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Mitochondrial dysfunction and its role in neurological diseases.

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Introduction

Mitochondria, often referred to as the "powerhouses" of the cell, are essential organelles responsible for producing adenosine triphosphate through oxidative phosphorylation. Beyond their role in bioenergetics, mitochondria are involved in a wide range of cellular processes, including calcium homeostasis, reactive oxygen species regulation, apoptosis, and the synthesis of key metabolites. Given their central role in maintaining cellular function, it is unsurprising that mitochondrial integrity is critical for the health of neurons, which are highly energy-dependent and particularly sensitive to metabolic disturbances. Neurons require vast amounts of ATP to support synaptic transmission, axonal transport, and the maintenance of ion gradients. Even subtle impairments in mitochondrial function can have profound effects on neuronal survival and function, making mitochondrial dysfunction a common feature in many neurological diseases [1].

Mitochondrial dysfunction can arise from genetic mutations in either nuclear or mitochondrial DNA, environmental insults, oxidative stress, or secondary to other pathological processes. Mutations in mitochondrial DNA can affect proteins essential for oxidative phosphorylation, impairing ATP synthesis and causing a decline in energy availability. Nuclear DNA mutations affecting mitochondrial biogenesis, dynamics, and quality control pathways can also disrupt mitochondrial function. Unlike most cellular organelles, mitochondria have their own genome, which is inherited maternally, and mutations in this genome can accumulate with age, further compromising function. Additionally, mitochondrial proteins encoded by nuclear DNA must be imported into the organelle, and defects in import machinery can exacerbate dysfunction [2].

One hallmark of mitochondrial dysfunction is the overproduction of reactive oxygen species. While mitochondria normally produce ROS as a byproduct of oxidative phosphorylation, excessive ROS generation can damage proteins, lipids, and nucleic acids, creating a vicious cycle in which mitochondrial damage begets further oxidative stress. Neurons are particularly vulnerable to oxidative stress due to their high oxygen consumption and relatively limited antioxidant defenses. Chronic oxidative stress contributes to neuronal degeneration in a range of neurological disorders, including Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, and multiple sclerosis [3].

In Parkinson's disease, mitochondrial dysfunction has been extensively documented, particularly in the dopaminergic neurons of the substantia nigra. These neurons show a pronounced reduction in complex I activity of the electron transport chain, impairing ATP production and increasing oxidative stress. Mutations in genes such as PINK1, Parkin, DJ-1, and LRRK2 disrupt mitochondrial quality control mechanisms, including mitophagy—the process by which damaged mitochondria are selectively degraded. Impaired mitophagy leads to the

accumulation of dysfunctional mitochondria, further exacerbating neuronal injury. Experimental exposure to mitochondrial toxins such as MPTP reproduces key features of Parkinson's disease, underscoring the central role of mitochondrial impairment in its pathogenesis [4].

Alzheimer's disease also features prominent mitochondrial abnormalities. Mitochondria in Alzheimer's-affected neurons display structural alterations, reduced respiratory chain activity, and impaired calcium buffering capacity. Amyloid-beta peptides, a hallmark of the disease, can localize to mitochondria and interfere with mitochondrial enzymes, while hyperphosphorylated tau protein disrupts mitochondrial transport along axons, limiting energy supply to synaptic terminals. These mitochondrial defects contribute to synaptic failure, oxidative damage, and neuronal death. Furthermore, mitochondrial DNA mutations and reduced expression of mitochondrial biogenesis regulators such as PGC-1α have been reported in Alzheimer's patients, suggesting both functional and structural mitochondrial deficits [5].

Conclusion

In conclusion, mitochondrial dysfunction plays a central role in the pathophysiology of a wide range of neurological diseases, from common neurodegenerative disorders such as Parkinson's and Alzheimer's to rare mitochondrial syndromes. Neurons' high energy demands make them exquisitely sensitive to deficits in mitochondrial function, whether arising from genetic mutations, oxidative stress, impaired dynamics, or secondary to other disease processes. The consequences—energy failure, oxidative damage, calcium dysregulation, and impaired synaptic maintenance—converge to drive neuronal injury and loss.

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