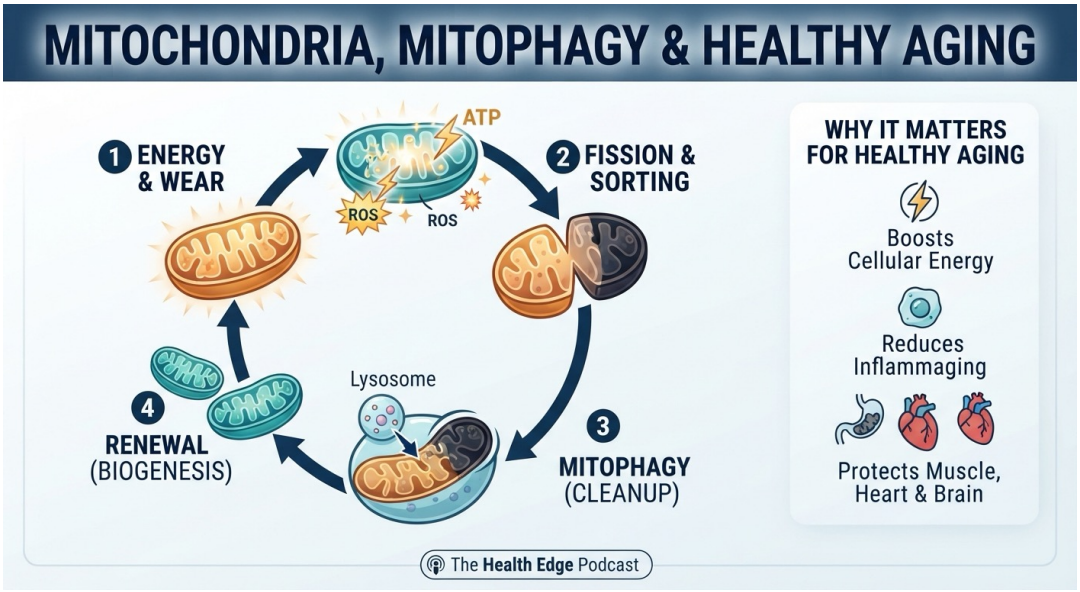


1

An average adult human body is estimated to contain roughly 30 to 50 trillion mitochondria, though plausible scientific estimates range widely from 10 trillion to 100 trillion.

- Cell Count: The human body consists of an estimated 30 to 37 trillion cells.
- Cell Type and Energy Needs: Different cell types have drastically different requirements:
  - Red blood cells: 0 mitochondria.
  - Skin or immune cells (lymphocytes): Just a few (about 1 to 3).
  - Liver cells: About 1,000 to 2,000 per cell.
  - Heart muscle cells (cardiomyocytes): Around 5,000 or more per cell due to constant high-energy demands.
  - Egg cells (oocytes): Up to 100,000 mitochondria

2

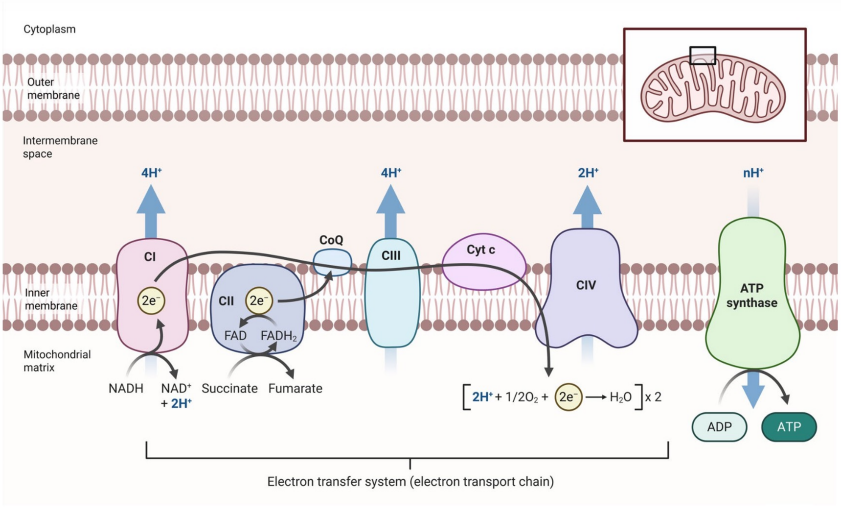


Fig. 1 An overview of mitochondria and their connection to aging. The electron transport chain (ETC) complexes, cristae, and mitochondrial DNA (mtDNA) are at the center of this mitochondrial diagram. The "spokes" encircling the perimeter represent significant aging-related events, such as changes in dynamics (fission/fusion), a decrease in mitophagy, a depletion of NAD+, and connections to cellular senescence and inflammaging

3

Marei *Journal of Translational Medicine* (2026) 24:716
https://doi.org/10.1186/s12967-026-08047-8

