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Energizing Mitochondria to Prevent Mobility Loss in Aging: Rationale and Hypotheses

Qu Tian, Ph.D., MS[1], **Philip R. Lee, BS**[1], **Keenan A. Walker, Ph.D.**[2], **Luigi Ferrucci, MD, Ph.D.**[1]

[1]Longitudinal Studies Section, Translational Gerontology Branch, National Institute on Aging, Baltimore, MD 21224

[2]Laboratory of Behavioral Neuroscience, National Institute on Aging, Baltimore, MD 21224

Abstract

Based on recent studies from our group and others, we hypothesize that mitochondrial dysfunction during aging may be the root cause of mobility decline through deficits in the musculoskeletal and central nervous systems. Mitochondrial dysfunction could be a therapeutic target to prevent mobility decline in aging.

Summary for table of contents:

Mitochondria energetics and mobility.

Keywords

mitochondria; skeletal muscle; brain; mobility; aging; physical activity; energetics

INTRODUCTION

Mobility decline, often operationalized as declining gait speed, is common in older adults. Healthy mobility depends on a well-coordinated network of physiological systems that include the central and peripheral nervous systems, muscles and joints, energetic metabolism, and the sensory system. There is overwhelming evidence that poor lower extremity function predicts future physical disability, cognitive impairment, dementia, and mortality (1, 2). Thus, preventing mobility decline and preserving physical function may reduce future disease risks and extend the health span. Two key contributors to mobility decline in older adults are progressive loss of skeletal muscle function and central nervous system (CNS) dysfunction (3). In fact, it has been consistently shown that both deficits in muscle function and aging- and disease-related brain changes are associated with overall mobility decline and physical frailty (4, 5). Understanding the core biological processes which can jointly promote declines in muscle function and brain health is key for identifying

Correspondence to Qu Tian, Ph.D., 251 Bayview Blvd., Suite 100, RM04B316, Baltimore, MD 21224., Phone: 410-558-8232. Tax: Fax: 410-558-8674. qu.tian@nih.gov.

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and developing strategies to prevent mobility decline. The aerobic metabolism taking place in mitochondria generates the majority of the energy required by cells to maintain vitality and functionality. There is strong evidence that both mitochondrial mass and function decline with aging and that such declines negatively affect the integrity and function of multiple physiological systems (6). The musculoskeletal system and the CNS may be particularly vulnerable to mitochondrial health decline because they are more energy dependent relative to other systems.

The central hypothesis

Studies conducted to date suggest that the decline of mitochondrial function that occurs with aging may contribute to mobility decline and disability in older persons. An extension of this hypothesis is that mobility decline could be slowed or even reversed by enhancing mitochondrial function (see the Figure for the central hypothesis). Several aging studies from our group and others have demonstrated that mitochondrial function declines with aging and that such declines are associated with slower gait speed, greater declines in gait speed, and impairment of other aspects of physical function in community-dwelling older adults (7–10). Recent findings from our group further demonstrated that the association between mitochondrial function and mobility is mediated in part by reduced muscle function both cross-sectionally and longitudinally in the Baltimore Longitudinal Study of Aging (9, 10). Both human and animal studies suggested that maintaining good mitochondrial function plays a key role in maintaining a healthy brain with aging, yet whether loss of mitochondrial function affects mobility decline through the CNS dysfunction is unexplored. In this review of mitochondrial dysfunction in human aging and mobility decline, we refer to mitochondrial function in terms of their capacity to produce adenosine triphosphate (ATP) through oxidative phosphorylation. Other essential physiological functions exerted by mitochondria, such as heat production, triggering apoptosis, and the production of certain steroids, may also be important but cannot be easily measured in human studies.

