes that respond to changes in acetyl-CoA and α -KG/succinate levels. These changes affect gene expression in the nucleus through DNA methylation and post-translational modifications of histones, which are important parts of the “histone code” [156]. Besides, *S*-adenosine-*L*-methionine (SAM) is a major donor of methylation, affecting histone methylation, especially H3K4me3. The changes in mitochondrial metabolism affect SAM levels, which in turn affect histone and DNA methylation, profoundly affecting cell homeostasis and body lifespan [30]. Two important metabolites involved in the process of epigenetic control are FAD⁺ and ATP. FAD⁺ serves as a cofactor in the process of histone demethylation. LSD1, also known as lysine-specific demethylase 1, utilizes FAD⁺ as a catalyst to oxidize methylated lysine residues, resulting in the formation of a highly reactive intermediate capable of hydrolytically eliminating methyl groups. ATP serves as an essential energy source for numerous enzyme activities involved in epigenetic modification. Additionally, it acts as a substrate for kinases responsible for phosphorylating histones [30].

The epigenome's alterations brought about by metabolites, also known as metabolic epigenetics, are linked to the advancement of disease and the reprogramming of gene expression in response to stress and physiological changes [157]. When mtDNA mutations build up, a condition called heteroplasmy, for example, changes in nuclear gene expression are made easier by abnormal metabolite production that leads to specific epigenetic modifications. These modifications, in turn, help control transcription by changing the way chromatin moves [158]. Alterations in the methylation status of genes encoded in the nucleus in response to deficiencies in the copy number of mitochondrial DNA (mtDNA) have been documented in relation to osteosarcoma and breast cancer [159]. These findings emphasize the association between metabolite-induced changes in epigenetic modifications and transcriptional abnormalities associated with pathogenic phenotypes and the evolution of diseases, thereby emphasizing the critical relationship between genetics, mitochondrial retrograde signaling, and metabolites.

Ca²⁺ homeostasis

Ca²⁺ are widely present and highly adaptable cellular messengers. They have a vital function in orchestrating and regulating many cellular activities, ranging from cell survival to cell death. The expansive nature of Ca²⁺ cascades is influenced by two significant factors: its capacity to interact with multiple effectors and its ability to self-regulate [160]. Within the cell, the coordination of these signaling events is facilitated by a complex system called the Ca²⁺ toolkit, which consists of several organelles and proteins. The ER, mitochondria, nucleus, and plasma membrane, including its channels and transporters, play a crucial role in facilitating the movement of Ca²⁺ from outside the cell to within the cell [161]. The ER stores intracellular Ca²⁺, while the mitochondria act as crucial Ca²⁺ buffers by detecting and regulating intracellular Ca²⁺ levels [162]. Recent research has emphasized the active function of mitochondrial Ca²⁺ in regulating energy production and programmed cell death, both in normal physiological processes and in

disease states. The Ca^{2+} signaling toolbox consists of four main divisions: initiation of Ca^{2+} mobilizing signals in response to stimuli, the release of Ca^{2+} from internal stores into the cytoplasm, activation of Ca^{2+} sensitive activities, and transport of Ca^{2+} from the cytoplasm back to internal stores [163].

Maintaining the balance of Ca^{2+} in the mitochondria relies not only on the entry of Ca^{2+} but also on the pace at which it is removed. During a stable condition, the rate at which calcium ions are released from the mitochondria should be the same as the rate at which they are taken in, to preserve a state of equilibrium. The $\text{Na}^+ - \text{Ca}^{2+} - \text{Li}^+$ Exchanger (NCLX) is responsible for the export of Ca^{2+} from the mitochondria through the IMM, using Na^+ or Li^+ as exchange ions. The NCLX transporter is electrogenic, meaning it imports three Na^+ ions to extrude one Ca^{2+} ion from the mitochondria. The approximate rate of rotation for the above process is 1,000 cycles per second [162]. Entry of Ca^{2+} into the mitochondria impacts its functionality, leading to temporary depolarization of the mitochondrial membrane potential and governing metabolism [164]. The TCA cycle is a significant metabolic system that is controlled by the amounts of calcium ions in the mitochondria. The function of several enzymes in the tricarboxylic acid (TCA) cycle relies on the amounts of calcium ions within the mitochondria. The enzyme PDH connects the metabolic pathways of glycolysis and the TCA by transforming the last product of glycolysis, pyruvate, into acetyl CoA. Ca^{2+} triggers the activation of pyruvate dehydrogenase phosphatase (PDP), which in turn dephosphorylates the E1 subunit of PDH, leading to its activation [165, 166]. Furthermore, elevated amounts of Ca^{2+} can stimulate the function of the TCA cycle enzymes isocitrate dehydrogenase and oxoglutarate dehydrogenase, hence promoting the TCA cycle [167, 168]. Gaining insight into the mechanisms of intracellular mitochondrial Ca^{2+} homeostasis can enhance our understanding of mitochondrial communication and offer valuable insights for the advancement of therapeutic approaches for age-related illnesses.

Mitogenome stability

MtDNA can participate in inflammatory response by combining with TLR, NLRP, and other receptors. The TLR pathway is triggered by the binding of DAMPs to neutrophils and activates the subsequent inflammatory response through nuclear factor- κB (NF- κB) signal transduction. The NLRP pathway works through NLRP3 inflammatory bodies [169, 170]. Activation of NLRP3 leads to increased expression of caspase-1, which divides and activates IL-1 β and IL-18. In addition, redox-sensitive inflammatory and inflammatory body-mediated pathways can also cooperate to aggravate the inflammatory response: the cGAS–STING DNA pathway is an integral part of the innate immune system [171, 172]. After binding to mtDNA, the cGAS pathway triggers the phosphorylation of interferonregulatoryfactor3 (IRF-3) through chemotaxis of STING protein, and it acts through TANK-binding kinase (TBK). At the same time, the phosphorylation of IRF-3 can induce the production of type I and type III interferons (β and $\lambda 1$). Persistent inflammatory stimulation can activate circulating immune cells, which in turn may induce inflammatory pathways by activating mtDNA, thus producing systemic reactions. Cytokines, chemokines, nitric oxide, and ROS released by inflammatory cells in circulation can further induce mitochondrial damage, thus forming a vicious circle and strengthening the whole process [173, 174].

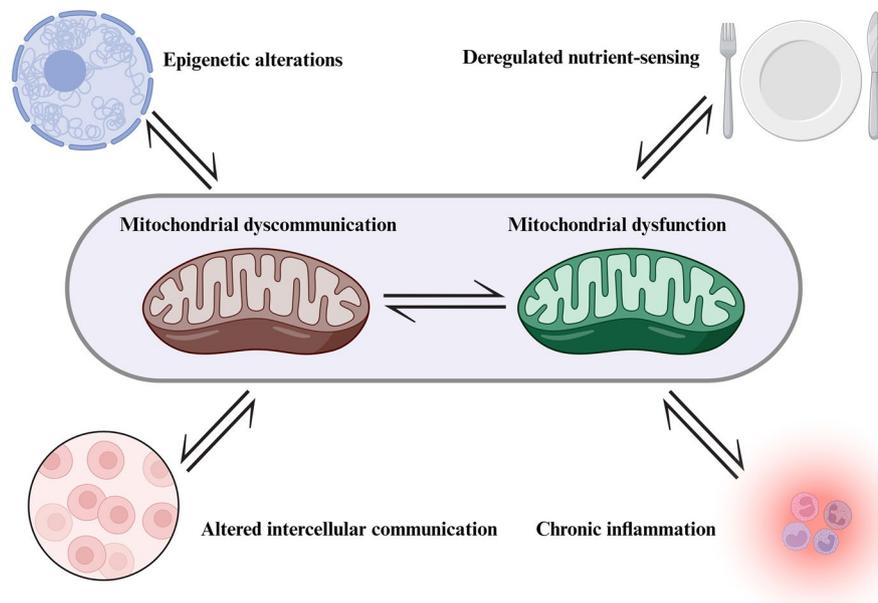


Fig. 4 Cross talks between mitochondria communication and hallmarks of aging The figure was created with Biorender.com

Mitochondrial communication and hallmarks of aging

There are bidirectional crosstalks between mitochondrial communication and hallmarks of aging. In this review, we focus on mitochondrial dysfunction, epigenetic alterations, chronic inflammation, altered intercellular communication, and deregulated nutrient sensing (Fig. 4).

Mitochondrial dysfunction

Mitochondria are the center of biological energy and metabolism and widely participate in a variety of biological processes, with complex adaptation mechanisms, which can maintain the normal morphology and function of mitochondria to cope with the effects of mitochondrial damage and aging and other factors. Mitochondrial dysfunction is considered to be one of the hallmarks of aging and is associated with many age-related diseases [175].

Mitochondrial dysfunction refers to the decrease of mitochondrial respiratory capacity and membrane potential. Mitochondria undergo morphological and functional changes with age and continuous exposure to different pressures, which increases the possibility of dysfunction [176]. Similarly, aging is usually accompanied by a decline in the quality and function of mitochondria [108]. The quality control of mitochondria is the basis of maintaining the normal physiological function of mitochondria, and the dynamic balance of mitochondrial production and degradation is an important factor to maintain the function of mitochondria in cells [177]. Mitochondria have a complex quality control system. The mechanism of MQC is multilevel, showing changes at the protein, organelle, and cellular level. As aging occurs, mitochondria with accumulated damage can realize self-repair through a series of mechanisms. There are five types of

MQC: UPR^{mt}, mitochondrial dynamics, mitophagy, mitochondrial biogenesis, and mitochondrial-derived vesicles [178, 179].

Aging is an intricate process characterized by a decrease in the functionality of several organelles. While mitochondrial malfunction is proposed as a contributing element to the aging process, the precise role of mitochondrial quality control (MQC) in aging remains inadequately comprehended [108]. Increasing data suggest that ROS promote alterations in mitochondrial structure and enhances the buildup of oxidized byproducts via mitochondrial proteases and the mitochondrial UPR^{mt} [180]. MDVs are the primary means of implementing MQC to eliminate oxidized byproducts. In addition, mitophagy assists in the elimination of partially impaired mitochondria to ensure the overall health and functionality of mitochondria. While numerous interventions on MQC have been studied, excessive activation or inhibition of any kind of MQC can potentially worsen aberrant energy metabolism and contribute to senescence caused by mitochondrial malfunction [93, 130]. Therefore, implementing suitable measures to address MQC can potentially slow down the aging process and increase lifetime.