Journal of Translational Medicine

REVIEW Open Access

Mitochondria at the heart of aging: structure, function, and failure

Hany E. Marei[1*]

Abstract

Background Mitochondria are critical for cellular metabolism, signaling, and health throughout life. Evidence increasingly links age-related mitochondrial dysfunction to a progressive decline in tissue homeostasis. Mitochondrial dysfunction is caused by various mitochondrial DNA (mtDNA) structural and genetic alterations, impaired oxidative phosphorylation, and increased reactive oxygen species (ROS) production. Advances in high-resolution sequencing have revealed vulnerabilities and mutation signatures in tissues previously unknown, reinforcing the precarious balance between mitochondrial damage and injury compensatory response.

Main body Age-related changes in mitochondrial dynamics, including fission, fusion, and cristae remodeling, are closely related to declining bioenergetic efficiency and cell survival. Disruption of crucial mediators (Drp1, MFN1/2, Screenshot cristae degeneration, mimicking pathogenic changes seen in human mitochondrial disorders.

4

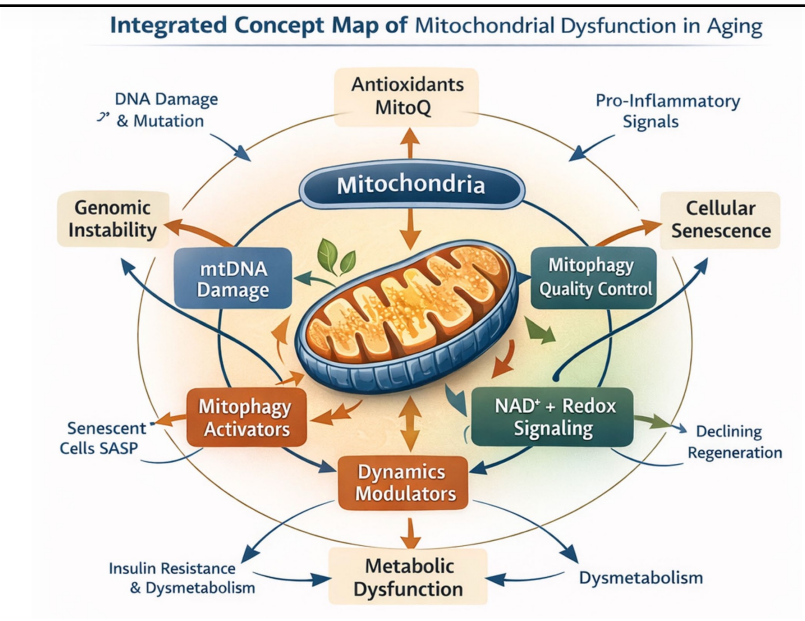
Key Findings on Mitochondria, Health, and Aging

- Energy Production Decline: Mitochondria generate roughly 90% of cellular energy in the form of ATP (adenosine triphosphate). As people age, mitochondrial efficiency and number naturally decline (for instance, skeletal muscle mitochondrial function drops by an estimated 25% to 30% between ages 30 and 70), leading to reduced energy output and lower physical stamina.
- Accumulated DNA Damage: Unlike nuclear DNA, mitochondrial DNA (mtDNA) sits close to the electron transport chain where reactive oxygen species (ROS) are produced. Over time, oxidative damage leads to mtDNA mutations, impairing energy production and creating a cycle of escalating cellular stress.
- Systemic Inflammation and Senescence: Damaged or leaking mitochondria release molecular patterns that trigger inflammatory pathways (inflammasomes), promoting chronic, low-grade systemic inflammation (inflammaging) and driving cells into senescence .

5

- Impaired Quality Control (Mitophagy): Healthy cells rely on mitophagy—a specialized recycling process that clears out broken or inefficient mitochondria. When mitophagy slows down with age, damaged organelles accumulate, worsening tissue decay in organs with high energy demands like the heart, brain, and muscles.
- Link to Age-Related Diseases: Mitochondrial impairment is heavily implicated in the pathogenesis of type 2 diabetes, cardiovascular disease, neurodegenerative disorders (such as Alzheimer's and Parkinson's), and sarcopenia (age-related muscle loss).
- Therapeutic and Lifestyle Avenues: Research indicates that mitochondrial decline is not strictly irreversible. Interventions such as regular exercise, caloric/dietary management, and experimental strategies aimed at boosting NAD+ levels (via precursors like nicotinamide riboside or niacin) or improving mitochondrial dynamics (fission and fusion) show promise in preserving cellular capacity and healthspan.