THE ROOT CAUSE: MITOCHONDRIAL DYSFUNCTION

Mitochondrial dysfunction is a hallmark of aging and is related to a wide range of pathologies (6). Studies have shown that mitochondrial related measures across different tissues decline with aging, such as skeletal muscle oxidative capacity and respiratory activity, insulin resistance, brain metabolism, mitochondrial DNA (mtDNA) copy number (11–13). Mitochondrial DNA copy number estimated from whole-genome sequencing data shows an average decrease of 1.5 for every 10-year increase in age (11). Magnetic resonance spectroscopy (MRS) can non-invasively access mitochondrial function in the skeletal muscle and brain and studies have shown the post-exercise rate of recovery of phosphocreatine in skeletal muscle and ATP and other metabolites in the whole brain decrease with aging (7, 13). The cause of progressive mitochondrial dysfunction with aging is unknown and understanding the underlying mechanisms is a preliminary step that can facilitate the development of effective interventions aimed at preventing age-related loss of mobility and disability. Here, we discuss three potential mechanisms - altered metabolism, impaired mitophagy, and impaired perfusion - and review the evidence from both human and animal studies.

Potential mechanism 1:

Metabolic regulation is key to maintaining healthy mitochondria. Altered or impaired metabolism during aging can be detrimental to mitochondrial morphology and function (14). Metabolic conditions, such as metabolic syndrome, type 2 diabetes, non-alcoholic fatty liver disease, and insulin resistance, have all been associated with mitochondrial dysfunction, although whether they cause mitochondrial dysfunction or are caused by mitochondrial dysfunction, or both remains unclear. Mechanisms may include increased lipid oxidation, modifications in the mitochondrial oxidative phosphorylation (OXPHOS) system, decreased electronic transport chain (ETC) complex activity and decreased sirtuin-3 (SIRT3) activity, all of which converge on the development of mitochondrial dysfunction and subsequent reduced ATP production (14).

Potential mechanism 2:

Mitophagy is a special form of autophagy that specifically recycles dysfunctional mitochondria that cannot be repaired. Although the multiplicity of mechanisms that trigger mitophagy is not fully understood, the reduction of intermembrane electrical potential is considered the early event that trigger the accumulation of PTEN-induced kinase 1 (PINK1) and Parkin RBR E3 ubiquitin-protein ligase (PARKIN) on the outer membrane and causes their removal via selective mitophagy (15). Elimination of dysfunctional mitochondria by mitophagy is essential to reduce ROS production and ultimately to avoid further deterioration of mitochondrial health that results in the opening of the transition pore, with Cytochrome C entering the cytoplasm and triggering the apoptotic pathway (16). In addition, when this “quality control” mechanism fails to remove dysregulated or fragmented mitochondria, it likely interferes with the production of new, efficient mitochondria through biogenesis, which in the long term creates an energetic crisis. Previous data have shown that defective autophagy has been detected in age human and mouse satellite cells. It has been suggested that loss of autophagy in satellite cells causes impaired mitophagy, mitochondrial dysfunction, and excessive ROS which induce subsequent cell senescence (17). The lack of consistent mitophagy, assessed by mitophagy flux, results in a buildup of ROS which increases oxidative stress, accelerates cellular damage, and increases oxidation of cardiolipin (18). Sustained elevated levels of ROS may drive the oxidation of membrane lipids, proteins, and mtDNA mutations (6). mtDNA is especially sensitive to oxidative damage and susceptibility to mutations due to its lack of protective histones and its proximity to the site of ROS production. In animal models, higher mitochondrial ROS is associated with greater mtDNA strand breaks. It has been hypothesized that age-related increase in mtROS results in mtDNA damage which alters the structure and function of respiratory chain complexes and further increases mtROS (19). Emerging evidence also suggests that impaired mitophagy leads to increased inflammation and muscle damage (20, 21). Recent findings from the Baltimore Longitudinal Study of Aging have shown that older adults have decreased gene expression specific to oxidative phosphorylation and the ETC pathways, dysfunctional oxidative phosphorylation and energy metabolism, and impaired mitochondrial respiration in CD4(+) T cells compared to younger individuals (22). It may indicate that impaired mitophagy due to aging contributes to dysfunctional mitochondria in CD4(+) T cells which may result in chronic inflammation and compromised immune responses in older adults.