Epigenetic alterations

The significance of mitochondria in regulating the nuclear epigenome is widely recognized. SAM, a methyl group donor that is universally applicable, is produced in the mitochondria through a metabolic cycle involving one-carbon compounds. Methionine is synthesized in the cytosol by the enzymatic reaction of adenosine-5'-triphosphate (ATP) as a component of the methionine cycle, resulting in the formation of SAM. The methionine cycle in the cytosol is linked to the folate cycle [181]. 5-Methyl tetrahydrofolate (5-MTHF) transfers a methyl group to homocysteine (Hcy), resulting in the formation of tetrahydrofolate (THF) and L-methionine. This process is facilitated by the enzyme methionine synthase (MS), which is dependent on vitamin B12. Additionally, 5-MTHF is involved in the remethylation of Hcy. Therefore, the synthesis of SAM is controlled by ATP generation and folate. The processes of the folate cycle take place in both the mitochondria and cytosol and are connected by the transfer of the serine and glycine amino acid pool via methylenetetrahydrofolate (methionine-THF), which is derived from THF [182]. The mitochondrion is crucial in controlling the transition between nucleotide synthesis and SAM through the mitochondrial bifunctional enzyme (MBE). This enzyme is active in embryonic and cancer cells to facilitate nucleotide synthesis, but it becomes inactive in adult cells to promote the synthesis of SAM [183]. SAM, which is produced in the cytosol, is transferred to the mitochondria through a specialized mitochondrial carrier called SAM carrier (SAMC). Once inside the mitochondria, SAM influences the methylation pattern of the mitochondria [184]. Therefore, any malfunction in the process of one-carbon metabolism would cause changes in the patterns of DNA methylation in mtDNA and disrupt the communication between the nucleus and mitochondria. This communication takes place through the transportation of metabolites from the mitochondria to the nucleus and vice versa, occurring through the cytosol. MiRNAs, which are noncoding tiny RNAs, are observed to be specifically located within the mitochondria [185]. Nuclear-encoded miRNAs regulate nuclear and mtDNA-encoded genes epigenetically and coordinate nuclear–mitochondrial activity. In

addition, intermediates of mitochondrial TCA metabolites, such as α -KG, could affect TET protein activity [186], suggesting the potential involvement of mitochondria in the process of demethylation. Noncoding short RNAs have also been identified in the mitochondrial genomes of both mice and humans, although they have received less research attention [187]. The TCA cycle produces metabolites in the mitochondria that regulate epigenetic alterations. These modifications include DNA methylation, histone methylation, and acetylation. The metabolites act as cofactors and facilitate nuclear–mitochondrial communication [30]. Substrates of the TCA cycle, α KG and succinate, perform a vital function in modulating the methylation of DNA and histones as well as the activity of TET demethylase. On the other hand, histone acetylation is regulated by acetyl-CoA [30].

Chronic inflammation

Not only do mitochondria exchange electrochemical information with the mitochondrial reticulum, but they also exchange mtDNA through membrane contact points between neighboring mitochondria. Nevertheless, when mitochondria experience stress, it can lead to the release of proteins associated with mitochondrial damage (mtDAMPs) into the cytosol, extracellular matrix, and bloodstream [188] and comprise several elements of mitochondria, including mtDNA [189]. One possible method is to distribute material, such as subunits of the oxidative phosphorylation machinery, to other mitochondria. Recently, it has been proposed that mtDNA can not only detect genotoxic stress but also function as a signaling factor to improve the repair of nuclear DNA [190]. Cell-free mtDNA is released into the bloodstream after cellular damage, triggering widespread proinflammatory reactions and activating the immune system [188]. This could be attributed to the resemblance between mtDNA and bacterial DNA, which leads to the immune system identifying mtDNA and triggering a comparable response mechanism employed to combat bacteria [191]. The relationship between mtDNA and the inflammatory response has been demonstrated to occur through the stimulation of polymorphonuclear neutrophils production by mtDNA/Toll-like receptor (TLR)-9 and activation of the NF- κ B pathway [192].

Given that inflammation and the alteration of MQC pathways play significant roles in several clinical disorders, such as aging, it is crucial to investigate the involvement of mtDNA in this interplay.

Altered intercellular communication

The aging process is also characterized by gradual modifications in intercellular communication systems [175]. Intercellular communication can be impacted by mitochondrial dysfunction, which can influence a range of signaling mechanisms such as ROS, mtDNA, the release of MDVs, and metabolite signaling [193]. MDVs can cause the release of fragments of mtDNA, metabolites, and proteins into the space outside of cells. This process triggers immunological signaling pathways, disrupts the secretion of different chemicals, and impedes the transport of functioning mitochondria between cells [193, 194]. These changes have the potential to undermine cellular

functioning, impede tissue homeostasis and maybe contribute to the development of age-related disorders such as AD and PD. Gaining a thorough understanding of how mitochondrial malfunction affects communication between cells is essential for appreciating the underlying causes of these disorders and devising effective methods to reduce their impact. Remarkably, the process of mitochondrial transfer can effectively reinstate the proper functioning of mitochondria in the cells that receive them. This has proven to have a significant therapeutic effect in several illness models, such as PD, stroke, and ischemia [194]. Giving mitochondria through a shot into the middle forebrain bundle can lower oxidative damage, stop dopaminergic neurons from dying, and improve movement [195]. However, additional investigation is required to clarify the fundamental processes and investigate potential treatment measures to restore effective communication between cells in the presence of mitochondrial dysfunction.

Deregulated nutrient-sensing

Mitochondrial dysfunction can disrupt intercellular communication and impair the regulation of nutritional response and energy balance. Aging and metabolic diseases, such as obesity, insulin resistance, and type 2 diabetes, are linked to dysregulated nutrient sensing [175] and can be caused by mitochondrial dysfunction, which leads to compromised energy metabolism, heightened reliance on glucose metabolism rather than fatty acid oxidation, production of ROS, and modified metabolite release and activation of inflammation and stress responses. Mitochondria have crucial functions as sensors of nutrients [196], and there is a strong association between mitochondrial failure and metabolic disorders, including obesity [197]. Mitochondria and ER contact at specific locations known as MAMs. This interaction allows for the exchange of metabolites and calcium. Recent research suggests that MAMs play a crucial role in hepatic insulin signaling and nutrition sensing processes, serving as major hubs for these functions [198]. Furthermore, the primary pathways responsible for sensing nutrients (insulin/IGF1, mTOR, and AMPK) are closely linked to mitochondrial function and mitophagy. There is potential in preserving mitochondrial function, reducing oxidative stress, and restoring metabolic flexibility to address dysregulated nutrient-sensing and develop therapeutic strategies for related metabolic disorders [199].

Mitochondria-targeted interventions

Research on therapies that specifically target mitochondria has shown promise in the field of aging and age-related disorders (Table 1 and Fig. 5).

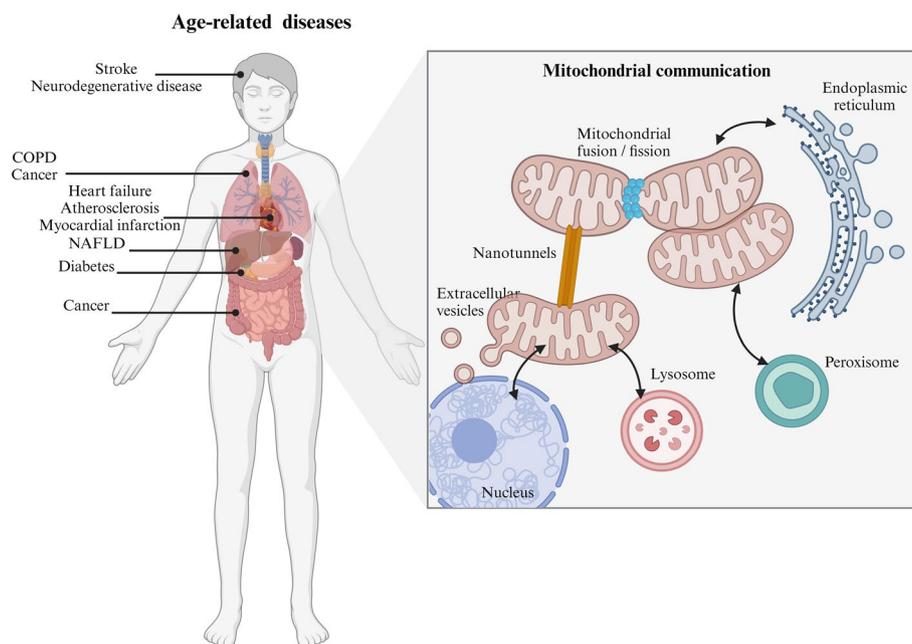
Various approaches have been investigated to selectively transport therapeutic drugs or chemicals to mitochondria, with the goal of improving their performance, reducing oxidative stress, and reinstating cellular homeostasis. These interventions can include several methods, such as tiny chemicals, peptides, antioxidants, and gene therapy. In recent years, researchers have suggested that mitophagy stimulators could be a promising approach to reducing the effects of age-related diseases. NAD⁺ precursors, including nicotinamide riboside, nicotinamide mononucleotide, and similar compounds, have been extensively studied

Table 1 Mitochondria-targeted interventions in aging and age-related diseases

Target	Interventions	Effect	Age-related diseases	References
Mitochondrial biogenesis	Nicotinamide riboside	Promoting PGC-1 α -mediated BACE1 ubiquitination and degradation	Alzheimer's disease	[200]
	Coq10	Improving lipid metabolism	Obesity/type 2 diabetes	[201]
	Metformin	Activation of AMPK	Diabetes, cardiovascular disease, cognitive decline, and cancer	[202]
	Resveratrol	Elevating Nrf1 and TFAM	Frailty	[203]
Mitochondrial dynamics	Mdivi-1	Inhibition of mitochondrial division	Heart failure and Parkinson's disease	[204, 205]
	P110	Inhibition of Drp1/Fis1 interaction	Alzheimer's disease and myocardial infarction	[206, 207]
	SAM β A	Improving metabolism of reactive aldehyde adducts	Heart failure	[208]
	Cilnidipine	Acting as a guanine nucleotide exchange factor for Drp1	I/R heart injury	[209]
Mitophagy	Urolithin A	Activating mitophagy, suppressing NLRP3 inflammasome activation	Alzheimer's disease, Parkinson's disease, liver injury, and metabolic cardiomyopathy	[210–213]
	Laempferol and rhapontigenin	Abrogating amyloid- β and tau pathologies	Alzheimer's disease	[214]
	Oleanolic acid	Modulating of FUNDC1, LC3B, p62, TOM20	Cardiac remodeling	[101]
UPR ^{mt}	PDI-6	Activation of Wnt/EGL-20	Extending lifespan	[90]
MDVs	Cannabidiol	Activation of PINK1/Parkin pathway	Parkinson's disease	[152]
Antioxidants	Coq10	Enhancing oxidative decomposition of lipids and inhibited de novo synthesis of fatty acids	Obesity/type 2 diabetes	[201]
	MitoQ	Decreasing hydrogen peroxide formation, improving mitochondrial respiration and improving mPTP opening	Alzheimer's disease, heart failure, and obesity	[215–217]
	MTP-131	Reducing production of reactive oxygen species and cytosolic cytochrome c level	Alzheimer's disease, heart failure, and myocardial infarction	[218–220]
	N-Acetylcysteine	Attenuating lipid peroxidation	Diabetic neuropathy	[221]
	NMN	Ameliorating glucose intolerance by restoring NAD ⁺ levels	Type 2 diabetes	[222]
	Resveratrol	Reduced IGF-I levels and increased AMPK and PGC-1 α activity	Alzheimer's disease, obesity, and Parkinson's disease	[223–225]