6



7

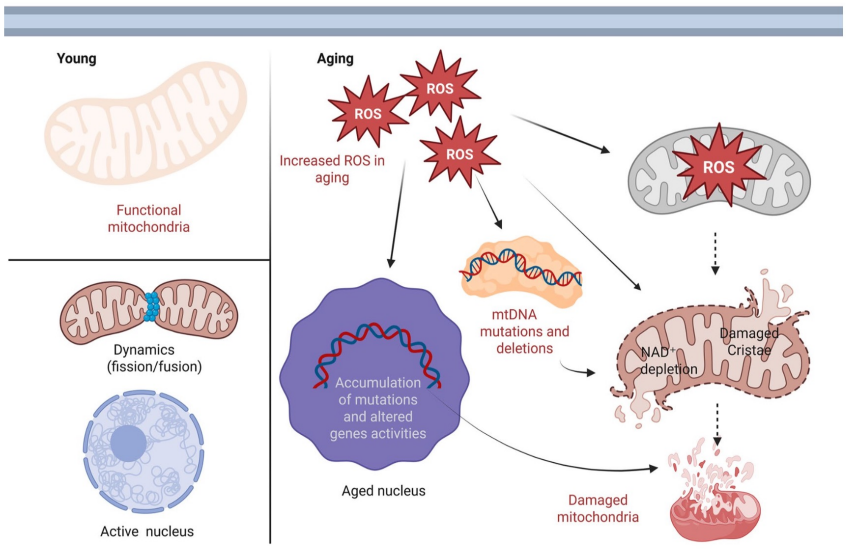


Fig. 3 Retaining the integrity of mitochondrial DNA with age. Comparing mitochondria from young and aged cells side by side. In contrast to aging mitochondria, which display mtDNA mutations or deletions, electron transport chain (ETC) malfunction, and elevated reactive oxygen species (ROS) levels, young mitochondria have intact mtDNA, stable oxidative phosphorylation (OXPHOS), and low ROS levels. Only by using deep sequencing can hidden mtDNA mutations with poor heteroplasmy be revealed, as seen in the inset

8

REVIEW ARTICLE OPEN

Mitochondrial quality control in health and disease: mechanisms and therapeutic targets

Agustina Creus[1,2], Shrestha Mohapatra[1,2], Leonardo Ortega[1,2] and David Sebastián[1,2,3]✉

Mitochondria are essential for cellular homeostasis, integrating various signals to control key cellular functions such as metabolism, apoptosis, inflammation, cell proliferation and redox balance. Given their multifaceted functions, it is not surprising that mitochondrial dysfunction has been implicated as a key contributor to the pathogenesis of numerous human diseases. Consequently, preserving mitochondrial integrity and functionality is vital for overall organismal health. Mitochondrial health is safeguarded by a sophisticated and tightly regulated network of quality control systems. These include mitochondrial proteostasis, which ensures proper protein folding and degradation; mitochondrial biogenesis, which governs the synthesis of new mitochondria; mitochondrial dynamics, encompassing fusion and fission processes; and mitophagy, the selective autophagic removal of damaged mitochondria. Additionally, these core systems are intricately connected to other crucial mitochondrial processes, such as the maintenance of mitochondrial DNA integrity, the regulation of cristae architecture, and the control of mitochondrial permeability transition, all of which are indispensable for optimal mitochondrial performance. Preclinical and clinical studies consistently demonstrate a strong link between impairments in these quality control mechanisms and both aging and the development of a wide spectrum of diseases. These include cancer, metabolic disorders, cardiovascular conditions, neurodegenerative diseases and autoimmune pathologies. In this review, we explore the different facets of mitochondrial quality control and discuss their implications in disease progression and aging. Furthermore, we highlight recent advances in interventions and therapies aimed at modulating mitochondrial quality control, providing an overview of their potential to mitigate disease burden and promote healthy aging.

