EDITORIAL

Mitochondria: Small Organelles, Big Impact

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INTRODUCTION

Mitochondria, long regarded as the cell's powerhouses, are now recognised as central regulators of cellular fate. Beyond ATP synthesis via oxidative phosphorylation (OXPHOS), they orchestrate key processes including apoptosis, lipid and amino acid metabolism, and reactive oxygen species (ROS) signalling. These dynamic organelles constantly remodel to match cellular energy demands and environmental cues. However, when mitochondrial integrity is compromised, disruptions in energy production and redox balance trigger cascades that contribute to metabolic, neurodegenerative, and malignant diseases. Understanding how mitochondria integrate metabolic signals with stress responses offers crucial insight into the mechanisms that sustain cellular homeostasis and underlie the pathogenesis of complex disorders.

CANCER

Mitochondria occupy a central role in cancer progression, serving as critical hubs that integrate energy metabolism, biosynthesis, and cell fate regulation. While aerobic glycolysis, or the Warburg effect, is a hallmark of cancer, accumulating evidence shows that mitochondrial OXPHOS remains indispensable for tumour growth and survival. Cancer cells exploit this metabolic plasticity, dynamically switching between glycolysis and OXPHOS in response to nutrient availability, oxygen tension, and oncogenic signalling. Beyond ATP production, mitochondria provide essential biosynthetic precursors for nucleotides, lipids, and amino acids, while sustaining redox homeostasis through NADPH generation and regulation of reactive oxygen species (ROS). At moderate levels, mitochondrial ROS act as signalling molecules to promote proliferation and genomic instability; however, excessive ROS can trigger apoptosis, necessitating tight control through antioxidant systems.

Mechanistically, oncogenes such as MYC and KRAS enhance mitochondrial biogenesis and glutamine metabolism, whereas loss of tumour suppressors like *p53* perturbs mitochondrial respiration and apoptotic signaling. Alterations in mitochondrial dynamics further reinforce tumor fitness: increased fission, mediated by DRP1, supports rapid proliferation and invasion, while defective mitophagy enables the persistence of damaged mitochondria that contribute to metabolic rewiring. Moreover, deregulated calcium flux between the endoplasmic reticulum and mitochondria shapes bioenergetics and apoptotic thresholds which is the basis of tumour resistance. Collectively, these interconnected processes suggest that mitochondria not merely as passive powerhouses, but as active architects of oncogenic transformation and progression.

METABOLIC DISEASES

Metabolic diseases such as obesity and diabetes mellitus result from an imbalance between energy intake and energy expenditure causing several changes in the body which include inflammation, oxidative stress, mitochondrial dysfunction and apoptosis. Recent studies indicate that dynamic changes in mitochondrial architecture act as an adaptive mechanism to balance energy demand with nutrient supply. Impaired mitochondrial biogenesis disrupts adipocyte function, contributing to altered insulin sensitivity. Dysfunctional mitochondria exhibit reduced substrate oxidation, particularly of fatty acids, leading to ectopic lipid accumulation and elevated diacylglycerols (DAG) and ceramides (CER), both of which impair insulin signalling. Excess nutrient availability suppresses mitochondrial oxidative ATP production and disrupts autophagic flux by impairing lysosomal acidification, a process essential for degrading autophagosomes and clearing damaged mitochondria. Reduced electron flow through the ETC enhances electron leakage and superoxide generation. Increased levels of ROS and metabolic stress may impair mitophagy resulting in the failure to clear damaged and dysfunctional mitochondria, further exacerbating the oxidative stress and causing apoptosis.

NEURODEGENERATIVE DISEASES

Neurons are uniquely vulnerable to mitochondrial dysfunction due to their reliance on ATP production and calcium buffering. Under metabolic stress, mitochondria activate several pathological pathways, including opening of the mitochondrial permeability

transition pore (mPTP), cytochrome c release which triggers intrinsic apoptosis pathway and mitophagy. Excessive Ca^{2+} accumulation within the matrix is the principal trigger for mPTP opening, which functions as a high-conductance channel. Although its precise molecular composition remains unresolved, cyclophilin D (CypD) is postulated to be the key regulator of mPTP. mPTP opening disrupts the proton electrochemical gradient, collapses membrane potential, and alters pH homeostasis that leads to increased in membrane permeability accelerates ROS accumulation, driving lipid peroxidation, membrane damage, and tissue injury.

These events diminish ATP production and activate the intrinsic apoptotic pathway, culminating in neuronal cell death. Importantly, such mitochondrial defects are increasingly recognized as central drivers of neurodegenerative diseases, including Alzheimer's and Parkinson's, where impaired energy metabolism, Ca^{2+} dysregulation, and defective mitophagy converge to accelerate disease progression.

Alzheimer Disease

The mitochondrial cascade hypothesis suggests that alterations in mitochondria-associated endoplasmic reticulum membranes (MAM) and dysregulation of the mPTP are central to Alzheimer's disease (AD) pathology. Although Aβ has been shown to impair mitochondrial function, accumulating evidence suggests that mitochondrial dysfunction can also arise independently of Aβ in the AD brain. These early mitochondrial abnormalities disrupt proteostasis thereby promoting the pathological aggregation of proteins such as Aβ and tau which initiates the cascade of neurodegeneration.

In the AD brain, impaired electron transport chain activity, abnormal mitochondrial dynamics, and disrupted calcium homeostasis converge to create a state of bioenergetic collapse. These abnormalities amplify reactive oxygen species, promote excessive mitochondrial fragmentation which in turn compromises quality control mechanisms resulting in neurons highly vulnerable to stress. Critically, this mitochondrial dysfunction not only exacerbates synaptic failure but also accelerates the aggregation and toxicity of Aβ and tau, thereby fueling the self-perpetuating cascade of neurodegeneration that defines AD.

Parkinson

Parkinson's disease (PD) has been closely linked to mitochondrial dysfunction, particularly the deficiency of complex I within the electron transport chain (ETC). Mitochondrial DNA (mtDNA) abnormalities have been implicated in neuronal degeneration, as evidenced by the reduced expression of the mitochondrial transcription factor A (Tfam) gene in dopaminergic neurons of PD patients. More recently, mutations in the PINK1/Parkin pathway have emerged as a predominant cause of early-onset PD. A reduction in mitochondrial membrane potential leads to stabilisation of PTEN-induced kinase 1 (PINK1) on the outer mitochondrial membrane, where it phosphorylates ubiquitin and recruits the E3 ubiquitin ligase Parkin. Subsequent phosphorylation of Parkin by PINK1 activates mitophagy through autophagosome formation and lysosomal degradation of damaged mitochondria. Genetic mutations in the Parkin gene account for approximately 50% of familial PD cases and represent the most common cause of PD in individuals under 20 years of age.

CONCLUSION

Once viewed merely as the cell's powerhouses, mitochondria have emerged as central architects of health and disease. Their influence extends far beyond energy production to shaping how cells communicate, adapt, and survive under stress. As the understanding deepens, it becomes increasingly clear that mitochondrial resilience underpins metabolic balance and cellular longevity. Unlocking their therapeutic potential will not only transform how chronic and degenerative diseases are treated but may also redefine the approach of disease management.

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