Potential mechanism 3:

Impaired perfusion results in insufficient delivery of oxygen and nutrient in the whole organism which can cause mitochondrial dysfunction. One example is the lower extremity skeletal muscle of patients with peripheral artery diseases (PAD). Insufficient oxygen delivery impairs OXPHOS by slowing down electron flow in the ETC resulting in excess ROS and reduced ATP production. PAD is associated with lower in-vivo maximal ATP synthesis rates and higher calf muscle levels of oxidative stress (23). In PAD, the extent of myofiber degeneration in skeletal muscle is associated with lower ankle-brachial index (ABI) (24). In the absence of PAD, those with a lower ABI of 0.90 to 1.10 have lower skeletal muscle mitochondrial function than those with a higher ABI of 1.10 to 1.40 (25). Greater decline in ABI over time is also associated with concurrent greater decline in skeletal muscle mitochondrial function in aging (26). Several age-related conditions may alter microcirculation perfusions, such as hypertension, atherosclerosis, tissue fibrosis, and chronic inflammation. Whether these conditions are sufficiently severe to cause mitochondrial dysfunction is unknown.

Consequences of mitochondrial dysfunction

Excessive ROS: Mitochondrial dysfunction leads to excessive ROS which can result in several pathophysiological changes, including cardiolipin peroxidation, oxidative cell damage, premature cellular apoptosis, mtDNA damage, and beta-amyloid accumulation. Cardiolipin is a mitochondria-exclusive phospholipid and is mainly located in the mitochondrial inner membrane, shaping the curvature of the mitochondrial cristae. The chemical structure of cardiolipin encompasses a glycerol backbone with two fatty acids. Note that in human skeletal and cardiac muscle, C16 and C18 constitute the large majority of cardiolipin fatty acids (27). Cardiolipin is particularly susceptible to lipid peroxidation due to its high composition of unsaturated acyl chains, proximity to the mitochondrial ETC, and tightly bound nature to Cytochrome c. Under excessive ROS, cardiolipin is oxidized, becomes misfolded, and warps the spatial organization of respiratory complexes. Due to its role in the structural integrity of the mitochondrial cristae, cardiolipin deficiency is thought to cause gradual disarrangement of the functional complexes of oxidative phosphorylation within the mitochondria. Cardiolipin plays a key role in the alignment of the respiratory complexes, a process that ensures the ETC complexes function and generates ATP. When cardiolipin is deficient due to oxidation, the ETC between the major respiratory complexes becomes disrupted, membrane potential drops, and the synthesis of ATP decreases (18). Lysophosphatidylcholines (lysoPCs) are the essential precursors in cardiolipin synthesis and are a biologically active major class of glycerophospholipids in human plasma that serve as ligands for specific G protein-coupled signaling receptors. Recent observational studies from our group and others have shown that specific lysoPCs, such as C16 and C18, are associated with skeletal muscle mitochondrial function, muscle mass and quality, and mobility impairment (28–30). Excessive ROS also induces oxidative cell damage. The highly chemically reactive superoxide (O_2^-) oxidize macromolecules mainly with mitochondria, it is transformed by superoxide dismutase (SOD) into molecular oxygen (O_2) and hydrogen peroxide (H_2O_2). H_2O_2 has moderate chemical reactivity and can leave the mitochondria and enter the cytosol to be scavenged by other antioxidants. However,

in the presence of ferrous and/or ferric cation the Fenton reaction decomposes hydrogen peroxide to generate powerful oxidizing agents, such as hydroxyl radical (OH) that are highly damaging for molecules and cells. Hydroxyl radical produced by excessive ROS can lead to oxidative damage on beta-amyloid peptides and promote beta-amyloid aggregation (31). Excessive ROS also contributes to the amyloid NLRP3 inflammasome pathway which leads to a cascade of pro-inflammatory cytokines inducing mitochondrial fragmentation and damaging mitochondrial energy production in astrocytes (32). Excessive ROS along with impaired Ca^{2+} handling can enable the mitochondrial permeability transition pore to open, releasing cytochrome c and other pro-apoptosis proteins that may contribute to the apoptosis of muscle fibers that are often detected from older persons and other cell types. In addition, oxidized cardiolipin favors the release of cytochrome c and other apoptotic factors in the cytosol, leading to cell death and tissue damage. Excessive ROS contributes to mtDNA mutations and impaired mitochondrial homeostasis (33). The direct oxidation byproducts of cardiolipin under excessive ROS may also lead to mtDNA somatic mutations.