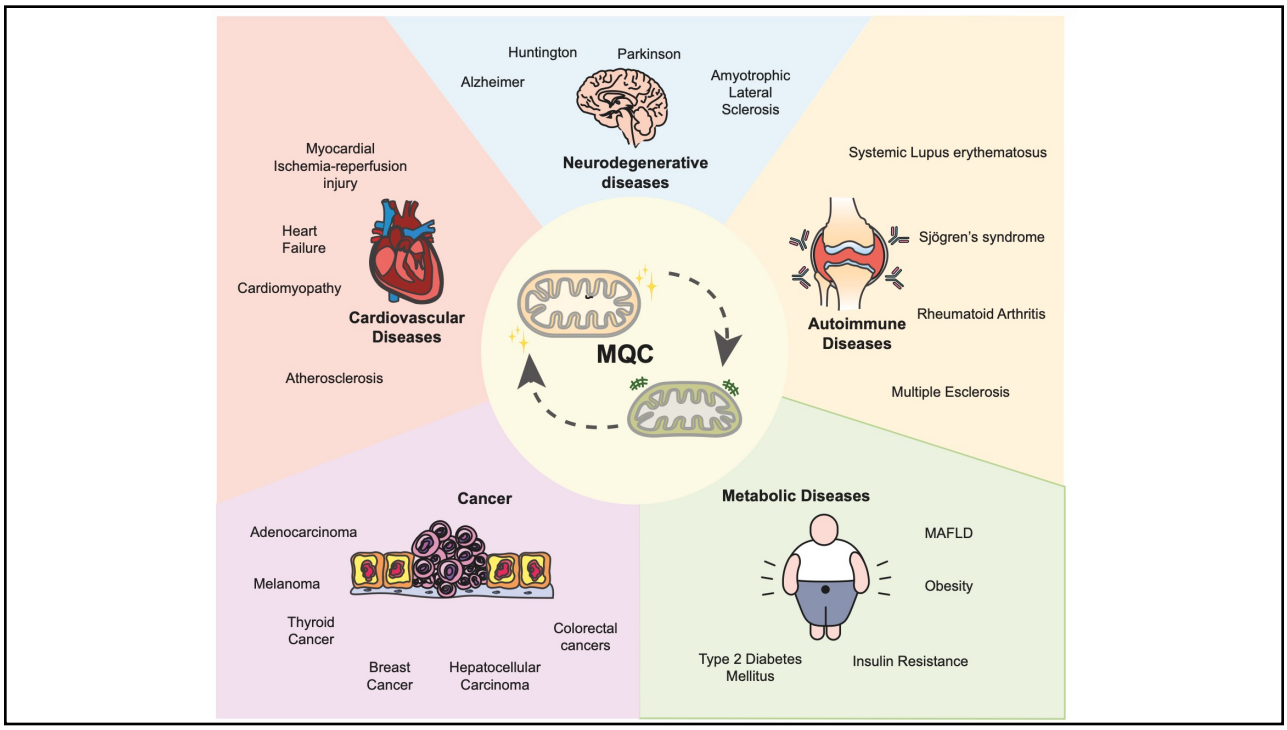
Signal Transduction and Targeted Therapy (2026)11:295 ; https://doi.org/10.1038/s41392-026-02813-2

