Mitochondrial Dysfunction and Its Role in Disease Pathogenesis

Sharipova Shaxzoda Sherzod qizi
Tashkent Medical Academy, Faculty of Medicine No. 1, student of group 107
Rasulova Sevara Uralboy qizi
Tashkent Medical Academy, Faculty of Medicine No. 1, student of group 107
Otajonova Aziza Nigmatullayevna
Scientific advisor: Senior lecturer of the Department of Histology and Medical Biology, Tashkent Medical Academy

Annotation:
This article defines that mitochondria are essential organelles responsible for cellular energy production through oxidative phosphorylation. Mitochondrial dysfunction plays a significant role in apoptosis, necrosis, and oxidative stress, influencing disease progression in conditions like Parkinson's disease, Alzheimer's disease, and multiple sclerosis. Inherited through maternal transmission or nuclear mutations, mitochondrial disorders exhibit complex inheritance patterns, with heteroplasmy and threshold effects impacting disease expression. Advances in genetic research and metabolic studies have improved understanding, but effective treatments remain limited. Future therapeutic strategies, including targeted gene therapy and metabolic interventions, hold promise for managing mitochondrial diseases and mitigating their systemic effects.

Key Words: Mitochondria, oxidative phosphorylation, mitochondrial DNA (mtDNA), nuclear DNA (nDNA), mitochondrial diseases, mitochondrial myopathy, neurodegenerative disorders, mitochondrial inheritance, metabolic disorders, mitochondrial dysfunction, mitochondrial biogenesis, reactive oxygen species (ROS), genetic mutations.

Mitochondria have played a key role in the evolution of complex life. Their existence as an organelle is linked to endosymbiosis, a process that suggests their origins align with the emergence of eukaryotic cells. Mitochondrial oxidative phosphorylation contributed to an increase in nuclear genome size, protein expression, and overall cellular complexity, ultimately leading to the development of multicellular organisms. Mitochondrial diseases are a heterogeneous group of disorders caused by genetic, structural, and biochemical defects of mitochondria. Clinical and biochemical analyses are essential for diagnosing mitochondrial diseases. The main biochemical indicator of

mitochondrial pathology is the development of lactic acidosis, which usually manifests along with hyperlactacidemia and hyperpyruvicemia. In mitochondrial diseases, an increase in the normal concentration of pyruvic and lactic acids in cerebrospinal fluid is observed.

Initially, mitochondrial diseases were studied in relation to nerve and muscle pathologies. Later, it was discovered that mitochondrial DNA (mtDNA) mutations could cause various conditions, including cardiomyopathy, endocrinopathy, gastrointestinal tract disorders, and bone marrow damage. However, among these, mitochondrial diseases predominantly affect muscle tissues and the central nervous system.

Myopathy manifests in muscles as intolerance to physical exertion, eye diseases without reflex involvement, ptosis (drooping eyelids), muscle atrophy, and weakness. Neurological disorders include epilepsy, strokes, neuro-sensory deafness, optic nerve atrophy, myoclonus, polyneuropathy, psychomotor developmental changes, migraines, intellectual disabilities, and cognitive decline. Additionally, mitochondrial dysfunctions not only contribute to various organ pathologies but are also significantly evident in myocardial damage.

Mutations in mitochondrial proteins are associated with various neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, motor neuron disorders (Lou Gehrig’s disease or amyotrophic lateral sclerosis), and multiple sclerosis. Furthermore, the presence of free radicals in mitochondria plays a crucial role in cell degradation and is fundamental to the aging process. It is hypothesized that certain genes protect mitochondria for extended periods and regulate the cell’s antioxidant defense mechanisms.

A decrease in ATP reserves in cells is a primary cause of cell death under anoxia/hypoxia, toxic effects of xenobiotics, and stress conditions. Changes in mitochondrial function are also observed in some tumor cells. Mitochondria play a key role in cell death through necrosis and apoptosis. In necrotic cell death, a gradual and prolonged increase in $Ca2+$ concentration in the cytosol is observed. Under these conditions, the influx of $Ca2+$ into the mitochondria occurs slowly through the uniport system. It has been noted that an increase in mitochondrial $Ca2+$ concentration does not significantly alter the matrix pH and prevents the opening of the pore in a low-conductance state.

Excessive accumulation of $Ca2+$ in mitochondria leads to changes in the mitochondrial membrane potential, causing a transition to a high-conductance state and mitochondrial swelling. Consequently, mitochondrial function is altered, leading to cell death through

necrosis or apoptosis. Mitochondrial membrane permeability is crucial in determining whether a cell undergoes apoptosis or necrosis. Many cell death signals target mitochondria, involving proteins such as Bid and Bad from the Bcl-2 family.

Additionally, mitochondrial permeability transition (MPT) induces the release of catabolic hydrolases and enzyme activators (caspases) from mitochondria. Thus, mitochondrial dysfunction (including pore opening, respiratory inhibition, oxidative phosphorylation uncoupling, and ROS generation) leads to necrosis. Although pore opening plays a major role in necrosis development, it also contributes to certain types of apoptosis.

Various intracellular signaling pathways contribute to caspase system activation, increasing cytosolic Ca2+, nitric oxide, amphipathic peptides, and ceramide concentrations, which directly or indirectly alter mitochondrial ion permeability.