Pro-inflammatory responses: Mitochondria have been recently considered ad the hub for most inflammatory responses (34). Mitochondrial dysfunction can cause inflammation via cGAS-STING signal activation. Mitochondrial transcription factor A (TFAM) stabilizes mtDNA and protects against the cGAS activation and subsequent mitochondrial stress. In dysfunctional mitochondria, activation of the cGAS pathway may trigger the production of pro-inflammatory cytokines and type I interferons (Interferon α and Interferon β). Nuclear factor-kB (NF-kB), a group of transcription factors, is shown to induce pro-inflammatory genes expression, increase inflammatory cytokines, chemokines, and adhesion molecules, and also affect cell proliferation, apoptosis, morphogenesis, and differentiation (35). Pro-inflammatory cytokines, such as TNF-α and IL-6, are shown to be associated with both mobility and cognition. Note that high levels of TNF-α also induce a cGAS-STING interferon response and affect mitochondrial function by reducing mitophagy and releasing oxidized mtDNA. Mitochondrial dysfunction can also trigger pro-inflammatory responses by activating the NLRP3 inflammasome pathway. NLRP3 is one of the four key inflammasomes (i.e. NLRP1, NLRP3, NLRC4, and AIM2). Data have suggested that assembly and activation of the NLRP3 inflammasome impair mitophagy which leads to excessive ROS and oxidation of mtDNA (36). The downstream inflammatory markers IL-1β and IL-18 are shown to induce cell death. Recent data also suggests that defective mitochondrial recycling or turnover associated with older age can induce chronic inflammation (22).

Pathways linking mitochondrial dysfunction to mobility decline—The maintenance of mobility requires the harmonic integration of multiple systems and functions including the brain, peripheral nerves, muscles, joints, and energetic metabolism (5, 37). With aging, the primary drivers of mobility decline are thought to be the musculoskeletal system and the CNS (3). Both systems are among the most energy-demanding and therefore require mitochondrial integrity to be fully functional for adequate ATP production. Therefore, we hypothesize that age-related mitochondria dysfunction, particularly within the musculoskeletal system and CNS, is a primary cause of mobility loss in older persons.

Mitochondria - musculoskeletal system – mobility pathway—The contraction and relaxation of skeletal muscles are dependent on mitochondrial respiration and ATP production to meet the energy demands of muscle cells. ATP consumption increases up to 100 folds during contraction compared to rest, and the amount of ATP available for contraction would only last a few seconds without mitochondrial activity. Using data from the Baltimore Longitudinal Study of Aging, we demonstrate that lower mitochondrial function in skeletal muscle is associated with poorer mobility and subsequent mobility decline and these associations are in part explained or mediated by compromised muscle function (9, 10). The relationship between mitochondrial function and mobility may not only be due to a lack of energy during walking but also the effect of chronic impaired mitochondrial function on muscle health. Here, we discuss how the consequences of mitochondrial dysfunction may affect the musculoskeletal system which further contributes to future mobility loss. Mitochondrial dysfunction leads to excessive ROS which can cause oxidative damage to muscle cells and subsequent muscle atrophy (38). Excessive ROS-induced cardiolipin oxidation affects signaling pathways related to muscle atrophy, such as the AMP-activated protein kinase activation and FOXO3 signaling (39), and also impairs mitophagy through the protein kinase C pathway (40). Excessive ROS contributes to increased mtDNA mutations and high levels of mtDNA mutations in skeletal muscle are associated with sarcopenia in older adults (41).