Table 1 (continued)

Target	Interventions	Effect	Age-related diseases	References
Membrane potential	FMU200	Reducing oxidative stress and apoptosis	Neurodegenerative disorders	[226]
	Mefundone	Lowering the ratio of apoptotic cells	Lung fibrosis	[227]
Proteostasis	Nicotinamide riboside triflate	Decreasing A β accumulation	Alzheimer's disease	[228]
Ca ²⁺ homeostasis	Ruthenium 360	Protecting against plaque deposition and neuronal death	Alzheimer's disease	[186]
	CGP37157	Preventing toxic mitochondrial Ca ²⁺ overload	Alzheimer's disease	[229]
Mitogenome stability	Mitochondria-targeted gene delivery	Decreasing the mutated mtDNA ratio by introducing WT mtDNA	Neurodegenerative diseases, diabetes, and cancer	[230]
Mitochondrial transplantation		Supplementing healthy mitochondria	I/R heart injury	[231, 232]

**Fig. 5** Mitochondrial communication in age-related diseases The figure was created with Biorender.com

in models of age-related diseases [233]. It has several benefits for mitochondria and recovers the compromised diversity and destroyed microbial compositions in AD [234]. Urolithin A is an additional small molecule that has demonstrated considerable promise in its ability to enhance muscle functions, promote amyloid- β and tau pathology, and stimulate mitophagy [235]. It is noteworthy that peptides designed to enhance mitochondrial functions emphasize elamipretide (SS-31), a synthetic tetrapeptide that interacts with cardiolipin in the inner mitochondrial membrane, which is enriched in mitochondria [236].

Resveratrol, being a potent Sirt1 activator, can stimulate the production of mitochondria and improve oxidative metabolism. Resveratrol not only helps to avoid cardiovascular illnesses but also has a preventive effect on metabolic syndrome and muscular ailments [237]. A recent report introduced a novel strategy involving the utilization of pioglitazone and iron oxide nanoparticles in mesenchymal stem cells to stimulate mitochondrial biosynthesis and enhance the rate of mitochondrial transfer. This approach was successfully applied in a mouse model of pulmonary fibrosis, demonstrating the promising potential of mitochondrial replacement therapy [238]. An alternative approach involves utilizing genome editing techniques to modify mitochondrial genes. For instance, mitochondrially targeted zinc-finger nucleases have been employed in various mouse models [239], mitochondrial-targeted meganucleases (mitoARCUS) [240], double-stranded DNA deaminase-derived cytosine base editor (DdCBE) [241] or an adenine base editor (ABE8e), and a potent AAV9 delivery of RNA-guided Cas9 nuclease [242]. Its primary application has been to rectify severe hereditary genetic disorders [243], but the swift advancement of novel editing technologies may provide comprehensive examinations of age-related alterations in mitochondrial function in preclinical *in vivo* studies and furnish sufficient proof for potential applications in people. Recently, mitochondrial transmission and transplantation techniques have been utilized for treating mitochondrial illnesses. Additionally, the usage of organelles as therapeutic agents has been tested in animal models and clinical studies, showing promising results. There is potential for increased research, application, and promotion of mitochondrial therapy in the future.

Targeting mitochondria through interventions provides a promising approach to prevent aging and age-related disorders by directly addressing the underlying deficiencies in mitochondria. Although numerous techniques are still in the preliminary phases of research and development, they possess significant potential for enhancing mitochondrial health, safeguarding cellular function, and prolonging a healthy lifespan. Further progress in comprehending mitochondrial biology and enhancing precise intervention approaches could result in revolutionary medicines that significantly influence human health and the aging process.

Challenges and prospects for the future

Mitochondria, being a major organelle of the cell, have other crucial functions apart from generating energy. Instead of being viewed as a solitary cellular powerhouse, mitochondria should be regarded as a critical signaling hub. The organelle constantly receives information regarding nutrition and health conditions from external sources. In response, it releases molecular messengers to either modify cellular transcriptional, metabolic, or proteomic states or carry out the necessary tasks itself. The active listening and acting tasks performed by mitochondria are most likely a result of their endosymbiotic origin. Originally, mitochondria were independent proteobacterial entities that had their own self-contained cellular functions. However, as they developed, they acquired a necessity and capability to communicate signals with the remaining eukaryotic cells and, subsequently, other tissues within the body.

There are still numerous unresolved inquiries in the domain of mitochondrial communication. The expanding body of research reveals an increasing number of molecular components, organelles, and tissues that are governed by the mitochondrial signal network.

However, numerous issues persist: How significantly does mitochondrial communication contribute to the aging process? How is every signal molecule in this huge communication network used by mitochondrial communication? How do we exclude the indirect influence of signal molecules by mitochondria in the process of energy metabolism? Given the complex involvement of mitochondria in so many different signal pathways, how can we target mitochondrial communication and clarify the crosstalk between mitochondrial communication and aging markers to reduce the prevalence of age-related disorders? Much remains to be done to understand the detailed role of mitochondrial communication networks in age-related diseases and how to use this understanding to design treatments.

Conclusions

Mitochondrial dysfunction can have extensive effects on the entire body, impacting multiple physiological systems and playing a role in the onset of different diseases. Mitochondrial communication is vital in protecting mitochondrial health and safeguarding mitochondrial function by facilitating the transfer of material and information between mitochondria. Still, it is important to remember that increasing mitochondrial communication can also expedite the spread of substances and signals in impaired mitochondria, potentially exacerbating cellular damage. The relationship between cellular health and mitochondrial health in the aging process is well-recognized to be closely interconnected. Furthermore, manipulating the state of mitochondrial health and the exchange of information has been demonstrated to impact the progression of aging in numerous experimental organisms. Observations have revealed defects in many molecular components involved in mitochondrial signaling pathways in aging and age-related illnesses. This suggests that molecular deterioration may occur as a result of disrupted mitochondrial communication. Gaining insight into the process of mitochondrial communication and the interplay between mitochondrial communication and aging would surely enhance our understanding of age-related disorders from a novel standpoint and offer potential targets for their diagnosis and therapy.

Abbreviations

acetyl-CoA	Acetyl-coenzyme A
α -KG	α -Ketoglutaric acid
ARE	Antioxidant responsive element
ATP	Adenosine 5'-triphosphate
DdCBE	Double-stranded DNA deaminase-derived cytosine base editor
ER	Endoplasmic reticulum
ETC	Electron transport chain complex
EVs	Extracellular vesicles
FIS1	Fission 1 protein
GDP	Guanosine diphosphate
GTP	Guanosine triphosphate
Hcy	Homocysteine
IRF-3	Interferonregulatoryfactor3
Keap1	Kelch-like epichlorohydrin-related protein 1
MAMs	Mitochondrial-associated endoplasmic reticulum
MBE	Mitochondrial bifunctional enzyme
methionine-THF	Methylenetetrahydrofolate
MOMP	Mitochondrial outer membrane
miRNA	MicroRNA
MQC	Mitochondrial quality control
MIRI	Myocardial ischemia-reperfusion injury
mitoARCUS	Mitochondrial-targeted meganucleases
MS	Methionine synthase

MSCs	Mesenchymal stem cells
mtDAMPs	Proteins associated with mitochondrial damage
mtDNA	Mitochondrial DNA
5-MTHF	5-Methyl tetrahydrofolate
NAD ⁺	Nicotinamide adenine dinucleotide
NCLX	Na ⁺ Ca ²⁺ -Li ⁺ Exchanger
NF-κB	Nuclear factor-κB
NRF1	Nuclear respiratory factor 1
NRF2	Nuclear factor erythroid 2-related factor 2
OMM	Outer mitochondrial membrane
PA	Phosphatidic acid
PAH	Pulmonary arterial hypertension
PE	Phosphatidylethanolamine
PDH	Pyruvate dehydrogenase
PDP	Pyruvate dehydrogenase phosphatase
PGC-1α	Peroxisome proliferator-activated receptor-γ-coactivator 1α
PMP34	Peroxisomal membrane protein 34
PS	Phosphatidylserine
PSD	Phosphatidylserine decarboxylase
Rab7	Ras-associated GTP binding protein 7
ROS	Reactive oxygen species
SAM	S-Adenosine-L-methionine
SAMC	SAM carrier
TBC1D15	Tbc1 domain family 15
TBK	TANK-binding kinase
TCA	Tricarboxylic acid
TFAM	Mitochondrial transcription factor A
TFB2M	Mitochondrial transcription factor B2
THF	Tetrahydrofolate
TLR	Toll-like receptor
TNT	Tunnelling nanotubes
TOMM20	Translocase of outer mitochondrial membrane 20
UPRmt	Mitochondrial unfolded protein response

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Author contributions

M.Z. drafted the original manuscript. J.W. and C.H. reviewed and edited the manuscript. L.S. and C.J. gathered information. X.Z. and X.P. revised and approved the manuscript. All authors have read and agreed to the published version of the manuscript.

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References

1. Monzel AS, Enriquez JA, Picard M. Multifaceted mitochondria: moving mitochondrial science beyond function and dysfunction. *Nat Metab.* 2023;5(4):546–62.
2. Spinelli JB, Haigis MC. The multifaceted contributions of mitochondria to cellular metabolism. *Nat Cell Biol.* 2018;20(7):745–54.
3. Martínez-Reyes I, Chandel NS. Mitochondrial TCA cycle metabolites control physiology and disease. *Nat Commun.* 2020;11(1):102.

