Mitochondria: Central Regulators of Cellular Health and Disease

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Abstract:

The mitochondria are integral organelles found in eukaryotic cells which are recognized mainly for the production of ATP via oxidative phosphorylation. While their prominent role pertains to energy production, they also serve to control significant cellular processes like the maintenance of calcium homeostasis, reactive oxygen species (ROS) signaling, apoptosis, and the biosynthesis of crucial metabolites. Their structure, which includes double membranes, cristae, and a matrix containing its own DNA, has been used to trace its evolutionary lineage to bacteria. The mitochondria possesses an inefficient DNA repair system which leads to its mutation rate being 10 times greater than that of nuclear DNA[54]. These defects give rise to a host of rare diseases including genetic diseases (such as MELAS and Leigh syndrome), some neurodegenerative disorders (like Parkinson's and Alzheimer's), metabolic disorders, cardiovascular diseases, malignancies, and aged deterioration. Some recent therapeutic developments, including mitochondrial replacement therapy and gene editing, hold great potential for treating disorders associated with mitochondria, but ethical and technical difficulties still persist.

Introduction:

The mitochondrial structure reflects its evolutionary origin from endosymbiotic alpha-proteobacteria, as evidenced by its double-membrane architecture and mitochondrial DNA[1].Mitochondria are double-membraned organelles present in most eukaryotic cells, primarily known for their role in ATP production through oxidativephosphorylation. However, contemporary research has unveiled their involvement in diverse cellular functions, including apoptosis, ROS generation, and calcium signaling. Given their centrality in cellular homeostasis, mitochondrial dysfunction can precipitate various pathologies.

Structure:

Mitochondria can be seen under light microscope in specially stained preparations[2] like iron haematoxylin and acid fuschin after fixing the tissue with osmium tetroxide, chromic acid, or potassium dichromate and supravital staining by Janus Green B Stain.[3] . As mentioned by different authors shape of mitochondria can be granulated, rod, oval, filamentous, cigar or sausage shaped[2],[4],[5],[6],[7] .

Structurally, mitochondria comprise an outer membrane, an intermembrane space, an inner membrane, and a matrix.

Outer membrane is 50-60A thick, smooth-contoured and trilaminar substructure[3] having mostly phospholipids, cholesterol and contains some specific membrane protein which forms 'porin' which are channels that permit substances with molecular weight less than 10,000 da to diffuse freely across membrane[6]

Inner membrane has ratio of lipid to protein as 0.27 to 1 and is virtually impermeable to polar and ionic substances[6] and forms in foldings known as cristae mitochondriales which can be complete, septate or incomplete.[8].

The mitochondrial matrix is a gel-like, protein-rich compartment surrounded by the highly impermeable membrane , which regulates the exchange of metabolites, ions and genome[9]. Matrix has enzymes for citric acid cycle, respiratory chain oxidation, coenzymes and dense granules having inorganic ions like calcium and magnesium[5],[8].

Mitochondria possess their own genome, including both RNA and DNA, which encodes some essential components required for oxidative phosphorylation; however, approximately 99% of mitochondrial proteins are encoded by nuclear genes.[[54]. Mitochondrial DNA is a double-stranded, circular molecule comprising approximately 16,500 base pairs. It encodes 13 protein subunits that combine with nuclear-encoded proteins to form four enzyme complexes, along with two ribosomal RNAs and 22 transfer RNAs essential for protein synthesis by intramitochondrial ribosomes.[54]. RNA remain in combination with protein as ribonucleoprotein (RNP) [8].