Mitochondrial dysfunction leads to pro-inflammatory responses which further affect muscle function. Circulating inflammatory markers, such as C-reactive protein, IL-6, and TNFα, have been associated with sarcopenia and lower skeletal muscle strength and muscle mass (42). TNFα-mediated signaling has been shown to impair oxidative phosphorylation and impede muscle protein synthesis which is essential for the synthesis of new muscle fibers (43). Studies have shown that the activation of NF-kB regulates the release of cytokines and chemokines which are important proteins and peptides from skeletal muscle, mediated by mitochondria-generated free radicals. Thus, NF-kB is thought to play a critical role in mediating muscle atrophy (44).

Mitochondria – CNS – mobility pathway: Neurons contain mitochondria and require consistently active and fine-tuned energy metabolism to carry out complex functions and maintain cellular activity to meet the extensive energy demands. Neuronal function and viability depend on OXPHOS and energy homeostasis, and mobility depends on neuronal and brain function (33). Accordingly, age- and disease-related changes to brain structure have been consistently associated with mobility decline. For example, brain atrophy, white matter hyperintensities, microscopic white matter tract abnormalities, and molecular pathology (e.g., β-amyloid) have each been associated with mobility decline (5, 45). Recent data have shown that brain metabolism measured by MRS is also associated with mobility in individuals with multiple sclerosis (46). Whether brain metabolism is associated with mobility in older adults without overt neurological diseases is unknown. Moreover, increasing age has been linked with mitochondria decline within the CNS in nonhuman primates, and the degree to which mitochondrial function is compromised has been associated with the extent of motor dysfunction (47–49). Emerging research suggests that age- and disease-related changes to the CNS may affect mobility decline

via a breakdown in brain-muscle crosstalk. It can be hypothesized that a signaling or communication in aging biology contributes to the decline of OXPHOS in both skeletal muscle and the brain. Brain metabolism has been associated with mobility in patients with neurological conditions but data in older adults without overt neurological disease are limited (46, 50, 51). A breakdown of mitochondrial function within the CNS can lead to declines in mobility via disruptions in cortical-spinal signaling or extrapyramidal basal ganglia circuits, and damage to neuronal white matter (myelin) structure, each of which can contribute to reduced efficiency of neural processing. We hypothesize that mitochondrial dysfunction in the CNS may represent a key determinant of mobility decline either directly or indirectly through the musculoskeletal system. Several lines of research have shown the consequence of excessive ROS and pro-inflammatory responses are associated with CNS deficits. Cardiolipin oxidation is associated with neuronal dysfunction, impaired neurogenesis, age-related cognitive decline, and neurodegeneration (52). In mouse models of AD, cardiolipin deficiency may contribute to the aberrant neuroinflammatory response (52). Oxidative cell damage induced by excessive ROS contributes to progressive neuronal loss which is associated with neurodegenerative diseases and mobility decline. It is hypothesized that mtDNA mutations can cause the accumulation of beta-amyloid which is associated with both cognition and mobility in older adults. Mitochondrial dysfunction-triggered pro-inflammatory responses may cause accelerated cognitive decline and neurogenerative diseases. Although evidence from animals suggests that pro-inflammatory pathways, such as cGAS-STING, NF-kB, and NLRP3, play important roles in neurodegeneration mediated by inflammation, data on humans during normal aging are sparse.

MITOCHONDRIAL DYSFUNCTION AS A THERAPEUTIC TARGET IN AGING

Preventing the decline of mitochondrial function with aging may slow the loss of skeletal muscle function and deterioration in brain health in a manner that preserves mobility decline. What can be done to preserve mitochondrial function in aging? Here, we discuss some existing evidence on the effects of exercise and supplements on mitochondrial function in humans and make hypotheses on potential underlying mechanisms.