4. Boardman NT, Trani G, Scalabrin M, Romanello V, Wüst RCI. Intracellular to interorgan mitochondrial communication in striated muscle in health and disease. *Endocr Rev.* 2023;44(4):668–92.
5. Guo J, Huang X, Dou L, Yan M, Shen T, Tang W, et al. Aging and aging-related diseases: from molecular mechanisms to interventions and treatments. *Signal Transduct Target Ther.* 2022;7(1):391.
6. Campisi J, Kapahi P, Lithgow GJ, Melov S, Newman JC, Verdin E. From discoveries in ageing research to therapeutics for healthy ageing. *Nature.* 2019;571(7764):183–92.
7. Guarente L, Sinclair DA, Kroemer G. Human trials exploring anti-aging medicines. *Cell Metab.* 2024;36(2):354–76.
8. Salvioli S, Basile MS, Bencivenga L, Carrino S, Conte M, Damanti S, et al. Biomarkers of aging in frailty and age-associated disorders: state of the art and future perspective. *Ageing Res Rev.* 2023;91: 102044.
9. Son JM, Lee C. Aging: all roads lead to mitochondria. *Semin Cell Dev Biol.* 2021;116:160–8.
10. Copeland DE, Dalton AJ. An association between mitochondria and the endoplasmic reticulum in cells of the pseudobranch gland of a teleost. *J Biophys Biochem Cytol.* 1959;5(3):393–6.
11. Vance JE. Phospholipid synthesis in a membrane fraction associated with mitochondria. *J Biol Chem.* 1990;265(13):7248–56.
12. Csordás G, Renken C, Várnai P, Walter L, Weaver D, Buttle KF, et al. Structural and functional features and significance of the physical linkage between ER and mitochondria. *J Cell Biol.* 2006;174(7):915–21.
13. Ding Y, Liu N, Zhang D, Guo L, Shang Q, Liu Y, et al. Mitochondria-associated endoplasmic reticulum membranes as a therapeutic target for cardiovascular diseases. *Front Pharmacol.* 2024;15:1398381.
14. He Q, Qu M, Shen T, Su J, Xu Y, Xu C, et al. Control of mitochondria-associated endoplasmic reticulum membranes by protein S-palmitoylation: novel therapeutic targets for neurodegenerative diseases. *Ageing Res Rev.* 2023;87: 101920.
15. Janikiewicz J, Szymański J, Malinska D, Patalas-Krawczyk P, Michalska B, Duszyński J, et al. Mitochondria-associated membranes in aging and senescence: structure, function, and dynamics. *Cell Death Dis.* 2018;9(3):332.
16. Jin C, Kumar P, Gracia-Sancho J, Dufour JF. Calcium transfer between endoplasmic reticulum and mitochondria in liver diseases. *FEBS Lett.* 2021;595(10):1411–21.
17. D'Elletto M, Rossin F, Occhigrossi L, Farrace MG, Faccenda D, Desai R, et al. Transglutaminase type 2 regulates ER-mitochondria contact sites by interacting with GRP75. *Cell Rep.* 2018;25(13):3573–3581.e4.
18. Yuan M, Gong M, He J, Xie B, Zhang Z, Meng L, et al. IP3R1/GRP75/VDAC1 complex mediates endoplasmic reticulum stress-mitochondrial oxidative stress in diabetic atrial remodeling. *Redox Biol.* 2022;52: 102289.
19. Stoica R, De Vos KJ, Paillusson S, Mueller S, Sancho RM, Lau KF, et al. ER-mitochondria associations are regulated by the VAPB-PTPIP51 interaction and are disrupted by ALS/FTD-associated TDP-43. *Nat Commun.* 2014;5:3996.
20. Sutendra G, Dromparis P, Wright P, Bonnet S, Haromy A, Hao Z, et al. The role of Nogo and the mitochondria-endoplasmic reticulum unit in pulmonary hypertension. *Sci Transl Med.* 2011;3(88):88ra55.
21. Chan DC. Mitochondrial dynamics and its involvement in disease. *Annu Rev Pathol.* 2020;15:235–59.
22. de Brito OM, Scorrano L. Mitofusin 2 tethers endoplasmic reticulum to mitochondria. *Nature.* 2008;456(7222):605–10.
23. Filadi R, Greotti E, Turacchio G, Luini A, Pozzan T, Pizzo P. Mitofusin 2 ablation increases endoplasmic reticulum-mitochondria coupling. *Proc Natl Acad Sci USA.* 2015;112(17):E2174–81.
24. Yedida G, Milani M, Cohen GM, Varadarajan S. Apogossypol-mediated reorganization of the endoplasmic reticulum antagonises mitochondrial fission and apoptosis. *Cell Death Dis.* 2019;10(7):521.
25. Stone SJ, Vance JE. Phosphatidylserine synthase-1 and -2 are localized to mitochondria-associated membranes. *J Biol Chem.* 2000;275(44):34534–40.
26. Hernández-Alvarez MI, Sebastián D, Vives S, Ivanova S, Bartocconi P, Kakimoto P, et al. Deficient endoplasmic reticulum-mitochondrial phosphatidylserine transfer causes liver disease. *Cell.* 2019;177(4):881–895.e17.
27. Barazzuol L, Giamogante F, Brini M, Cali T. PINK1/Parkin mediated mitophagy, Ca²⁺ signalling, and ER-mitochondria contacts in Parkinson's disease. *Int J Mol Sci.* 2020;21(5):1772.
28. Gelmetti V, De Rosa P, Torosantucci L, Marini ES, Romagnoli A, Di Rienzo M, et al. PINK1 and BECN1 relocate at mitochondria-associated membranes during mitophagy and promote ER-mitochondria tethering and autophagosome formation. *Autophagy.* 2017;13(4):654–69.
29. Hu Z, Yang L, Zhang M, Tang H, Huang Y, Su Y, et al. A novel protein CYTB-187AA encoded by the mitochondrial gene CYTB modulates mammalian early development. *Cell Metab.* 2024;36(7):1586–1597.e7.
30. Zhu D, Li X, Tian Y. Mitochondrial-to-nuclear communication in aging: an epigenetic perspective. *Trends Biochem Sci.* 2022;47(8):645–59.
31. Shukla P, Singh KK. Uncovering mitochondrial determinants of racial disparities in ovarian cancer. *Trends Cancer.* 2021;7(2):93–7.
32. Dasgupta D, Mahadev Bhat S, Price AL, Delmotte P, Sieck GC. Molecular mechanisms underlying TNF α -induced mitochondrial biogenesis in human airway smooth muscle. *Int J Mol Sci.* 2023;24(6):5788.
33. Tabebi M, Łysiak M, Dutta RK, Lomazzi S, Turkina MV, Brunaud L, et al. Genetic alterations in mitochondrial DNA are complementary to nuclear DNA mutations in pheochromocytomas. *Cancers.* 2022;14(2):269.
34. Sturm G, Karan KR, Monzel AS, Santhanam B, Taivassalo T, Bris C, et al. OxPhos defects cause hypermetabolism and reduce lifespan in cells and in patients with mitochondrial diseases. *Commun Biol.* 2023;6(1):22.
35. Liu Y, Huang Y, Xu C, An P, Luo Y, Jiao L, et al. Mitochondrial dysfunction and therapeutic perspectives in cardiovascular diseases. *Int J Mol Sci.* 2022;23(24):16053.
36. English J, Son JM, Cardamone MD, Lee C, Perissi V. Decoding the rosetta stone of mitonuclear communication. *Pharmacol Res.* 2020;161: 105161.
37. Wiese M, Bannister AJ. Two genomes, one cell: mitochondrial-nuclear coordination via epigenetic pathways. *Mol Metab.* 2020;38: 100942.
38. Wong YC, Ysselstein D, Krainc D. Mitochondria-lysosome contacts regulate mitochondrial fission via RAB7 GTP hydrolysis. *Nature.* 2018;554(7692):382–6.
39. Onoue K, Jofuku A, Ban-Ishihara R, Ishihara T, Maeda M, Koshiba T, et al. Fis1 acts as a mitochondrial recruitment factor for TBC1D15 that is involved in regulation of mitochondrial morphology. *J Cell Sci.* 2013;126(Pt 1):176–85.

40. Yu W, Sun S, Xu H, Li C, Ren J, Zhang Y. TBC1D15/RAB7-regulated mitochondria-lysosome interaction confers cardioprotection against acute myocardial infarction-induced cardiac injury. *Theranostics*. 2020;10(24):11244–63.
41. Fransén M, Lismont C, Walton P. The peroxisome-mitochondria connection: how and why? *Int J Mol Sci*. 2017;18(6):1126.
42. Lismont C, Nordgren M, Van Veldhoven PP, Fransén M. Redox interplay between mitochondria and peroxisomes. *Front Cell Dev Biol*. 2015;3:35.
43. Wanders RJ, Waterham HR, Ferdinandusse S. Metabolic interplay between peroxisomes and other subcellular organelles including mitochondria and the endoplasmic reticulum. *Front Cell Dev Biol*. 2015;3:83.
44. Agrimi G, Russo A, Scarcia P, Palmieri F. The human gene SLC25A17 encodes a peroxisomal transporter of coenzyme A, FAD and NAD⁺. *Biochem J*. 2012;443(1):241–7.
45. Bennett CF, O'Malley KE, Perry EA, Balsa E, Latorre-Muro P, Riley CL, et al. Peroxisomal-derived ether phospholipids link nucleotides to respirasome assembly. *Nat Chem Biol*. 2021;17(6):703–10.
46. Schrader M, Costello JL, Godinho LF, Azadi AS, Islinger M. Proliferation and fission of peroxisomes—an update. *Biochem Biophys Acta*. 2016;1863(5):971–83.
47. Vallese F, Catoni C, Cieri D, Barazzuol L, Ramirez O, Calore V, et al. An expanded palette of improved SPLICS reporters detects multiple organelle contacts in vitro and in vivo. *Nat Commun*. 2020;11(1):6069.
48. Fan J, Li X, Issop L, Culty M, Papadopoulos V. ACBD2/EC12-mediated peroxisome-mitochondria interactions in Leydig cell steroid biosynthesis. *Mol Endocrinol*. 2016;30(7):763–82.
49. Peeters A, Shinde AB, Dirx R, Smet J, De Bock K, Espeel M, et al. Mitochondria in peroxisome-deficient hepatocytes exhibit impaired respiration, depleted DNA, and PGC-1 α independent proliferation. *Biochem Biophys Acta*. 2015;1853(2):285–98.
50. Liu Y, Fu T, Li G, Li B, Luo G, Li N, et al. Mitochondrial transfer between cell crosstalk—an emerging role in mitochondrial quality control. *Ageing Res Rev*. 2023;91: 102038.
51. Sato M, Sato K. Maternal inheritance of mitochondrial DNA: degradation of paternal mitochondria by allogeneic organelle autophagy, allophagy. *Autophagy*. 2012;8(3):424–5.
52. Tan AS, Baty JW, Dong LF, Bezawork-Geleta A, Endaya B, Goodwin J, et al. Mitochondrial genome acquisition restores respiratory function and tumorigenic potential of cancer cells without mitochondrial DNA. *Cell Metab*. 2015;21(1):81–94.
53. Davis DM, Sowinski S. Membrane nanotubes: dynamic long-distance connections between animal cells. *Nat Rev Mol Cell Biol*. 2008;9(6):431–6.
54. Rogers RS, Bhattacharya J. When cells become organelle donors. *Physiology*. 2013;28(6):414–22.
55. Jiang D, Gao F, Zhang Y, Wong DS, Li Q, Tse HF, et al. Mitochondrial transfer of mesenchymal stem cells effectively protects corneal epithelial cells from mitochondrial damage. *Cell Death Dis*. 2016;7(11): e2467.
56. Kitani T, Kami D, Matoba S, Gojo S. Internalization of isolated functional mitochondria: involvement of macropinocytosis. *J Cell Mol Med*. 2014;18(8):1694–703.
57. Sun C, Liu X, Wang B, Wang Z, Liu Y, Di C, et al. Endocytosis-mediated mitochondrial transplantation: transferring normal human astrocytic mitochondria into glioma cells rescues aerobic respiration and enhances radiosensitivity. *Theranostics*. 2019;9(12):3595–607.
58. Cabrera F, Castañeda V, Morales E, Velarde F, Ortega M, Leon-Sosa A, et al. Early evidence of the artificial transfer/transplant of mitochondria to oocytes and zygotes by MitoCeption. *Mitochondrion*. 2022;65:102–12.
59. Liu Z, Sun Y, Qi Z, Cao L, Ding S. Mitochondrial transfer/transplantation: an emerging therapeutic approach for multiple diseases. *Cell Biosci*. 2022;12(1):66.
60. Geng Z, Guan S, Wang S, Yu Z, Liu T, Du S, et al. Intercellular mitochondrial transfer in the brain, a new perspective for targeted treatment of central nervous system diseases. *CNS Neurosci Ther*. 2023;29(11):3121–35.
61. Cui M, Atmanli A, Morales MG, Tan W, Chen K, Xiao X, et al. Nrf1 promotes heart regeneration and repair by regulating proteostasis and redox balance. *Nat Commun*. 2021;12(1):5270.
62. Ribeiro-Rodrigues TM, Martins-Marques T, Morel S, Kwak BR, Girão H. Role of connexin 43 in different forms of intercellular communication—gap junctions, extracellular vesicles and tunnelling nanotubes. *J Cell Sci*. 2017;130(21):3619–30.
63. Liu F, Lu J, Manaenko A, Tang J, Hu Q. Mitochondria in ischemic stroke: new insight and implications. *Aging Dis*. 2018;9(5):924–37.
64. Bukoreshtliev NV, Wang X, Hodneland E, Gurke S, Barroso JF, Gerdes HH. Selective block of tunneling nanotube (TNT) formation inhibits intercellular organelle transfer between PC12 cells. *FEBS Lett*. 2009;583(9):1481–8.
65. Rustom A, Saffrich R, Markovic I, Walther P, Gerdes HH. Nanotubular highways for intercellular organelle transport. *Science*. 2004;303(5660):1007–10.
66. He K, Shi X, Zhang X, Dang S, Ma X, Liu F, et al. Long-distance intercellular connectivity between cardiomyocytes and cardiofibroblasts mediated by membrane nanotubes. *Cardiovasc Res*. 2011;92(1):39–47.
67. Liu K, Ji K, Guo L, Wu W, Lu H, Shan P, et al. Mesenchymal stem cells rescue injured endothelial cells in an in vitro ischemia–reperfusion model via tunneling nanotube like structure-mediated mitochondrial transfer. *Microvasc Res*. 2014;92:10–8.
68. Han H, Hu J, Yan Q, Zhu J, Zhu Z, Chen Y, et al. Bone marrow-derived mesenchymal stem cells rescue injured H9c2 cells via transferring intact mitochondria through tunneling nanotubes in an in vitro simulated ischemia/reperfusion model. *Mol Med Rep*. 2016;13(2):1517–24.
69. Jackson MV, Morrison TJ, Doherty DF, McAuley DF, Matthay MA, Kissenpfennig A, et al. Mitochondrial transfer via tunneling nanotubes is an important mechanism by which mesenchymal stem cells enhance macrophage phagocytosis in the in vitro and in vivo models of ARDS. *Stem Cells*. 2016;34(8):2210–23.
70. Wang Y, Cui J, Sun X, Zhang Y. Tunneling-nanotube development in astrocytes depends on p53 activation. *Cell Death Differ*. 2011;18(4):732–42.
71. Lou E, Fujisawa S, Morozov A, Barlas A, Romin Y, Dogan Y, et al. Tunneling nanotubes provide a unique conduit for intercellular transfer of cellular contents in human malignant pleural mesothelioma. *PLoS ONE*. 2012;7(3): e33093.