9

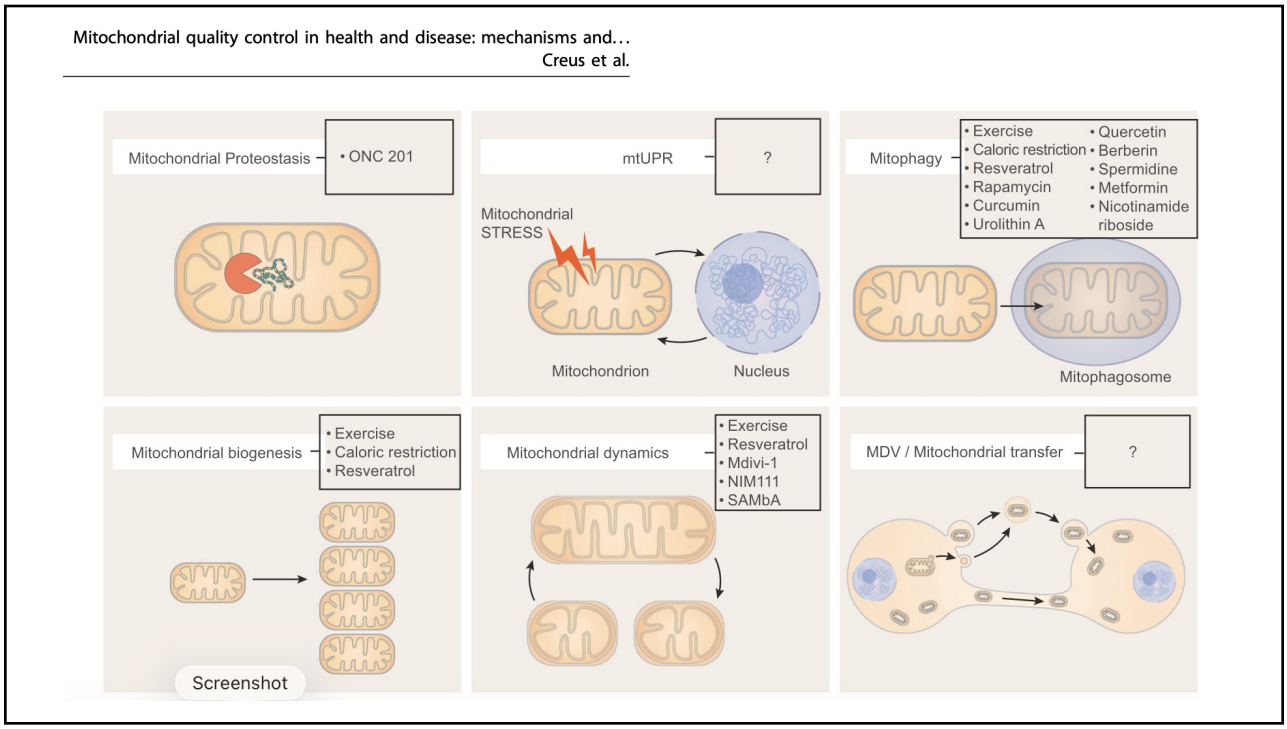
Mitophagy

- Mitophagy is the selective "cellular cleanup" process that tags, breaks down, and recycles damaged or energy-depleted mitochondria (the power plants of your cells).
- **Energy Production & Function**: It clears out faulty mitochondria that fail to produce adequate ATP (cellular energy) and restore a healthy mitochondrial pool.
- **Preventing Harmful Byproducts**: Damaged mitochondria leak dangerous reactive oxygen species (ROS / free radicals) and trigger inflammation. [1, 2]
- **Protecting High-Energy Tissues**: Organs with massive energy demands—such as the heart and skeletal muscles—rely heavily on mitophagy to maintain contractility and prevent age-related decline or heart failure.
- **Combating Aging and Disease**: Impaired mitophagy causes a buildup of cellular waste, which is linked to neurodegenerative conditions (like Alzheimer's and Parkinson's), metabolic disorders, and muscle loss (sarcopenia). [

10


Huntington
Parkinson
Alzheimer
Amyotrophic Lateral Sclerosis
Neurodegenerative diseases
Myocardial Ischemia-reperfusion injury
Heart Failure
Cardiomyopathy
Cardiovascular Diseases
Atherosclerosis
MQC
Systemic Lupus erythematosus
Sjögren's syndrome
Rheumatoid Arthritis
Autoimmune Diseases
Multiple Esclerosis
Cancer
Adenocarcinoma
Melanoma
Thyroid Cancer
Colorectal cancers
Breast Cancer
Hepatocellular Carcinoma
Metabolic Diseases
MAFLD
Obesity
Type 2 Diabetes Mellitus
Insulin Resistance

11


Mitochondrial quality control in health and disease: mechanisms and…
Creus et al.
Mitochondrial Proteostasis
• ONC 201
mtUPR
?
Mitochondrial STRESS
Mitochondrion
Nucleus
Mitophagy
• Exercise
• Caloric restriction
• Resveratrol
• Rapamycin
• Curcumin
• Urolithin A
• Quercetin
• Berberin
• Spermidine
• Metformin
• Nicotinamide riboside
Mitophagosome
Mitochondrial biogenesis
• Exercise
• Caloric restriction
• Resveratrol
Mitochondrial dynamics
• Exercise
• Resveratrol
• Mdivi-1
• NIM111
• SAMbA
MDV / Mitochondrial transfer
?
Screenshot

12

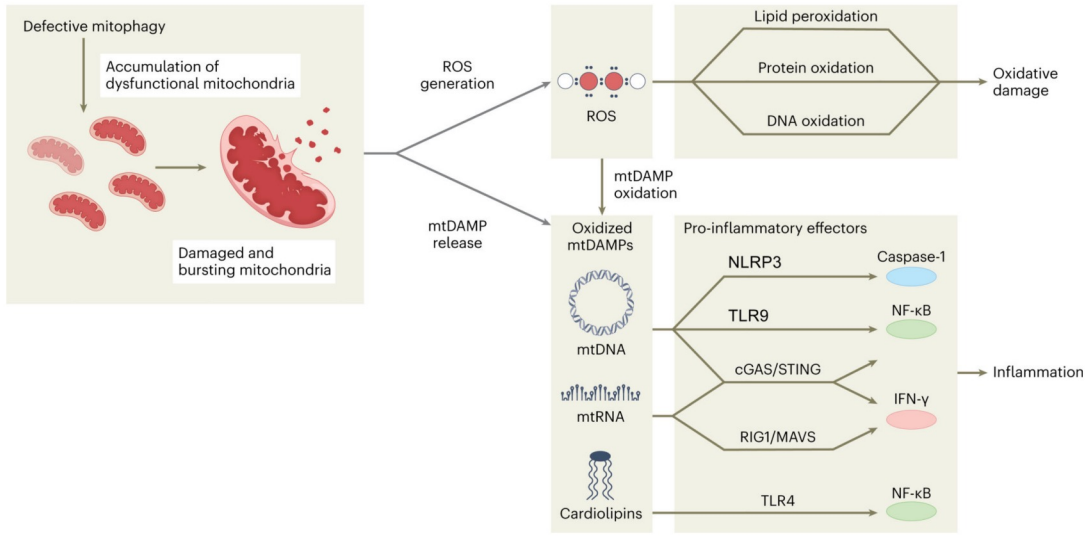


Fig. 3 |. Mitophagy dysfunction links to sterile inflammatory responses.