Exercise interventions:

Exercise has been shown to improve mitochondria content and function in humans and have positive effects on the musculoskeletal system and CNS (53). Physical exercise may affect mitochondrial content and function through increased chronic contractile activity, reduction of mitophagy flux, and decreased ROS production. Studies including older individuals have shown that exercise training increases cardiolipin content, mitochondrial volume density, mtDNA copy number, ATPmax, and mitochondrial complex activity of the ETC (Table; see the Supplemental Digital Content, which provides further studies referenced in the Table). Some studies (but not all) have also shown that key regulators for the mitochondrial biogenesis, such as PGC-1α, SIRT1, TFAM, dynamin-related protein 1 (Drp1), Mfn1, Mfn2, and Nuclear Respiratory Factor 1 (NRF1) are upregulated by exercise training. The upregulation of the PGC-1α and TFAM may contribute to the increase in mitochondrial volume. Exercise-induced changes in PGC-1α, the master regulator for the mitochondrial biogenesis, are at the protein and gene expression levels. Exercise training

also improves skeletal muscle mitochondrial respiration and mitochondrial enzymes activity, including citrate synthase and cytochrome c oxidase (Table). Little is known about the effect of exercise training on mitochondrial content and function in human brain, although some animal studies have shown exercise increases mitochondria biogenesis in the brain (54). Potential neuroprotective effects of exercise on brain mitochondria may translate to better mobility in aging by preserving the brain-muscle crosstalk. However, this hypothesis remains to be tested.

Supplement interventions:

Several supplements are shown to improve mitochondrial function and related markers in both animal models and humans. Here, we focus on three dietary supplements that are currently under investigation in humans: urolithin-A, medium-chain triglycerides, and oleuropein (Table). Urolithin-A (UA) is a gut-microbiome-derived postbiotic metabolite of ellagitannins and polyphenolic compounds. It is found commonly in foods such as walnuts, pomegranates, and berries. UA supplementation is shown to stimulate mitophagy and improve muscle health in animal studies. Recent human studies in young and middle-aged individuals have shown that UA supplementation improves muscle function and has an overall positive effect on markers of mitochondrial health and inflammation, such as the decreased plasma levels of C-reactive protein, several acylcarnitines, ceramides, and cytokines. It is shown to be safe and well-tolerated. Medium-chain triglyceride (MCT) supplementation is shown to elevate lysoPC levels in the plasma and increases in these specific lysoPCs are associated with improved cognition. In line with these findings, we recently found that increases in these specific lysoPCs are associated with less decline in skeletal muscle mitochondrial function (30). It is possible that MTC supplement could affect mitochondrial function by making high levels of lysoPCs available for the resynthesis of oxidized cardiolipin, but this hypothesis warrants further investigation. Preliminary investigation suggests that olive-oil-derived polyphenols, such as oleuropein and hydroxytyrosol affect mitophagy in human cell culture, and it is suggested that this effect plays an important role in the beneficial effects of the Mediterranean diet. Intervention studies are needed to confirm these findings in humans. Findings on polyunsaturated fatty acids in humans are mixed. Some showed positive effects on mitochondrial biogenesis while others found a decrease in mitochondria biogenesis. Other supplements, such as quercetin and NMN, have shown positive effects on mitochondrial function in animal studies but these findings are not yet translated to humans (Table).

CONCLUSION

Mitochondrial dysfunction, a hallmark of aging, may be a root cause of progressive loss of skeletal muscle function and CNS dysfunction, both of which contribute to future mobility decline and ultimately physical disability. Understanding the pathways to mobility decline is a key route in designing prevention strategies. Emerging human trials have shown the positive effects of exercise and some supplements on mitochondrial function. Future studies are warranted to test this mechanistic hypothesis of mobility decline and investigate pharmacological and non-pharmacological approaches targeting mitochondria dysfunction in aging.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points

- As aerobic metabolism in mitochondria generates the bulk of energy used by cells to maintain vitality, mitochondrial dysfunction leads to reduced energy which curtails resilience capacity and allows damage accumulation.
- As the musculoskeletal and central nervous systems have high energy demands, mitochondrial dysfunction may cause subtle deterioration of muscle and brain health, both of which contribute to subsequent mobility decline and disability.
- Our recent findings have shown that among well-functioning older adults, lower skeletal muscle mitochondrial function is associated with poorer mobility and greater mobility decline over time, and these associations are explained in part by muscle function, suggesting temporality and causality. Circulating lipids important for mitochondrial integrity, such as lysophosphatidylcholines, have been associated with both mobility and cognition.
- Future research should examine whether preserving or improving mitochondrial function slows aging effects on muscle and the brain and thereby age-related mobility decline and expand health span in humans.