72. Pitt JM, Kroemer G, Zitvogel L. Extracellular vesicles: masters of intercellular communication and potential clinical interventions. *J Clin Investig.* 2016;126(4):1139–43.
73. Phinney DG, Di Giuseppe M, Njah J, Sala E, Shiva S, St Croix CM, et al. Mesenchymal stem cells use extracellular vesicles to outsource mitophagy and shuttle microRNAs. *Nat Commun.* 2015;6:8472.
74. Alvarez-Dolado M, Pardal R, Garcia-Verdugo JM, Fike JR, Lee HO, Pfeffer K, et al. Fusion of bone-marrow-derived cells with Purkinje neurons, cardiomyocytes and hepatocytes. *Nature.* 2003;425(6961):968–73.
75. Nygren JM, Liuba K, Breitbach M, Stott S, Thorén L, Roell W, et al. Myeloid and lymphoid contribution to non-haematopoietic lineages through irradiation-induced heterotypic cell fusion. *Nat Cell Biol.* 2008;10(5):584–92.
76. Oh H, Bradfute SB, Gallardo TD, Nakamura T, Gaussin V, Mishina Y, et al. Cardiac progenitor cells from adult myocardium: homing, differentiation, and fusion after infarction. *Proc Natl Acad Sci USA.* 2003;100(21):12313–8.
77. Figeac F, Lesault PF, Le Coz O, Damy T, Souktani R, Trébeau C, et al. Nanotubular crosstalk with distressed cardiomyocytes stimulates the paracrine repair function of mesenchymal stem cells. *Stem Cells.* 2014;32(1):216–30.
78. Newell C, Sabouny R, Hittel DS, Shutt TE, Khan A, Klein MS, et al. Mesenchymal stem cells shift mitochondrial dynamics and enhance oxidative phosphorylation in recipient cells. *Front Physiol.* 2018;9:1572.
79. Islam MN, Das SR, Emin MT, Wei M, Sun L, Westphalen K, et al. Mitochondrial transfer from bone-marrow-derived stromal cells to pulmonary alveoli protects against acute lung injury. *Nat Med.* 2012;18(5):759–65.
80. Berridge MV, Schneider RT, McConnell MJ. Mitochondrial transfer from astrocytes to neurons following ischemic insult: guilt by association? *Cell Metab.* 2016;24(3):376–8.
81. Lyamzaev KG, Nepryakhina OK, Saprunova VB, Bakeeva LE, Pletjushkina OY, Chernyak BV, et al. Novel mechanism of elimination of malfunctioning mitochondria (mitoptosis): formation of mitoptotic bodies and extrusion of mitochondrial material from the cell. *Biochem Biophys Acta.* 2008;1777(7–8):817–25.
82. Boudreau LH, Duchez AC, Cloutier N, Soulet D, Martin N, Bollinger J, et al. Platelets release mitochondria serving as substrate for bactericidal group IIA-secreted phospholipase A2 to promote inflammation. *Blood.* 2014;124(14):2173–83.
83. Nakajima A, Kurihara H, Yagita H, Okumura K, Nakano H. Mitochondrial extrusion through the cytoplasmic vacuoles during cell death. *J Biol Chem.* 2008;283(35):24128–35.
84. Popov LD. Mitochondrial biogenesis: an update. *J Cell Mol Med.* 2020;24(9):4892–9.
85. Cardanho-Ramos C, Morais VA. Mitochondrial biogenesis in neurons: how and where. *Int J Mol Sci.* 2021;22(23):13059.
86. Quirós PM, Mottis A, Auwerx J. Mitonuclear communication in homeostasis and stress. *Nat Rev Mol Cell Biol.* 2016;17(4):213–26.
87. Baird L, Yamamoto M. The molecular mechanisms regulating the KEAP1–NRF2 pathway. *Mol Cell Biol.* 2020;40(13):e00099–20.
88. Li S, Wen P, Zhang D, Li D, Gao Q, Liu H, et al. PGAM5 expression levels in heart failure and protection ROS-induced oxidative stress and ferroptosis by Keap1/Nrf2. *Clin Exp Hypertens.* 2023;45(1):2162537.
89. Huang CY, Deng JS, Huang WC, Jiang WP, Huang GJ. Attenuation of lipopolysaccharide-induced acute lung injury by hispolon in mice, through regulating the TLR4/PI3K/Akt/mTOR and Keap1/Nrf2/HO-1 pathways, and suppressing oxidative stress-mediated ER stress-induced apoptosis and autophagy. *Nutrients.* 2020;12(6):1742.
90. Li X, Li J, Zhu D, Zhang N, Hao X, Zhang W, et al. Protein disulfide isomerase PDI-6 regulates Wnt secretion to coordinate inter-tissue UPR(mt) activation and lifespan extension in *C. elegans*. *Cell Rep.* 2022;39(10):110931.
91. Maldonado E, Rojas DA, Urbina F, Solari A. The use of antioxidants as potential co-adjuvants to treat chronic Chagas disease. *Antioxidants.* 2021;10(7):1022.
92. Chong H, Wei Z, Na M, Sun G, Zheng S, Zhu X, et al. The PGC-1 α /NRF1/miR-378a axis protects vascular smooth muscle cells from FFA-induced proliferation, migration and inflammation in atherosclerosis. *Atherosclerosis.* 2020;297:136–45.
93. Peng T, Xie Y, Sheng H, Wang C, Lian Y, Xie N. Mitochondrial-derived vesicles: gatekeepers of mitochondrial response to oxidative stress. *Free Radic Biol Med.* 2022;188:185–93.
94. Wu Y, Sun L, Zhuang Z, Hu X, Dong D. Mitochondrial-derived peptides in diabetes and its complications. *Front Endocrinol.* 2021;12:808120.
95. Merry TL, Chan A, Woodhead JST, Reynolds JC, Kumagai H, Kim SJ, et al. Mitochondrial-derived peptides in energy metabolism. *Am J Physiol Endocrinol Metab.* 2020;319(4):E659–66.
96. Kim SJ, Miller B, Kumagai H, Silverstein AR, Flores M, Yen K. Mitochondrial-derived peptides in aging and age-related diseases. *GeroScience.* 2021;43(3):1113–21.
97. Niikura T, Chiba T, Aiso S, Matsuoka M, Nishimoto I. Humanin: after the discovery. *Mol Neurobiol.* 2004;30(3):327–40.
98. Gilon C, Gitlin-Domagalska A, Lahiani A, Yehoshua-Alshanski S, Shumacher-Klinger A, Gilon D, et al. Novel humanin analogs confer neuroprotection and myoprotection to neuronal and myoblast cell cultures exposed to ischemia-like and doxorubicin-induced cell death insults. *Peptides.* 2020;134:170399.
99. Boutari C, Pappas PD, Theodoridis TD, Vavilis D. Humanin and diabetes mellitus: a review of in vitro and in vivo studies. *World J Diabetes.* 2022;13(3):213–23.
100. Rochette L, Meloux A, Zeller M, Cottin Y, Vergely C. Role of humanin, a mitochondrial-derived peptide, in cardiovascular disorders. *Arch Cardiovasc Dis.* 2020;113(8–9):564–71.
101. Gong Y, Luo Y, Liu S, Ma J, Liu F, Fang Y, et al. Pentacyclic triterpene oleanolic acid protects against cardiac aging through regulation of mitophagy and mitochondrial integrity. *Biochim Biophys Acta.* 2022;1868(7):166402.
102. Hazafa A, Batoool A, Ahmad S, Armjad M, Chaudhry SN, Asad J, et al. Humanin: a mitochondrial-derived peptide in the treatment of apoptosis-related diseases. *Life Sci.* 2021;264:118679.
103. Coradduzza D, Congiargiu A, Chen Z, Cruciani S, Zinellu A, Carru C, et al. Humanin and its pathophysiological roles in aging: a systematic review. *Biology.* 2023;12(4):558.
104. Wijenayake S, Storey KB. The role of humanin in natural stress tolerance: an underexplored therapeutic avenue. *Biochim Biophys Acta.* 2022;1866(1):130022.
105. Xiao J, Kim SJ, Cohen P, Yen K. Humanin: functional interfaces with IGF-I. *Growth Horm IGF Res.* 2016;29:21–7.