13

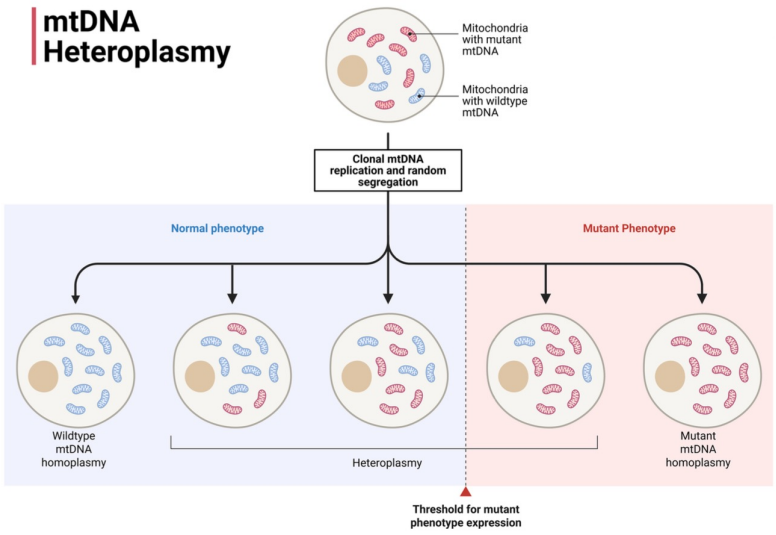


Fig. 7 Multiple copy-number anomalies in mitochondrial DNA. The presence of both wild-type and mutant mitochondrial DNA molecules within a single cell or mitochondrion results in heteroplasmy. Shows how heteroplasmy levels change over time and how they affect OXPHOS capacity, with a focus on threshold effects in disease and aging

14

CDD press

www.nature.com/cddiscovery

REVIEW ARTICLE OPEN

Check for updates

Targeting mitochondrial autophagy for anti-aging

Wenjun Shan[1,4], Yuling Liu[1,4], Ruying Tang[1], Hui Li[1,2✉], Hongjun Yang[3✉] and Longfei Lin[1✉]

© The Author(s) 2025, modified publication 2026

Mitochondrial dysfunction is one of the core drivers of aging. It is manifested by reactive oxygen species (ROS) accumulation, mitochondrial DNA (mtDNA) mutations, imbalanced energy metabolism, and abnormal biosynthesis. Mitochondrial autophagy maintains cellular homeostasis by selectively removing damaged mitochondria through mechanisms including the ubiquitin-dependent pathway (PINK1/Parkin pathway) and the ubiquitin-independent pathway (mediated by receptors such as BNIP3/FUNDC1). During aging, the decrease in mitochondrial autophagy efficiency leads to the accumulation of damaged mitochondria, forming a cycle of mitochondrial damage-ROS-aging damage and aggravating aging-related diseases such as neurodegenerative diseases and cardiovascular pathologies. The targeted regulation of mitochondrial autophagy (drug modulation and exercise intervention) can restore mitochondrial function and slow aging. However, autophagy has a double-edged sword effect; moderate activation is anti-aging, but excessive activation or dysfunction accelerates the pathological process. Therefore, targeting mitochondrial autophagy may be an effective anti-aging technique; however, future focus should be on the tissue-specific regulatory threshold and the dynamic balance mechanism to achieve precise intervention.

Cell Death Discovery (2026)12:78 ; https://doi.org/10.1038/s41420-025-02913-y

15

Lifestyle habits support mitophagy—the cell's specialized quality-control cleanup process that removes damaged or worn-out mitochondria—by triggering controlled cellular stress, energy depletion, and specific nutrient signaling.

1. Regular Exercise

Activates Signaling Pathways: Physical activity creates a temporary increase in energy demand and mild oxidative stress. This upregulates pathways like AMPK and PGC-1α, which signal the cell to clear out defective mitochondria via mitophagy and build fresh ones through mitochondrial biogenesis. [1]
Types of Exercise: Both aerobic training (running, cycling) and high-intensity interval training (HIIT) effectively stimulate mitochondrial turnover in skeletal muscle and metabolic tissues.

2. Fasting and Time-Restricted Eating

Shifts Cellular Mode: Intermittent fasting or overnight caloric restriction (such as a 12- to 18-hour fast) lowers nutrient availability and insulin signaling.
Triggers Cleanup: Deprived of an incoming energy surplus, cells switch from storage and growth mode to maintenance and repair, prompting the breakdown and recycling of old mitochondrial components.

16

3. Nutrition and Specific Compounds

Polyphenols and Antioxidants: Eating foods rich in polyphenols—such as pomegranates, walnuts, and berries—provides natural molecules that assist cellular defense and repair systems.
Urolithin A: A postbiotic metabolite produced by the gut microbiome from ellagitannins (found in pomegranates and walnuts) is clinically shown to directly activate and enhance mitophagy.