Functions:

As the basic and most important function of mitochondria is production of ATP it also has some other functions like-

1. Calcium Homeostasis

Regulating intracellular calcium levels by acting both as dynamic buffers and signaling hubs is one of the critical roles of mitochondria. They modulate cytosolic calcium concentrations to influence vital cellular processes such as signal transduction, muscle contraction, and enzyme activation. Mitochondrial calcium uniporter (MCU) primarily mediates the process of calcium uptake into mitochondrial matrix which stimulates dehydrogenases in the tricarboxylic acid (TCA) cycle, thus enhances ATP production. To maintain calcium homeostasis, mitochondria also employ efflux mechanisms that prevent calcium overload and ensure proper cellular function.[10],[11],[12]

2. Reactive Oxygen Species Signaling

Mitochondria serve as a major source of reactive oxygen species (ROS), which are produced as by-products during the activity of the electron transport chain (ETC).While excessive ROS can lead to oxidative stress and cellular damage, controlled ROS production plays a crucial role in intracellular signaling, influencing processes such as hypoxic responses, immune signaling, and cellular differentiation. Mitochondria hasantioxidant defense systems (to aid in maintaining this balance), including enzymes like superoxide dismutase and glutathione peroxidase, which help mitigate ROS levels and protect against oxidative damage.[13],[14],[15]

3. Apoptosis and Programmed Cell Death

Mitochondria play a crucial role in the intrinsic pathway of apoptosis by releasing pro-apoptotic factors like cytochrome c from the intermembrane space. This triggers caspase activation and programmed cell death in response to cellular stress.[16],[17]

4. Biosynthesis of Metabolites

Mitochondria serve as critical biosynthetic hubs, orchestrating the synthesis of essential macromolecular precursors, including amino acids, nucleotides, fatty acids, cholesterol, glucose, and heme. These biosynthetic pathways, central to cellular metabolism, are vital for processes such as gene expression, protein modification, cellular differentiation, and stress responses, and their dysregulation is often implicated in various diseases. A key component of this function is the tricarboxylic acid (TCA) cycle, housed in the mitochondrial matrix, which generates crucial intermediates for the biosynthesis of these molecules, including heme, iron-sulfur clusters, and amino acids. This integrated biosynthetic capacity underscores the mitochondrion’s pivotal role in maintaining cellular homeostasis and regulating metabolic processes.[18],[19],[20]

5. Thermoregulation and Heat Production

Mitochondria are essential for thermoregulation via non-shivering thermogenesis, particularly in brown adipose tissue (BAT), where numerous mitochondria express elevated levels of uncoupling protein 1 (UCP1).UCP1 disrupts the link between oxidative phosphorylation and ATP synthesis by permitting protons to leak across the inner mitochondrial membrane, thereby dissipating the proton gradient as heat. This mechanism is essential for maintaining body temperature in

mammals during cold exposure or hibernation and contributes to energy expenditure and metabolic regulation. Additionally, mitochondria modulate thermoregulation by regulating thermogenic gene expression through signaling pathways involving mitochondrial reactive oxygen species (ROS) and metabolites like succinate, which activate transcription factors such as PGC-1α to upregulate UCP1 and other thermogenic proteins in BAT and beige adipose tissue.[21],[22],[23]

Mitochondrial Dynamics:

Mitochondrial dynamics encompass the tightly regulated processes of fission (division), fusion (joining), and transport, all of which are crucial for optimal mitochondrial function and the maintenance of cellular homeostasis.Fission, mediated by Drp1 and Fis1, divides mitochondria to facilitate distribution, metabolic adaptability, and mitophagy, though excessive fission causes fragmentation and dysfunction. Fusion, regulated by mitofusins (Mfn1, Mfn2) and OPA1, forms interconnected mitochondrial networks, promoting content mixing, energy efficiency, and stress mitigation. Mitochondrial transport, driven by motor proteins and the Miro-Milton complex, ensures proper positioning, especially in neurons, to meet calcium buffering needs andlocal energy. Together, fission and fusion balance mitochondrial quality control, with fission enabling mitophagy to remove damaged mitochondria and fusion enhancing resilience. Dysregulated dynamics impair mitophagy and contribute to diseases like neurodegeneration and cancer.[24],[25],[26],[27],[28]

Diseases and Disorders Associated with Mitochondrial Dysfunction:

Mitochondrial dysfunction is implicated in a broad range of diseases, ranging from rare genetic conditions to widespread complex disorders. These conditions are driven by defects in oxidative phosphorylation, mtDNA mutations, dysregulated ROS, impaired mitochondrial dynamics, or disrupted mitophagy, impacting cellular homeostasis and organ function.

