


Mitochondrial and metabolic dysfunction in ageing and age-related diseases

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Abstract

Organismal ageing is accompanied by progressive loss of cellular function and systemic deterioration of multiple tissues, leading to impaired function and increased vulnerability to death. Mitochondria have become recognized not merely as being energy suppliers but also as having an essential role in the development of diseases associated with ageing, such as neurodegenerative and cardiovascular diseases. A growing body of evidence suggests that ageing and age-related diseases are tightly related to an energy supply and demand imbalance, which might be alleviated by a variety of interventions, including physical activity and calorie restriction, as well as naturally occurring molecules targeting conserved longevity pathways. Here, we review key historical advances and progress from the past few years in our understanding of the role of mitochondria in ageing and age-related metabolic diseases. We also highlight emerging scientific innovations using mitochondria-targeted therapeutic approaches.

Key points

- The rate of ageing is coordinated, at least in part, by conserved genetic and biochemical pathways.
- A complex network of interactions between longevity pathways reveals an intricate regulation of mitochondrial physiology during ageing.
- Cellular metabolism interconnects the nine hallmarks of ageing, and deregulation of energy metabolism by environmental variations is an essential process leading to mitochondrial dysfunction during ageing.
- A better understanding of mitochondrial dysfunction during ageing and age-related metabolic diseases will provide fundamental knowledge to develop therapies to combat late-life morbidities.
- Human longitudinal studies will be essential to understand individuals' risk of diseases much earlier in life, and will inform health choices and medical care options.

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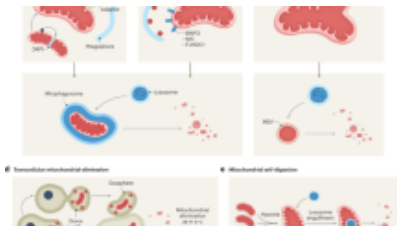
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J.A.A., G.C., A.P.R. and C.M.P. researched data for the article and wrote the manuscript. J.M.R. and D.A.S. reviewed and/or edited the manuscript. All authors made substantial

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Ethics declarations

Competing interests

D.A.S. is a founder, equity owner, advisor to, director of, board member of, consultant to, investor in and/or inventor on patents licensed to Revere Biosensors, UpRNA, GlaxoSmithKline, Wellomics, DaVinci Logic, InsideTracker (Segterra), Caudalie, Animal Biosciences, Longwood Fund, Catalio Capital Management, Frontier Acquisition Corporation, AFAR (American Federation for Aging Research), Life Extension Advocacy Foundation (LEAF), Cohbar, Galilei, EMD Millipore, Zymo Research, Immetas, Bayer Crop Science, EdenRoc Sciences (and affiliates Arc-Bio, Dovetail Genomics, Claret Bioscience, MetroBiotech, Astrea, Liberty Biosecurity and Delavie), Life Biosciences, Alterity, ATAI Life Sciences, Levels Health, Tally (aka Longevity Sciences) and Bold Capital. D.A.S. is an inventor on a patent application filed by Mayo Clinic and Harvard Medical School that has been licensed to Elysium Health. The other authors declare no competing interests.

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Glossary

Oxidative phosphorylation

(OXPHOS). A metabolic pathway in which nutrients are oxidized, releasing energy in the form of ATP resulting from electron transfer from NADH and FADH₂ to O₂.

Electron transport chain

(ETC). A series of electron transporters (complexes I–IV) embedded in the inner mitochondrial membrane that transport electrons from NADH and FADH₂ to O₂, in which O₂ is reduced to water. In parallel, a proton efflux is driven from the mitochondrial matrix towards the intermembrane space via proton pumps in complexes I, III and IV. The movement of protons back into the matrix occurs through ATP synthase (also known as complex V or FoF1 ATPase).

Mitophagy

A process that selectively degrades damaged mitochondria following damage or stress.

β-Oxidation

A metabolic process involving multiple steps of fatty acid molecule breakdown to produce energy.

Respiratory quotient

The ratio used to measure basal metabolic rate by estimating the volume of carbon dioxide released in relation to the volume of oxygen produced during respiration.

TCA cycle

A series of chemical reactions taking place in the mitochondrial matrix that uses acetyl-CoA derived from carbohydrates, fat and proteins to provide electrons to the electron transport chain.

Mitochondrial biogenesis

A process in which the mitochondrial mass of cells is increased.

Antagonistic pleiotropy

A theory that describes opposing effects, both harmful and beneficial, on an organism, in which a given gene or process controls more than one trait, which are maintained in the population due to a decline in the force of natural selection. At least one of these traits is beneficial to the organism's fitness early on in life, and at least one is detrimental to the organism's fitness later in life.

CpG islands

Regions with a high frequency of CpG sites, which correspond to a cytosine nucleotide followed by a guanine nucleotide, in the 5' to 3' direction.

D-loop region

A non-coding region of 1,124 base pairs, containing essential transcription and replication elements, that acts as a promoter for both heavy and light strands in mtDNA.

Prediabetes

A condition characterized by moderately elevated fasting or postprandial blood levels of glucose.

Haplogroup

A genetic population comprising a group of people who share a common ancestor on the patriline or the matriline.

Proton leak

The dissipation of proton motive force (Δp), where protons migrate into the mitochondrial matrix without producing ATP.

Cytochrome c

A haem protein localized in the mitochondrial intermembrane space that functions as an electron transporter between complex III and complex IV of the electron transport chain.

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