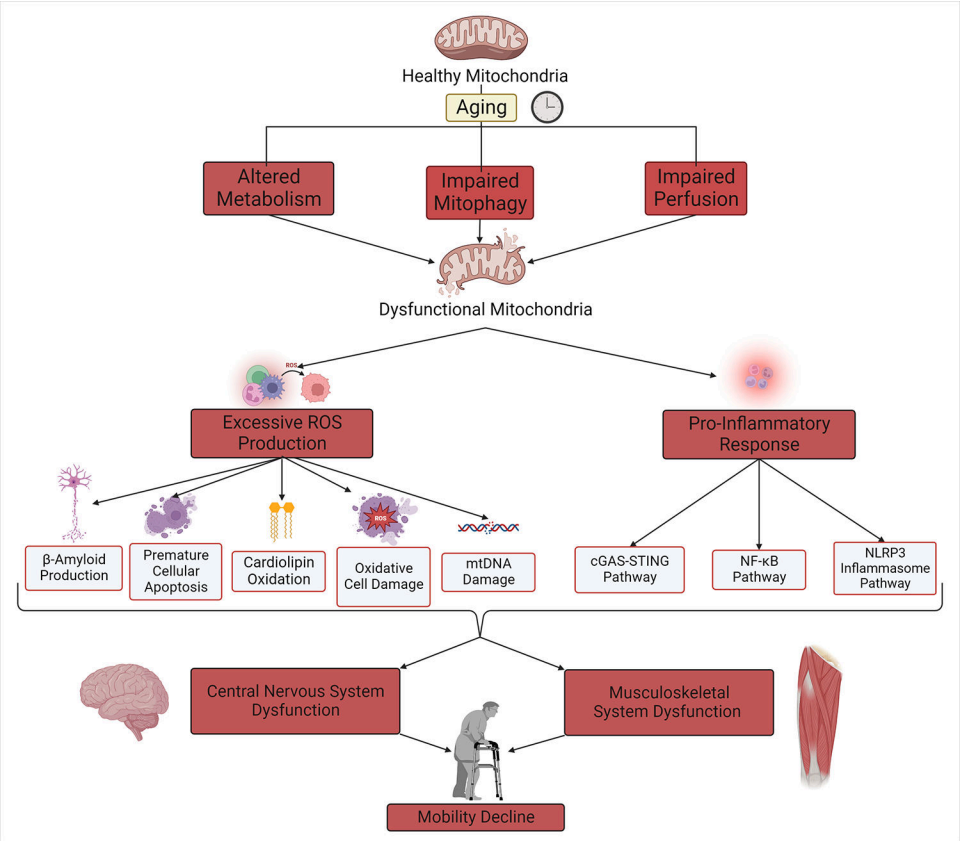
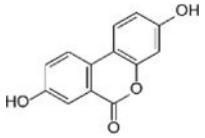
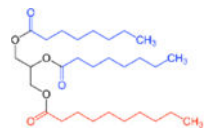


Figure. Conceptual framework. We hypothesize that mitochondrial dysfunction in aging leads to future mobility decline through several intermediate pathways that affect both the musculoskeletal system and the central nervous system.

In dysfunctional mitochondria, decreased proton membrane potential causes the accumulation of PTEN-induced kinase 1 (PINK1) and Parkin RBR E3 ubiquitin-protein ligase (PARKIN) on the outer membrane of dysfunctional and drives their removal via selective mitophagy. The fine-tuning of mitochondria quality control is essential for the preservation of energy metabolism. Dysfunctional mitochondria produce excessive radical oxygen species (ROS), oxidized cardiolipin and oxidized mitochondrial DNA that activate several pro-inflammatory mechanisms, including the cGAS (type I Interferon mediators), NF-kB (TNF-α, IL-6) and NLRP3 inflammasome (IL-1β, IL-18). Oxidated cardiolipin interferes with the respiratory chain function and it is thought to be recycled and resynthesized from fatty acids donated by specific phospholipids, especially lysophosphatidylcholines. Created with BioRender.com.

