MITOCHONDRIAL DYSFUNCTION IN HUMAN DISEASE

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Abstract. Mitochondria are essential organelles responsible for energy production, metabolic regulation, and apoptosis. Beyond their classical role in ATP synthesis through oxidative phosphorylation, mitochondria are central to cellular signaling, redox homeostasis, and programmed cell death. Mitochondrial dysfunction has emerged as a key contributor to a wide range of human diseases, including neurodegenerative disorders, metabolic syndromes, cardiovascular diseases, and aging-related conditions. This review summarizes the biochemical basis of mitochondrial function, the molecular mechanisms underlying mitochondrial dysfunction, and its role in disease pathogenesis, along with current and emerging therapeutic strategies.

Keywords: mitochondria, ATP synthesis, oxidative phosphorylation, metabolic regulation, apoptosis, cellular signaling, redox homeostasis, mitochondrial dysfunction, neurodegenerative diseases, metabolic disorders, cardiovascular diseases

Introduction. Mitochondria are double-membraned organelles often referred to as the "powerhouses" of the cell due to their role in adenosine triphosphate (ATP) production. However, their functions extend far beyond energy metabolism. They are involved in calcium homeostasis, generation of reactive oxygen species (ROS), regulation of apoptosis, and intermediary metabolism. Mitochondrial dysfunction refers to a state in which these processes are impaired, leading to decreased ATP production, increased oxidative stress, and altered cellular signaling. Accumulating evidence suggests that mitochondrial dysfunction plays a central role in the pathogenesis of many human diseases.

1. Normal Mitochondrial Function:

1.1. Oxidative Phosphorylation

ATP production occurs through oxidative phosphorylation (OXPHOS) in the inner mitochondrial membrane. Electrons derived from NADH and FADH2 pass through the electron transport chain (ETC), consisting of complexes I–IV, ultimately reducing oxygen to water. This electron flow generates a proton gradient across the inner membrane, which drives ATP synthesis via ATP synthase (Complex V).

1.2. Reactive Oxygen Species (ROS)

During electron transport, a small proportion of electrons leak and react with oxygen to form ROS. At physiological levels, ROS function as signaling molecules. However, excessive ROS production leads to oxidative damage.

1.3. Apoptosis Regulation

Mitochondria play a key role in intrinsic apoptosis. Release of cytochrome c from the intermembrane space activates caspases, leading to programmed cell death.

1.4. Mitochondrial DNA (mtDNA)

Mitochondria possess their own genome, encoding essential components of the ETC. mtDNA is particularly susceptible to mutations due to its proximity to ROS and limited repair mechanisms.

2. Mechanisms of Mitochondrial Dysfunction:

2.1. Impaired Electron Transport Chain

Defects in ETC complexes reduce ATP production and increase electron leakage, leading to excessive ROS generation. Mutations in nuclear or mitochondrial genes encoding ETC proteins can disrupt normal function.

2.2. Oxidative Stress

An imbalance between ROS production and antioxidant defenses results in oxidative stress. This damages lipids, proteins, and DNA, further impairing mitochondrial function.

2.3. mtDNA Mutations

Mutations in mtDNA can be inherited or acquired. These mutations impair protein synthesis within mitochondria, leading to defective oxidative phosphorylation.

2.4. Defective Mitophagy

Mitophagy is the selective degradation of damaged mitochondria. Impairment of this process leads to accumulation of dysfunctional mitochondria, exacerbating cellular stress.

2.5. Altered Mitochondrial Dynamics

Mitochondria undergo continuous fusion and fission. Disruption of these processes affects mitochondrial distribution, function, and quality control.

2.6. Increased Membrane Permeability

Opening of the mitochondrial permeability transition pore (mPTP) leads to loss of membrane potential, swelling, and release of pro-apoptotic factors.