Mitochondrial diseases present significant clinical variability. The same genetic mutation can result in different disorders (e.g., MELAS, MIDD, and CPEO from m.3243A > G mutations), while the same disorder can arise from multiple genetic mutations (e.g., Leigh syndrome has over 75 possible genetic causes). Additionally, nuclear DNA mutations have been identified in mitochondrial aminoacyl-tRNA synthetases (mtARSs), which play a crucial role in mitochondrial translation. Variants in these genes can cause severe conditions such as brain malformations and fatal infantile lactic acidosis.

Inheritance and Genetic Complexity. Mitochondrial disorders can be inherited through various patterns, including autosomal dominant, autosomal recessive, X-linked, or maternal inheritance via mtDNA. The concept of heteroplasmy explains variable disease expression within the same family, as different cells and tissues carry varying levels of mutant mtDNA. The "bottleneck effect" during oocyte development influences mutation load, and the "threshold effect" determines when mitochondrial dysfunction occurs in affected organs. Over time, mitotic segregation can alter disease expression within an individual.

Energy Metabolism Disorders. Mitochondria generate energy through glucose metabolism, with pyruvate playing a key role in connecting glycolysis to the Krebs cycle. Defects in pyruvate metabolism often result in primary lactic acidosis, where excess pyruvate is converted into lactate and alanine. The ratio of lactate to pyruvate can help identify specific metabolic disorders, including:

Pyruvate Dehydrogenase Complex (PDHC) Deficiency: PDHC is a multi-enzyme complex composed of E1, E2, and E3 subunits. PDHA1 deficiency, an X-linked condition, can cause fatal lactic acidosis or neurological impairments, but high-dose

thiamine therapy has shown some benefits. PDHE2 and PDHE3 deficiencies are autosomal recessive and lead to severe metabolic disturbances.

Pyruvate Carboxylase (PC) Deficiency: This autosomal recessive disorder presents in three forms:

Group A (North American phenotype): Lactic acidosis with intellectual disability.

Group B (French phenotype): Severe neonatal lactic acidosis with hyperammonemia and neurological symptoms, often fatal in infancy.

Group C: Mild, episodic lactic acidosis with no significant cognitive impairment.

Oxidative Phosphorylation (OXPHOS) Defects. Mitochondria produce ATP through oxidative phosphorylation, a process driven by electron transport across five respiratory chain complexes (I-V). Mutations in both mtDNA and nDNA can disrupt this process, leading to various inherited disorders with neurocognitive and developmental symptoms.

Complex I Deficiency: The most common OXPHOS disorder, it can cause severe conditions like Leigh syndrome, cardiomyopathy, and exercise intolerance. While there is no cure, some patients respond to riboflavin supplementation.

Complex II Deficiency: Often linked to Leigh syndrome, this disorder affects the brainstem and basal ganglia, leading to neurological regression, muscle weakness, respiratory issues, and movement disorders.

Despite the complexity of mitochondrial diseases, ongoing research is enhancing our understanding of these conditions. Advances in genetic studies, disease modeling, and targeted therapies may lead to improved diagnosis and treatments for mitochondrial disorders in the future.

Conclusion

Mitochondria play a crucial role in cellular energy production, and their dysfunction is linked to various diseases affecting multiple organ systems. Mitochondrial diseases, caused by genetic mutations in mtDNA and nDNA, primarily impact high-energy-demanding organs like the brain, heart, and muscles. These disorders exhibit significant clinical variability, with different mutations leading to the same condition and vice versa. The complex inheritance patterns, including maternal transmission and heteroplasmy, further complicate disease expression. Metabolic disturbances, such as defects in pyruvate metabolism and oxidative phosphorylation, contribute to mitochondrial dysfunction and associated pathologies. While treatment options remain limited, advances in genetic research and therapeutic approaches offer hope for better

diagnosis and management. Understanding mitochondrial function is also essential in studying aging, neurodegenerative diseases, and cancer. Ongoing research on mitochondrial genetics and targeted therapies may lead to novel interventions, improving patient outcomes and expanding knowledge of cellular energy metabolism and disease mechanisms.

References:

1.Murphy A.N., Fiskum G., Beal M.F. Mitochondria in Neurodegeneration:
Bioenergetic Function in Cell Life and Death // Journal of Cerebral Blood Flow & Metabolism.- 1999. - V. 19. - P. 231-245
2.Treem W.R., Sokol R.J. Disorders of the mitochondria// Semin. Liver Dis. - 1998. - V.18. - P.237-253.
3. Hekimi S., Guarente L. Genetics and the specificity of the aging process // Science. - 2003. - V. 299. - P. 1351-1354.
4. Correa F., Soto V., Zazueta C. Mitochondrial permeability transition relevance for apoptotic triggering in the post-ischemic heart. // Int. J. Biochem. Cell Biol. - 2007. - V. 39.- P. 787-798.
5. Brookes P.S., Yoon Y., Robotham J.L., Anders M.W., Sheu Sh.Sh. Calcium, ATP, and ROS: a mitochondrial love-hate triangle// Am. J. Physiol. Cell. Physiol. - 2004. - V. 287.- P. C817-C833.
6.Fu, et al. "Organ Crosstalk Between Heart and Kidney." Annals of Translational Medicine, vol. 6, no. 24, 2018, pp. 475. atm.amegroups.com.
7.Kanungo, et al. "Mitochondrial Disorders." Annals of Translational Medicine, vol. 6, no. 24, 2018, pp. 475. atm.amegroups.com.