4. Hormetic Stress (Cold and Heat Exposure)

Adaptive Resilience: Brief physiological stressors—like cold plunges, cold showers, or sauna sessions—apply mild thermal or metabolic strain to tissues.
Stimulates Renewal: This "good stress" forces cells to adapt, increasing mitochondrial density and clearing out sub-par powerhouses.

5. Quality Sleep and Stress Management

Cellular Maintenance: Deep, consistent sleep (7 to 9 hours nightly) provides the baseline physiological window required for cellular repair, metabolic clearing, and mitochondrial preservation.
Mitigates Cortisol Damage: Chronic high stress and elevated cortisol levels accelerate mitochondrial damage, making stress-reduction habits essential to protect existing mitochondrial networks

17

Clinical research confirms that NAD+ boosters effectively raise NAD+ levels in human blood, but evidence that this translates into noticeable health benefits, disease reversal, or anti-aging effects in humans remains limited and inconsistent.

- The data shows a distinct gap between the remarkable results seen in animal studies and the modest outcomes observed in human clinical trials.
- While mouse models demonstrate reversed cardiovascular aging and dramatic stamina gains, human trials tell a more subdued story.
- They do successfully raise NAD+ levels: Oral precursors like Nicotinamide Riboside (NR) and Nicotinamide Mononucleotide (NMN) are reliably absorbed by the human body and significantly increase the concentration of NAD+ in the bloodstream.
- Isolated metabolic benefits: A prominent trial published in Science found that oral NMN improved muscle insulin sensitivity in prediabetic, overweight women. Other smaller studies have occasionally noted minor improvements in walking speed or grip strength in older adults.
- Cardiovascular signals: Some early clinical trials show that NAD+ precursors may help reduce arterial stiffness and lower systolic blood pressure in adults with existing hypertension.

The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences, 2023, 78(12), 2435–244

18

Clinical evidence in humans demonstrates that urolithin A (UA) promotes mitophagy and induces a molecular and physiological signature of improved mitochondrial and muscle health.

• First-in-Human Safety & Biomarker Study (Andreux et al., 2019): In a Phase I clinical trial of healthy, sedentary elderly individuals, daily oral supplementation with urolithin A (at 500 mg and 1,000 mg doses for 4 weeks) was safe, well-tolerated, and bioavailable. It modulated plasma acylcarnitines and upregulated skeletal muscle mitochondrial gene expression, demonstrating a clear molecular signature of enhanced mitochondrial and cellular health.

• Older Adults & Muscle Endurance (Liu et al., 2022): A randomized clinical trial involving 66 older adults who took 1,000 mg of urolithin A daily for 4 months showed significant improvements in skeletal muscle endurance (number of muscle contractions until fatigue in hand and leg muscles) compared to the placebo group. Treatment also reduced plasma levels of acylcarnitines and ceramides—lipid biomarkers associated with improved mitochondrial efficiency.

• Middle-Aged Adults & Strength/Aerobic Performance (Singh et al., 2022): In a 4-month randomized, placebo-controlled trial of middle-aged adults, urolithin A supplementation led to significant gains in muscle strength (~12%), alongside improvements in aerobic endurance (VO_2 peak) and physical performance (6-minute walk test). Analyses confirmed increased expression of proteins linked to mitochondrial metabolism and mitophagy in skeletal muscle tissue.

• Immune & Systemic Effects: Recent randomized controlled trials have also noted that urolithin A supplementation improves immune cell composition (such as increasing naïve $CD8^+$ T cells) and reduces markers of chronic inflammation or immune exhaustion, tied downstream to better mitochondrial and cellular resilience

Nutrition Research Reviews , Volume 39 , 2026 , e8 DOI: https://doi.org/10.1017/S0954422425100292