3. Mitochondrial Dysfunction in Disease:

3.1. Neurodegenerative Diseases

Mitochondrial dysfunction is a hallmark of neurodegenerative diseases such as Parkinson’s and Alzheimer’s disease. In Parkinson’s disease, defects in Complex I and impaired mitophagy contribute to neuronal death. In Alzheimer’s disease, increased oxidative stress and mitochondrial damage are prominent features.

3.2. Metabolic Disorders

In type 2 diabetes, mitochondrial dysfunction contributes to insulin resistance. Impaired oxidative metabolism reduces ATP production and alters glucose and lipid metabolism.

3.3. Cardiovascular Diseases

Cardiac cells are highly dependent on mitochondrial ATP. During ischemia-reperfusion injury, excessive ROS production and mPTP opening lead to cell death and tissue damage.

3.4. Aging

Aging is associated with accumulation of mtDNA mutations and increased oxidative stress. Declining mitochondrial function contributes to reduced cellular energy and increased susceptibility to disease.

4. Therapeutic Approaches:

4.1. Antioxidants

Compounds such as vitamin C, vitamin E, and coenzyme Q10 aim to reduce oxidative stress. However, their clinical efficacy remains variable.

4.2. Mitochondria-Targeted Therapies

New drugs are being developed to specifically target mitochondria, including mitochondrial antioxidants and agents that stabilize membrane potential.

4.3. Enhancing Mitophagy

Strategies to improve mitophagy may help remove damaged mitochondria and restore cellular function.

5. Lifestyle Interventions:

Exercise and caloric restriction have been shown to improve mitochondrial function and biogenesis.

Conclusion

Mitochondrial dysfunction is a central feature of many human diseases. It involves complex interactions between impaired energy production, oxidative stress, and defective quality control mechanisms. Understanding these processes provides valuable insights into disease pathogenesis and highlights potential therapeutic targets. Continued research is necessary to develop effective strategies to prevent and treat mitochondrial-related disorders.

References

1. Douglas C. Wallace (2005). A mitochondrial paradigm of metabolic and degenerative diseases, aging, and cancer. *Science*, *307*(5708), 641–645. https://doi.org/10.1126/science.1104134
2. Nick Lane (2006). Mitochondrial disease: Powerhouse of disease. *Nature*, *440*(7084), 600–602. https://doi.org/10.1038/440600a
3. M. T. Lin, & M. F. Beal (2006). Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. *Nature*, *443*(7113), 787–795. https://doi.org/10.1038/nature05292
4. David C. Chan (2012). Fusion and fission: Interlinked processes critical for mitochondrial health. *Annual Review of Genetics*, *46*, 265–287. https://doi.org/10.1146/annurev-genet-110410-132529
5. Richard J. Youle, & D. P. Narendra (2011). Mechanisms of mitophagy. *Nature Reviews Molecular Cell Biology*, *12*(1), 9–14. https://doi.org/10.1038/nrm3028
6. Martin Picard, & Bruce S. McEwen (2018). Psychological stress and mitochondria: A conceptual framework. *Psychosomatic Medicine*, *80*(2), 126–140. https://doi.org/10.1097/PSY.0000000000000544
7. Antonio Andreux et al. (2013). Mitochondrial function and dysfunction in metabolic disorders. *Cell Metabolism*, *17*(6), 859–870. https://doi.org/10.1016/j.cmet.2013.05.005
8. Michael P. Murphy (2009). How mitochondria produce reactive oxygen species. *Biochemical Journal*, *417*(1), 1–13. https://doi.org/10.1042/BJ20081386
9. Vladimir P. Skulachev (2011). Mitochondrial-targeted antioxidants as promising therapeutics. *Biochemistry (Moscow)*, *76*(3), 273–281. https://doi.org/10.1134/S000629791103001X
10. Luigi Fontana, & Linda Partridge (2015). Promoting health and longevity through diet: From model organisms to humans. *Cell*, *161*(1), 106–118. https://doi.org/10.1016/j.cell.2015.02.02