Table.

The effects of exercise and supplements on mitohondrial morphology and function in huamns.

	Exercise	Urolithin-A	Medium Chain Triglycerides
			* 
Cardiolipin or its precursors (lysoPCs)	Increase in skeletal muscle cardiolipin content in inter-myofibrillar and sub-sarcolemmal mitochondrial fractions (Menshikova et al., 2006)	-	Increases in lysoPC (16:0), lysoPC (P-18:1(9Z)), lysoPC (20:2(11Z,14Z)), and lysoPC (22:5(4Z,7Z,10Z,13Z,16Z)) (Xu et al., 2020)
Mitochondrial volume density	Increase in mitochondrial volume density (e.g. COX activity) (Broskey et al., 2014; Greggio et al., 2017; Jacobs et al., 2013; Jubrias et al., 2001) Increase in mtDNA copy number (Menshikova et al., 2006)	-	-
mtDNA	Decrease in mtDNA mutations (Jeppesen et al., 2006)	-	-
Mitochondrial biogenesis or mitophagy	Increases in the gene expression of PGC-1α and TFAM, but not NRF1 or NRF2 (Broskey et al., 2014). Increases in the expression of mitochondrial gene and proteins in the skeletal muscle (Jeppesen et al., 2012). Increase in the protein levels of PGC1-α, dynamin-related protein (Drp) 1, and mitofusin (Mfn) 1 in PBMCs (Estebanez et al., 2019). Increases in the protein levels of Mfn1 and Mfn2 in skeletal muscle (Mesquita et al., 2020). Increase in the protein levels of PGC1-α, SIRT1, SIRT3, and SIRT6 in the serum (Hooshmand-Moghadam et al., 2020). Increase in skeletal muscle content of SIRT3 (Johnson et al., 2015). Increase in the mRNA level of PGC1-α (Irving et al., 2015; Norheim et al., 2014). Increase in the mRNA levels of mitochondrial genes (incluiding COX4 and ND4) and mitochondrial biogenesis regulators (including PGC-1α, NRF-1, and TFAM) (Short et al., 2003)	Stimulate mitophagy and mitochondrial biogenesis in the human skeletal muscle (Andreux et al., 2019) Stimulate mitophagy in primary chondrocytes (D'Amico et al., 2022) Increase in mitochondrial efficiency (indicated by reduced plasma acylcarnitines and C-reactive proteins (Singh et al., 2022). Activated PINK1/Parkin-mediated mitophagy in the human skeletal musle (Singh et al., 2022).	-
Mitochondrial respiration	Increase in muscle mitochondrial enzymes activity (including citrate synthase and cytochrome c oxidase) (Short et al., 2003) Increase in supercomplex content (Greggio et al., 2017). Increases in the protein levels of complexes III, VI, and V (Broskey et al., 2014). Increases in all respiratory states except for respiration specific to complex I (Jacobs et al., 2013). Increase in ATPmax (Broskey et al., 2014). Increase in NADH oxidase activity (Menshikova et al., 2006). Increases in the protein levels of complexes I-V, Drp1, Mfn1 and Mfn2 in skeletal muscle (Mesquita et al., 2020). Increase in OXPHOS (Irving et al., 2015).	Stimulate mitochondrial respiration in primary chondrocytes (D'Amico et al., 2022)	-

Note: Data are from studies including middle-aged and older adults. Findings on polyunsaturated fatty acids in humans are mixed (Isesele & Mazurak, 2021). Other supplements, such as quercetin and NMN, have shown positive effects on mitochondrial function in animal studies but these findings are not yet translated to humans (Davis et al., 2009; Nadeeshani et al., 2022). Please see supplementary digital content for specific references cited in this table.

* One example of medium chain triglycerides with three medium chain fatty acids.