106. Lee C, Zeng J, Drew BG, Sallam T, Martin-Montalvo A, Wan J, et al. The mitochondrial-derived peptide MOTS-c promotes metabolic homeostasis and reduces obesity and insulin resistance. *Cell Metab.* 2015;21(3):443–54.
107. Zhang Y, Yin K, Wang D, Wang Y, Lu H, Zhao H, et al. Polystyrene microplastics-induced cardiotoxicity in chickens via the ROS-driven NF- κ B-NLRP3-GSDMD and AMPK-PGC-1 α axes. *Sci Total Environ.* 2022;840: 156727.
108. Guo Y, Guan T, Shafiq K, Yu Q, Jiao X, Na D, et al. Mitochondrial dysfunction in aging. *Ageing Res Rev.* 2023;88: 101955.
109. Benayoun BA, Lee C. MOTS-c: a mitochondrial-encoded regulator of the nucleus. *BioEssays News Rev Mol Cell Dev Biol.* 2019;41(9): e1900046.
110. Gao Y, Wei X, Wei P, Lu H, Zhong L, Tan J, et al. MOTS-c functionally prevents metabolic disorders. *Metabolites.* 2023;13(1):125.
111. Cobb LJ, Lee C, Xiao J, Yen K, Wong RG, Nakamura HK, et al. Naturally occurring mitochondrial-derived peptides are age-dependent regulators of apoptosis, insulin sensitivity, and inflammatory markers. *Aging.* 2016;8(4):796–809.
112. Mendelsohn AR, Larrick JW. Mitochondrial-derived peptides exacerbate senescence. *Rejuvenation Res.* 2018;21(4):369–73.
113. Gong Z, Tas E, Muzumdar R. Humanin and age-related diseases: a new link? *Front Endocrinol.* 2014;5:210.
114. Miller B, Kim SJ, Kumagai H, Yen K, Cohen P. Mitochondria-derived peptides in aging and healthspan. *J Clin Invest.* 2022. <https://doi.org/10.1172/JCI158449>.
115. Özcan S, Alessio N, Acar MB, Mert E, Omerli F, Peluso G, et al. Unbiased analysis of senescence associated secretory phenotype (SASP) to identify common components following different genotoxic stresses. *Aging.* 2016;8(7):1316–29.
116. Sreekumar PG, Ishikawa K, Spee C, Mehta HH, Wan J, Yen K, et al. The mitochondrial-derived peptide humanin protects RPE cells from oxidative stress, senescence, and mitochondrial dysfunction. *Invest Ophthalmol Vis Sci.* 2016;57(3):1238–53.
117. van Niel G, D'Angelo G, Raposo G. Shedding light on the cell biology of extracellular vesicles. *Nat Rev Mol Cell Biol.* 2018;19(4):213–28.
118. Jeppesen DK, Zhang Q, Franklin JL, Coffey RJ. Extracellular vesicles and nanoparticles: emerging complexities. *Trends Cell Biol.* 2023;33(8):667–81.
119. Zhou X, Liu S, Lu Y, Wan M, Cheng J, Liu J. MitoEVs: a new player in multiple disease pathology and treatment. *J Extracell Vesicles.* 2023;12(4): e12320.
120. König T, McBride HM. Mitochondrial-derived vesicles in metabolism, disease, and aging. *Cell Metab.* 2024;36(1):21–35.
121. König T, Nolte H, Aaltonen MJ, Tatsuta T, Krols M, Stroh T, et al. MIROs and DRP1 drive mitochondrial-derived vesicle biogenesis and promote quality control. *Nat Cell Biol.* 2021;23(12):1271–86.
122. Cadete VJ, Deschênes S, Cuillerier A, Brisebois F, Sugiura A, Vincent A, et al. Formation of mitochondrial-derived vesicles is an active and physiologically relevant mitochondrial quality control process in the cardiac system. *J Physiol.* 2016;594(18):5343–62.
123. McLelland GL, Soubannier V, Chen CX, McBride HM, Fon EA. Parkin and PINK1 function in a vesicular trafficking pathway regulating mitochondrial quality control. *EMBO J.* 2014;33(4):282–95.
124. Howard M, Erickson J, Cuba Z, Kim S, Zhou W, Gade P, et al. A secretory form of Parkin-independent mitophagy contributes to the repertoire of extracellular vesicles released into the tumour interstitial fluid in vivo. *J Extracell Vesicles.* 2022;11(7): e12244.
125. Lee-Glover LP, Shutt TE. Mitochondrial quality control pathways sense mitochondrial protein import. *Trends Endocrinol Metab.* 2024;35(4):308–20.
126. Sugiura A, McLelland GL, Fon EA, McBride HM. A new pathway for mitochondrial quality control: mitochondrial-derived vesicles. *EMBO J.* 2014;33(19):2142–56.
127. Mondal P, Towers C. Beyond mitophagy: mitochondrial-derived vesicles can get the job done! *Autophagy.* 2022;18(2):449–51.
128. Popov LD. Mitochondrial-derived vesicles: recent insights. *J Cell Mol Med.* 2022;26(12):3323–8.
129. Soubannier V, McLelland GL, Zunino R, Braschi E, Rippstein P, Fon EA, et al. A vesicular transport pathway shuttles cargo from mitochondria to lysosomes. *Curr Biol.* 2012;22(2):135–41.
130. Picca A, Guerra F, Calvani R, Coelho-Junior HJ, Bossola M, Landi F, et al. Generation and release of mitochondrial-derived vesicles in health, aging and disease. *J Clin Med.* 2020;9(5):1440.
131. Picca A, Guerra F, Calvani R, Coelho-Júnior HJ, Landi F, Bucci C, et al. Mitochondrial-derived vesicles: the good, the bad, and the ugly. *Int J Mol Sci.* 2023;24(18):13835.
132. Roberts RF, Tang MY, Fon EA, Durcan TM. Defending the mitochondria: the pathways of mitophagy and mitochondrial-derived vesicles. *Int J Biochem Cell Biol.* 2016;79:427–36.
133. Todkar K, Chikhi L, Desjardins V, El-Mortada F, Pépin G, Germain M. Selective packaging of mitochondrial proteins into extracellular vesicles prevents the release of mitochondrial DAMPs. *Nat Commun.* 2021;12(1):1971.
134. Takenaga K, Koshikawa N, Nagase H. Intercellular transfer of mitochondrial DNA carrying metastasis-enhancing pathogenic mutations from high- to low-metastatic tumor cells and stromal cells via extracellular vesicles. *BMC Mol Cell Biol.* 2021;22(1):52.
135. Lazo S, Noren Hooten N, Green J, Eitan E, Mode NA, Liu QR, et al. Mitochondrial DNA in extracellular vesicles declines with age. *Aging Cell.* 2021;20(1): e13283.
136. McLelland GL, Lee SA, McBride HM, Fon EA. Syntaxin-17 delivers PINK1/parkin-dependent mitochondrial vesicles to the endolysosomal system. *J Cell Biol.* 2016;214(3):275–91.
137. Vasam G, Nadeau R, Cadete VJJ, Lavallée-Adam M, Menzies KJ, Burrelle Y. Proteomics characterization of mitochondrial-derived vesicles under oxidative stress. *FASEB J.* 2021;35(4): e21278.
138. Ryan TA, Phillips EO, Collier CL, Jb Robinson A, Routledge D, Wood RE, et al. Tollip coordinates Parkin-dependent trafficking of mitochondrial-derived vesicles. *EMBO J.* 2020;39(11): e102539.