1. Primary Mitochondrial Disorders

Primary mitochondrial disorders arise due to mutations in either mitochondrial DNA (mtDNA) or nuclear DNA (nDNA) that encode mitochondrial proteins.

These rare genetic conditions affect energy metabolism and include:

- Leigh Syndrome: A severe neurometabolic disorder characterized by progressive neurodegeneration, developmental regression, and lactic acidosis due to defects in oxidative phosphorylation complexes.[29]
- MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like Episodes): Caused by mtDNA mutations (e.g., m.3243A>G), leading to stroke-like episodes, seizures, and muscle weakness.[30]
- MERRF (Myoclonic Epilepsy with Ragged Red Fibers): Features myoclonus, epilepsy, and ataxia due to mtDNA mutations affecting tRNA function.[31]
- LHON (Leber's Hereditary Optic Neuropathy): Causes acute or subacute vision loss due to mtDNA mutations affecting complex I of the electron transport chain.[32]
- Kearns-Sayre Syndrome (KSS): It is a multisystem disorder with progressive external ophthalmoplegia, pigmentary retinopathy, and cardiac conduction defects due to large-scale mtDNA deletions.[33]

2. Neurodegenerative Diseases

Mitochondrial dysfunction is a key contributor to neurodegenerative diseases, where impaired energy metabolism, excessive ROS, and defective mitophagy lead to neuronal loss.

- Parkinson's Disease (PD): Mitochondrial complex I deficiency, ROS overproduction, and PINK1/parkin-mediated mitophagy defects contribute to dopaminergic neuron degeneration.[34]
- Alzheimer's Disease (AD): Impaired mitochondrial bioenergetics, oxidative stress, and amyloid-beta accumulation disrupt mitochondrial dynamics, exacerbating cognitive decline.[35]

- Amyotrophic Lateral Sclerosis (ALS): Mitochondrial calcium mishandling and defective transport in motor neurons contribute to motor neuron degeneration.[36]

- Huntington's Disease (HD): Mutant huntingtin impairs mitochondrial trafficking and energy production, promoting striatal neuron vulnerability.[37]

3. Metabolic Diseases

Mitochondrial dysfunction underlies metabolic disorders by impairing ATP production, fatty acid oxidation, and ROS homeostasis, leading to systemic metabolic dysregulation.

- Type 2 Diabetes: Reduced mitochondrial oxidative capacity and increased ROS contribute to insulin resistance and beta-cell dysfunction.[38]

- Obesity: Impaired mitochondrial fatty acid oxidation and biogenesis promote adipocyte dysfunction and metabolic inflexibility.[39]

4. Cardiovascular Diseases

Mitochondrial dysfunction drives cardiovascular diseases through energy deficits, oxidative stress, and apoptosis, particularly in high-energy-demand cardiac tissue.

- Heart Failure: Impaired oxidative phosphorylation and calcium dysregulation reduce cardiac contractility and promote fibrosis.[40]

- Ischemia-Reperfusion Injury: Excessive ROS and mitochondrial permeability transition pore opening during reperfusion exacerbate myocardial damage.[41]

5. Cancer

Mitochondrial dysfunction supports cancer progression by altering metabolism (e.g., Warburg effect), increasing ROS for oncogenic signaling, and impairing apoptosis.[42],[43]

6. Muscular and Neuromuscular Disorders

Mitochondrial dysfunction in skeletal muscle and neuromuscular systems leads to reduced energy availability and muscle weakness.

- Mitochondrial Myopathies: resulting from mutations in mtDNA or nDNA, are characterized by muscle weakness, exercise intolerance, and the presence of ragged red fibers.[44]

- Duchenne Muscular Dystrophy (DMD): Secondary mitochondrial dysfunction exacerbates muscle degeneration due to impaired calcium handling and ROS accumulation.[45]

7. Aging and Age-Related Disorders

Mitochondrial dysfunction accelerates aging by accumulating mtDNA mutations, increasing ROS, and impairing mitophagy, contributing to age-related decline in tissue function.[46]

Therapeutic Interventions Targeting Mitochondria:

1. Gene Editing for Mitochondrial DNA

Gene editing technologies, including zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and CRISPR-based systems like DdCBEs, target mitochondrial DNA (mtDNA) mutations causing diseases such as MELAS, LHON, and Leigh syndrome. These methods aim to shift heteroplasmy by degrading mutant mtDNA or correcting mutations, restoring mitochondrial function. Challenges include delivering editing tools to mitochondria, managing high mtDNA copy numbers, heteroplasmy dynamics, and off-target risks. Ethical concerns involve germline modifications and long-term safety. Future efforts focus on improving delivery, developing advanced base editors, and establishing regulatory frameworks.[47],[48],[49],[50]

2. Mitochondrial Replacement Therapy (MRT)

Mitochondrial replacement therapy (MRT) prevents the transmission of mitochondrial DNA (mtDNA) diseases, such as Leigh syndrome and MELAS, by replacing a mother's defective mitochondria with healthy donor mitochondria. Techniques include pronuclear transfer (PNT),

maternal spindle transfer (MST), and polar body transfer (PBT), which transfer nuclear DNA to a donor oocyte or embryo with healthy mitochondria, This results in a child who inherits nuclear DNA from both parents and mitochondrial DNA from a donor. MRT has led to successful births, notably in 2016 (Mexico) and 2023 (UK), but faces challenges like mtDNA carryover, mitochondrial-nuclear mismatch, and long-term safety concerns. Ethical issues include germline modification, the "three-parent baby" debate, and unequal access. Future research focuses on minimizing carryover, ensuring safety, and exploring alternatives like CRISPR. MRT is regulated in few countries (e.g., UK) but banned in others (e.g., USA).[51],[52],[53]

Implications:

Mitochondria's critical roles in ATP production, calcium homeostasis, ROS signaling, apoptosis, biosynthesis, thermoregulation, and dynamics highlight their importance in cellular health. Dysfunction contributes to diseases like Leigh syndrome, MELAS, neurodegenerative disorders (e.g., Parkinson's, Alzheimer's), metabolic conditions (e.g., diabetes), cardiovascular diseases, cancer, and aging. Mitochondrial replacement therapy (MRT) and gene editing (e.g., ZFNs, TALENs, DdCBEs) offer promising treatments by preventing or correcting mtDNA mutations, but face challenges like mtDNA carryover, delivery issues, and ethical concerns over germline modifications. These advances necessitate further research to ensure safety, address regulatory disparities, and expand personalized therapies for mitochondrial and related diseases.

Sno.	Topic	Point	Author and Reference
1	Mitochondrial Evolution	Mitochondria descent from endosymbiotic alpha-proteobacteria	Gray MW, Burger G, Lang BF ; [1]
2	Calcium Signaling	Mitochondria act as a calcium signaling hub via MCU complex	Brand, M. D., Orr, A. L., Perevoshchikova, I. V., & Quinlan, C. L.; [11]
3	Calcium Uniporter (MCU) discovery	40-kDa is an inner membrane protein which is an essential uniporter for calcium uptake	Rizzuto, R., De Stefani, D., Raffaello, A., & Mammucari, C ; [12]
4	ROS Production	Mitochondria produce ROS through electron transport chain (Complex I and III) as signaling and damaging agents	Murphy M. P.; [14]
5	Apoptosis	Mitochondria play an important role in apoptosis by releasing substances like cytochrome c	Green, D. R., & Kroemer, G. ; [17]
6	Alzheimer's disease	Some of early events in Alzheimer's disease is mitochondrial dysfunction and oxidative stress	Reddy, A. P., & Reddy, P. H. (2017); [36]

7	Mitochondrial Replacement Therapy	Spindle transfer prevent transmission of mitochondrial disease which helped in achieving live birth	Hyslop, L. A., Blakeley, P., Craven, L., Richardson, J., Fogarty, N. M., Fragouli, E., Lamb, M., Wamaitha, S. E., Prathalingam, N., Zhang, Q., O'Keefe, H., Takeda, Y., Arizzi, L., Alfarawati, S., Tuppen, H. A., Irving, L., Kalleas, D., Choudhary, M., Wells, D., Murdoch, A. P., Herbert, M. (20160 ; [52]

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