19

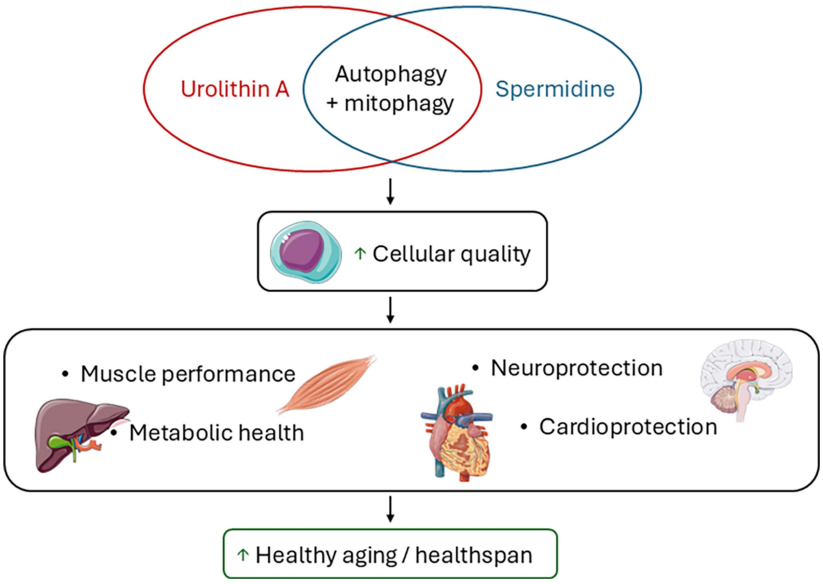
Spermadine

The link between spermidine and mitophagy is supported extensively by in vitro (cell culture) and in vivo (animal model) research. No human data.

- Cellular Mechanisms: Spermidine induces cellular recycling primarily by inhibiting acetyltransferases like EP300 and activating pathways such as AMPK and sirtuins, which lifts the "brake" on macroautophagy and helps clear out damaged mitochondria.
- Animal and Model Systems: Studies in worms, fruit flies, rodents, and human cell lines (such as fibroblasts, cardiomyocytes, and neuroblastoma/endothelial cells) show that spermidine restores mitochondrial membrane potential, improves ATP production, reduces reactive oxygen species (ROS), and upregulates mitophagy-related markers like PINK1/Parkin or BNIP3/LC3B.
- Spermidine vs. Urolithin A: Comparative reviews note that while compounds like urolithin A have direct clinical evidence demonstrating targeted mitophagy and muscle function in humans, spermidine's human data remain broader, focusing on general autophagy, cognitive support, and systemic health rather than direct clinical proof of mitochondrial turnover

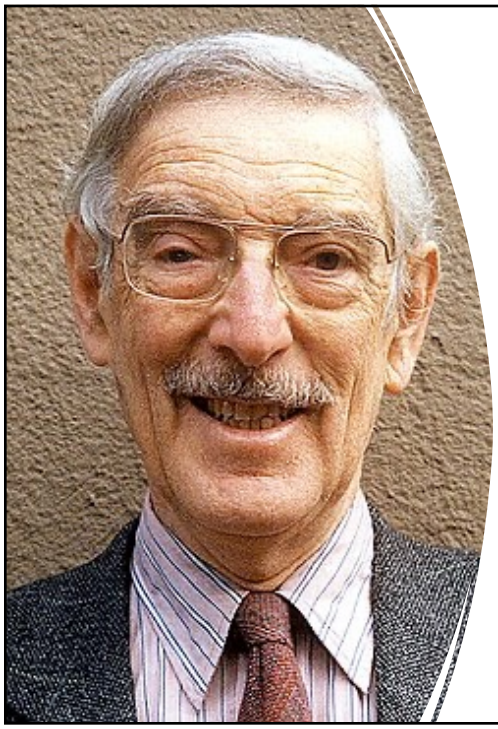
Nutrition Research Reviews , Volume 39 , 2026 , e8 DOI: https://doi.org/10.1017/S0954422425100292

20



Nutrition Research Reviews , Volume 39 , 2026 , e8 DOI: https://doi.org/10.1017/S0954422425100292

21



Bruce Ames, PhD

- Bruce Ames is a prominent American biochemist and professor emeritus of biochemistry and molecular biology at the University of California, Berkeley.
- Ames Test: He developed the Ames test, a widely used method to test whether a chemical compound can cause mutations in DNA (serving as a screen for potential carcinogens).
- Triage Theory: He proposed the Triage Theory of Aging, which suggests that the body prioritizes scarce micronutrients for short-term survival and reproduction functions at the expense of long-term maintenance and DNA repair, accelerating aging and chronic disease when intake is marginal.
- Mitochondrial Research: His laboratory investigated how mitochondrial decay and oxidative stress contribute to aging and degenerative diseases, pioneering studies on feeding aging animal models specific metabolic intermediates to restore mitochondrial function

22

Bruce Ames PhD, Triage Theory and Mitochondrial Cocktail

- A "mitochondrial cocktail" (or "Mito Cocktail") refers to a targeted combination of vitamins, coenzymes, and nutritional supplements frequently used to support energy production and cellular function in individuals with mitochondrial diseases or age-related mitochondrial decline.

Core Components Pioneered by Dr. Ames:

- Acetyl-L-carnitine
- R-alpha-lipoic acid
- Research finding: Dr. Ames's laboratory was among the first to document that combining acetyl-L-carnitine and R-alpha-lipoic acid worked synergistically to reverse age-related mitochondrial decay and improve metabolic and cognitive function in older rats

https://mcb.berkeley.edu/courses/mcb135k/ames.html
Front. Mol. Biosci. 12:1710944. doi: 10.3389/fmolb.2025.1710944

23