139. Terešák P, Lapao A, Subic N, Boya P, Elazar Z, Simonsen A. Regulation of PRKN-independent mitophagy. *Autophagy*. 2022;18(1):24–39.
140. Roberts RF, Fon EA. Presenting mitochondrial antigens: PINK1, Parkin and MDVs steal the show. *Cell Res*. 2016;26(11):1180–1.
141. Manickam DS. Delivery of mitochondria via extracellular vesicles—a new horizon in drug delivery. *J Control Release*. 2022;343:400–7.
142. Velarde F, Ezquerro X, Delbryere X, Caicedo A, Hidalgo Y, Khoury M. Mesenchymal stem cell-mediated transfer of mitochondria: mechanisms and functional impact. *Cell Mol Life Sci*. 2022;79(3):177.
143. Sanz-Ros J, Mas-Bargues C, Romero-García N, Huete-Acevedo J, Dromant M, Borrás C. The potential use of mitochondrial extracellular vesicles as biomarkers or therapeutical tools. *Int J Mol Sci*. 2023;24(8):7005.
144. Amari L, Germain M. Mitochondrial extracellular vesicles—origins and roles. *Front Mol Neurosci*. 2021;14: 767219.
145. Roberts RF, Bayne AN, Goiran T, Lévesque D, Boisvert FM, Trempe JF, et al. Proteomic profiling of mitochondrial-derived vesicles in brain reveals enrichment of respiratory complex sub-assemblies and small TIM chaperones. *J Proteome Res*. 2021;20(1):506–17.
146. Mohanty A, Zunino R, Soubannier V, Dilipkumar S. A new functional role of mitochondria-anchored protein ligase in peroxisome morphology in mammalian cells. *J Cell Biochem*. 2021;122(11):1686–700.
147. Di Florio DN, Beetler DJ, McCabe EJ, Sin J, Ikezu T, Fairweather D. Mitochondrial extracellular vesicles, autoimmunity and myocarditis. *Front Immunol*. 2024;15:1374796.
148. Ryan TA, Tumbarello DA. A central role for mitochondrial-derived vesicles in the innate immune response: implications for Parkinson's disease. *Neural Regen Res*. 2021;16(9):1779–80.
149. Rosina M, Ceci V, Turchi R, Chuan L, Borcherding N, Sciarretta F, et al. Ejection of damaged mitochondria and their removal by macrophages ensure efficient thermogenesis in brown adipose tissue. *Cell Metab*. 2022;34(4):533–48.e12.
150. Ikeda G, Santoso MR, Tada Y, Li AM, Vaskova E, Jung JH, et al. Mitochondria-rich extracellular vesicles from autologous stem cell-derived cardiomyocytes restore energetics of ischemic myocardium. *J Am Coll Cardiol*. 2021;77(8):1073–88.
151. Towers CG, Wodetzki DK, Thorburn J, Smith KR, Caino MC, Thorburn A. Mitochondrial-derived vesicles compensate for loss of LC3-mediated mitophagy. *Dev Cell*. 2021;56(14):2029–42.e5.
152. Ramirez A, Old W, Selwood DL, Liu X. Cannabidiol activates PINK1-Parkin-dependent mitophagy and mitochondrial-derived vesicles. *Eur J Cell Biol*. 2022;101(1): 151185.
153. Chaiyarit S, Thongboonkerd V. Mitochondria-derived vesicles and their potential roles in kidney stone disease. *J Transl Med*. 2023;21(1):294.
154. Chandel NS. Evolution of mitochondria as signaling organelles. *Cell Metab*. 2015;22(2):204–6.
155. Frezza C. Mitochondrial metabolites: undercover signalling molecules. *Interface focus*. 2017;7(2):20160100.
156. Allis CD, Jenuwein T. The molecular hallmarks of epigenetic control. *Nat Rev Genet*. 2016;17(8):487–500.
157. Shaughnessy DT, McAllister K, Worth L, Haugen AC, Meyer JN, Domann FE, et al. Mitochondria, energetics, epigenetics, and cellular responses to stress. *Environ Health Perspect*. 2014;122(12):1271–8.
158. Fetterman JL, Ballinger SW. Mitochondrial genetics regulate nuclear gene expression through metabolites. *Proc Natl Acad Sci USA*. 2019;116(32):15763–5.
159. Feeley KP, Bray AW, Westbrook DG, Johnson LW, Kesterson RA, Ballinger SW, et al. Mitochondrial genetics regulate breast cancer tumorigenicity and metastatic potential. *Can Res*. 2015;75(20):4429–36.
160. Sagar S, Kapoor H, Chaudhary N, Roy SS. Cellular and mitochondrial calcium communication in obstructive lung disorders. *Mitochondrion*. 2021;58:184–99.
161. Yousuf MS, Maguire AD, Simmen T, Kerr BJ. Endoplasmic reticulum-mitochondria interplay in chronic pain: the calcium connection. *Mol Pain*. 2020;16:1744806920946889.
162. Rizzuto R, De Stefani D, Raffaello A, Mammucari C. Mitochondria as sensors and regulators of calcium signalling. *Nat Rev Mol Cell Biol*. 2012;13(9):566–78.
163. Kaufman RJ, Malhotra JD. Calcium trafficking integrates endoplasmic reticulum function with mitochondrial bioenergetics. *Biochem Biophys Acta*. 2014;1843(10):2233–9.
164. Alevriadou BR, Patel A, Noble M, Ghosh S, Gohil VM, Stathopoulos PB, et al. Molecular nature and physiological role of the mitochondrial calcium uniporter channel. *Am J Physiol Cell Physiol*. 2021;320(4):C465–82.
165. Cortassa S, O'Rourke B, Winslow RL, Aon MA. Control and regulation of integrated mitochondrial function in metabolic and transport networks. *Int J Mol Sci*. 2009;10(4):1500–13.
166. Liu T, O'Rourke B. Regulation of mitochondrial Ca²⁺ and its effects on energetics and redox balance in normal and failing heart. *J Bioenerg Biomembr*. 2009;41(2):127–32.
167. Weidinger A, Milivojević N, Hosmann A, Duvigneau JC, Szabo C, Törö G, et al. Oxoglutarate dehydrogenase complex controls glutamate-mediated neuronal death. *Redox Biol*. 2023;62: 102669.
168. Pitt D, Mosley MJ. Oxidation of carbon sources via the tricarboxylic acid cycle during calcium-induced conidiation of *Penicillium notatum*. *Antonie Van Leeuwenhoek*. 1986;52(6):467–82.
169. Xian H, Watari K, Sanchez-Lopez E, Offenberger J, Onyuru J, Sampath H, et al. Oxidized DNA fragments exit mitochondria via mPTP- and VDAC-dependent channels to activate NLRP3 inflammasome and interferon signaling. *Immunity*. 2022;55(8):1370–85.e8.
170. De Gaetano A, Solodka K, Zanini G, Selleri V, Mattioli AV, Nasi M, et al. Molecular mechanisms of mtDNA-mediated inflammation. *Cells*. 2021;10(11):2898.
171. Jiménez-Loygorri JI, Villarejo-Zori B, Viedma-Poyatos Á, Zapata-Muñoz J, Benítez-Fernández R, Frutos-Lisón MD, et al. Mitophagy curtails cytosolic mtDNA-dependent activation of cGAS/STING inflammation during aging. *Nat Commun*. 2024;15(1):830.
172. Decout A, Katz JD, Venkatraman S, Ablasser A. The cGAS-STING pathway as a therapeutic target in inflammatory diseases. *Nat Rev Immunol*. 2021;21(9):548–69.

173. Oduro PK, Zheng X, Wei J, Yang Y, Wang Y, Zhang H, et al. The cGAS-STING signaling in cardiovascular and metabolic diseases: future novel target option for pharmacotherapy. *Acta Pharm Sin B*. 2022;12(1):50–75.
174. Kim J, Kim HS, Chung JH. Molecular mechanisms of mitochondrial DNA release and activation of the cGAS-STING pathway. *Exp Mol Med*. 2023;55(3):510–9.
175. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: an expanding universe. *Cell*. 2023;186(2):243–78.
176. Miwa S, Kashyap S, Chini E, von Zglinicki T. Mitochondrial dysfunction in cell senescence and aging. *J Clin Investig*. 2022. <https://doi.org/10.1172/JCI158447>.
177. Tian R, Colucci WS, Arany Z, Bachschmid MM, Ballinger SW, Boudina S, et al. Unlocking the secrets of mitochondria in the cardiovascular system: path to a cure in heart failure—a report from the 2018 national heart, lung, and blood institute workshop. *Circulation*. 2019;140(14):1205–16.
178. Song J, Herrmann JM, Becker T. Quality control of the mitochondrial proteome. *Nat Rev Mol Cell Biol*. 2021;22(1):54–70.
179. Wu L, Wang L, Du Y, Zhang Y, Ren J. Mitochondrial quality control mechanisms as therapeutic targets in doxorubicin-induced cardiotoxicity. *Trends Pharmacol Sci*. 2023;44(1):34–49.
180. Keerthiga R, Pei DS, Fu A. Mitochondrial dysfunction, UPR(mt) signaling, and targeted therapy in metastasis tumor. *Cell Biosci*. 2021;11(1):186.
181. Ducker GS, Rabinowitz JD. One-carbon metabolism in health and disease. *Cell Metab*. 2017;25(1):27–42.
182. Reina-Campos M, Diaz-Meco MT, Moscat J. The complexity of the serine glycine one-carbon pathway in cancer. *J Cell Biol*. 2020;219(1): e201907022.
183. Castegna A, Iacobazzi V, Infantino V. The mitochondrial side of epigenetics. *Physiol Genomics*. 2015;47(8):299–307.
184. Agrimi G, Di Noia MA, Marobbio CM, Fiermonte G, Lasorsa FM, Palmieri F. Identification of the human mitochondrial S-adenosylmethionine transporter: bacterial expression, reconstitution, functional characterization and tissue distribution. *Biochem J*. 2004;379(Pt 1):183–90.
185. Gusic M, Prokisch H. ncRNAs: new players in mitochondrial health and disease? *Front Genet*. 2020;11:95.
186. Calvo-Rodríguez M, Hou SS, Snyder AC, Kharitonova EK, Russ AN, Das S, et al. Increased mitochondrial calcium levels associated with neuronal death in a mouse model of Alzheimer's disease. *Nat Commun*. 2020;11(1):2146.
187. Lung B, Zemann A, Madej MJ, Schuelke M, Techritz S, Ruf S, et al. Identification of small non-coding RNAs from mitochondria and chloroplasts. *Nucleic Acids Res*. 2006;34(14):3842–52.
188. Zhang Q, Raoof M, Chen Y, Sumi Y, Sursal T, Junger W, et al. Circulating mitochondrial DAMPs cause inflammatory responses to injury. *Nature*. 2010;464(7285):104–7.
189. Nakayama H, Otsu K. Mitochondrial DNA as an inflammatory mediator in cardiovascular diseases. *Biochem J*. 2018;475(5):839–52.
190. Wu Z, Oeck S, West AP, Mangalharra KC, Sainz AG, Newman LE, et al. Mitochondrial DNA stress signalling protects the nuclear genome. *Nat Metab*. 2019;1(12):1209–18.
191. Qin C, Gu J, Hu J, Qian H, Fei X, Li Y, et al. Platelets activation is associated with elevated plasma mitochondrial DNA during cardiopulmonary bypass. *J Cardiothorac Surg*. 2016;11(1):90.
192. Bliksøen M, Mariero LH, Torp MK, Baysa A, Ytrehus K, Haugen F, et al. Extracellular mtDNA activates NF- κ B via toll-like receptor 9 and induces cell death in cardiomyocytes. *Basic Res Cardiol*. 2016;111(4):42.
193. Picca A, Guerra F, Calvani R, Coelho-Júnior HJ, Landi F, Bernabei R, et al. Extracellular vesicles and damage-associated molecular patterns: a Pandora's box in health and disease. *Front Immunol*. 2020;11: 601740.
194. Dong LF, Rohlena J, Zobalova R, Nahacka Z, Rodriguez AM, Berridge MV, et al. Mitochondria on the move: horizontal mitochondrial transfer in disease and health. *J Cell Biol*. 2023;222(3): e202211044.
195. Chang JC, Wu SL, Liu KH, Chen YH, Chuang CS, Cheng FC, et al. Allogeneic/xenogeneic transplantation of peptide-labeled mitochondria in Parkinson's disease: restoration of mitochondria functions and attenuation of 6-hydroxydopamine-induced neurotoxicity. *Transl Res*. 2016;170:40-56.e3.
196. Ahn BH, Kim HS, Song S, Lee IH, Liu J, Vassilopoulos A, et al. A role for the mitochondrial deacetylase Sirt3 in regulating energy homeostasis. *Proc Natl Acad Sci USA*. 2008;105(38):14447–52.
197. Bach D, Pich S, Soriano FX, Vega N, Baumgartner B, Oriola J, et al. Mitofusin-2 determines mitochondrial network architecture and mitochondrial metabolism. A novel regulatory mechanism altered in obesity. *J Biol Chem*. 2003;278(19):17190–7.
198. Theurey P, Rieusset J. Mitochondria-associated membranes response to nutrient availability and role in metabolic diseases. *Trends Endocrinol Metab*. 2017;28(1):32–45.
199. Andreux PA, Houtkooper RH, Auwerx J. Pharmacological approaches to restore mitochondrial function. *Nat Rev Drug Discov*. 2013;12(6):465–83.
200. Gong B, Pan Y, Vempati P, Zhao W, Knable L, Ho L, et al. Nicotinamide riboside restores cognition through an upregulation of proliferator-activated receptor- γ coactivator 1 α regulated β -secretase 1 degradation and mitochondrial gene expression in Alzheimer's mouse models. *Neurobiol Aging*. 2013;34(6):1581–8.
201. Xu Z, Huo J, Ding X, Yang M, Li L, Dai J, et al. Coenzyme Q10 improves lipid metabolism and ameliorates obesity by regulating CaMKII-mediated PDE4 inhibition. *Sci Rep*. 2017;7(1):8253.
202. Mohammed I, Hollenberg MD, Ding H, Triggle CR. A critical review of the evidence that metformin is a putative anti-aging drug that enhances healthspan and extends lifespan. *Front Endocrinol*. 2021;12: 718942.
203. Rodríguez-Bies E, Tung BT, Navas P, López-Lluch G. Resveratrol primes the effects of physical activity in old mice. *Br J Nutr*. 2016;116(6):979–88.
204. Givvimani S, Munjal C, Tyagi N, Sen U, Metreveli N, Tyagi SC. Mitochondrial division/mitophagy inhibitor (Mdivi) ameliorates pressure overload induced heart failure. *PLoS ONE*. 2012;7(3): e32388.
205. Rappold PM, Cui M, Grima JC, Fan RZ, de Mesy-Bentley KL, Chen L, et al. Drp1 inhibition attenuates neurotoxicity and dopamine release deficits in vivo. *Nat Commun*. 2014;5:5244.
206. Joshi AU, Saw NL, Vogel H, Cunningham AD, Shamloo M, Mochly-Rosen D. Inhibition of Drp1/Fis1 interaction slows progression of amyotrophic lateral sclerosis. *EMBO Mol Med*. 2018;10(3): e8166.

207. Disatnik MH, Hwang S, Ferreira JC, Mochly-Rosen D. New therapeutics to modulate mitochondrial dynamics and mitophagy in cardiac diseases. *J Mol Med*. 2015;93(3):279–87.
208. Ferreira JC, Mochly-Rosen D. Nitroglycerin use in myocardial infarction patients. *Circ J*. 2012;76(1):15–21.
209. Nishimura A, Shimauchi T, Tanaka T, Shimoda K, Toyama T, Kitajima N, et al. Hypoxia-induced interaction of filamin with Drp1 causes mitochondrial hyperfission-associated myocardial senescence. *Sci Signal*. 2018;11(556):eaat5185.
210. Jayatunga DPW, Hone E, Khaira H, Lunelli T, Singh H, Guillemin GJ, et al. Therapeutic potential of mitophagy-inducing microflora metabolite, urolithin A for Alzheimer's disease. *Nutrients*. 2021;13(11):3744.
211. Qiu J, Chen Y, Zhuo J, Zhang L, Liu J, Wang B, et al. Urolithin A promotes mitophagy and suppresses NLRP3 inflammasome activation in lipopolysaccharide-induced BV2 microglial cells and MPTP-induced Parkinson's disease model. *Neuropharmacology*. 2022;207: 108963.
212. Gao Z, Yi W, Tang J, Sun Y, Huang J, Lan T, et al. Urolithin A protects against acetaminophen-induced liver injury in mice via sustained activation of Nrf2. *Int J Biol Sci*. 2022;18(5):2146–62.
213. Huang JR, Zhang MH, Chen YJ, Sun YL, Gao ZM, Li ZJ, et al. Urolithin A ameliorates obesity-induced metabolic cardiomyopathy in mice via mitophagy activation. *Acta Pharmacol Sin*. 2023;44(2):321–31.
214. Xie C, Zhuang XX, Niu Z, Ai R, Lautrup S, Zheng S, et al. Amelioration of Alzheimer's disease pathology by mitophagy inducers identified via machine learning and a cross-species workflow. *Nat Biomed Eng*. 2022;6(1):76–93.
215. Manczak M, Mao P, Calkins MJ, Cornea A, Reddy AP, Murphy MP, et al. Mitochondria-targeted antioxidants protect against amyloid-beta toxicity in Alzheimer's disease neurons. *J Alzheimer's Dis*. 2010;20(Suppl 2):S609–31.
216. RibeiroJunior RF, Dabkowski ER, Shekar KC, Connell KAO, Hecker PA, Murphy MP. MitoQ improves mitochondrial dysfunction in heart failure induced by pressure overload. *Free Radic Biol Med*. 2018;117:18–29.
217. Fink BD, Herlein JA, Guo DF, Kulkarni C, Weidemann BJ, Yu L, et al. A mitochondrial-targeted coenzyme q analog prevents weight gain and ameliorates hepatic dysfunction in high-fat-fed mice. *J Pharmacol Exp Ther*. 2014;351(3):699–708.
218. Reddy PH, Manczak M, Kandimalla R. Mitochondria-targeted small molecule SS31: a potential candidate for the treatment of Alzheimer's disease. *Hum Mol Genet*. 2017;26(8):1483–96.
219. Dai W, Shi J, Gupta RC, Sabbah HN, Hale SL, Kloner RA, Bendavia, a mitochondria-targeting peptide, improves postinfarction cardiac function, prevents adverse left ventricular remodeling, and restores mitochondria-related gene expression in rats. *J Cardiovasc Pharmacol*. 2014;64(6):543–53.
220. Shi J, Dai W, Hale SL, Brown DA, Wang M, Han X, et al. Bendavia restores mitochondrial energy metabolism gene expression and suppresses cardiac fibrosis in the border zone of the infarcted heart. *Life Sci*. 2015;141:170–8.
221. Kamboj SS, Vasishtha RK, Sandhir R. N-Acetylcysteine inhibits hyperglycemia-induced oxidative stress and apoptosis markers in diabetic neuropathy. *J Neurochem*. 2010;112(1):77–91.
222. Yoshino J, Mills KF, Yoon MJ, Imai S. Nicotinamide mononucleotide, a key NAD(+) intermediate, treats the pathophysiology of diet- and age-induced diabetes in mice. *Cell Metab*. 2011;14(4):528–36.
223. Karuppagounder SS, Pinto JT, Xu H, Chen HL, Beal MF, Gibson GE. Dietary supplementation with resveratrol reduces plaque pathology in a transgenic model of Alzheimer's disease. *Neurochem Int*. 2009;54(2):111–8.
224. Baur JA, Pearson KJ, Price NL, Jamieson HA, Lerin C, Kalra A, et al. Resveratrol improves health and survival of mice on a high-calorie diet. *Nature*. 2006;444(7117):337–42.
225. Gérard C, Xiao X, Filali M, Coulombe Z, Arsenault M, Couet J, et al. An AAV9 coding for frataxin clearly improved the symptoms and prolonged the life of Friedreich ataxia mouse models. *Mol Ther Methods Clin Dev*. 2014;1:14044.
226. Rehfeldt SCH, Laufer S, Goettert MI. A highly selective in vitro JNK3 inhibitor, FMU200, restores mitochondrial membrane potential and reduces oxidative stress and apoptosis in SH-SY5Y cells. *Int J Mol Sci*. 2021;22(7):3701.
227. Han Y, Jiang M, He R, Lv X, Liao X, He Y, et al. Mefunidone ameliorates bleomycin-induced pulmonary fibrosis in mice. *Front Pharmacol*. 2021;12: 713572.
228. Sorrentino V, Romani M, Mouchiroud L, Beck JS, Zhang H, D'Amico D, et al. Enhancing mitochondrial proteostasis reduces amyloid- β proteotoxicity. *Nature*. 2017;552(7684):187–93.
229. Rysted JE, Lin Z, Walters GC, Rauckhorst AJ, Noterman M, Liu G, et al. Distinct properties of Ca(2+) efflux from brain, heart and liver mitochondria: the effects of Na(+), Li(+) and the mitochondrial Na(+)/Ca(2+) exchange inhibitor CGP37157. *Cell Calcium*. 2021;96: 102382.
230. Yoshinaga N, Numata K. Rational designs at the forefront of mitochondria-targeted gene delivery: recent progress and future perspectives. *ACS Biomater Sci Eng*. 2022;8(2):348–59.
231. Kaza AK, Wamala I, Friehs I, Kuebler JD, Rathod RH, Berra I, et al. Myocardial rescue with autologous mitochondrial transplantation in a porcine model of ischemia/reperfusion. *J Thorac Cardiovasc Surg*. 2017;153(4):934–43.
232. Masuzawa A, Black KM, Pacak CA, Ericsson M, Barnett RJ, Drumm C, et al. Transplantation of autologously derived mitochondria protects the heart from ischemia–reperfusion injury. *Am J Physiol Heart Circ Physiol*. 2013;304(7):H966–82.
233. Bertoldo MJ, Listijono DR, Ho WJ, Riepsamen AH, Goss DM, Richani D, et al. NAD(+) repletion rescues female fertility during reproductive aging. *Cell Rep*. 2020;30(6):1670–81.e7.
234. Chu X, Hou Y, Meng Q, Croteau DL, Wei Y, De S, et al. Nicotinamide adenine dinucleotide supplementation drives gut microbiota variation in Alzheimer's mouse model. *Front Aging Neurosci*. 2022;14: 993615.
235. Ryu D, Mouchiroud L, Andreux PA, Katsyuba E, Moullan N, Nicolet-Dit-Félix AA, et al. Urolithin A induces mitophagy and prolongs lifespan in *C. elegans* and increases muscle function in rodents. *Nat Med*. 2016;22(8):879–88.
236. Chavez JD, Tang X, Campbell MD, Reyes G, Kramer PA, Stuppard R, et al. Mitochondrial protein interaction landscape of SS-31. *Proc Natl Acad Sci USA*. 2020;117(26):15363–73.
237. Lagouge M, Argmann C, Gerhart-Hines Z, Meziane H, Lerin C, Daussin F, et al. Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1 α . *Cell*. 2006;127(6):1109–22.
238. Huang T, Lin R, Su Y, Sun H, Zheng X, Zhang J, et al. Efficient intervention for pulmonary fibrosis via mitochondrial transfer promoted by mitochondrial biogenesis. *Nat Commun*. 2023;14(1):5781.

239. Gammage PA, Viscomi C, Simard ML, Costa ASH, Gaude E, Powell CA, et al. Genome editing in mitochondria corrects a pathogenic mtDNA mutation in vivo. *Nat Med.* 2018;24(11):1691–5.
240. Zekonyte U, Bacman SR, Smith J, Shoop W, Pereira CV, Tomberlin G, et al. Mitochondrial targeted meganuclease as a platform to eliminate mutant mtDNA in vivo. *Nat Commun.* 2021;12(1):3210.
241. Silva-Pinheiro P, Nash PA, Van Haute L, Mutti CD, Turner K, Minczuk M. In vivo mitochondrial base editing via adeno-associated viral delivery to mouse post-mitotic tissue. *Nat Commun.* 2022;13(1):750.
242. Reichart D, Newby GA, Wakimoto H, Lun M, Gorham JM, Curran JJ, et al. Efficient in vivo genome editing prevents hypertrophic cardiomyopathy in mice. *Nat Med.* 2023;29(2):412–21.
243. Kang E, Wu J, Gutierrez NM, Koski A, Tippner-Hedges R, Agaronyan K, et al. Mitochondrial replacement in human oocytes carrying pathogenic mitochondrial DNA mutations. *Nature.* 2016;540(7632):270–5.

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