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Commentary

Redox Imbalance and Mitochondrial Failure in the Progression of Biological Aging

Robert Hofer*

Department of Global Health Research, University of Geneva, Geneva, Switzerland

DESCRIPTION

Biological aging is a complex, multifactorial process that involves a gradual decline in physiological function, increased vulnerability to disease, and ultimately death. At the cellular and molecular levels, two closely interconnected phenomena-mitochondrial dysfunction and redox imbalance-have emerged as central players in the aging process. Mitochondria, the energy powerhouses of cells, are not only responsible for ATP production but also play pivotal roles in regulating apoptosis, calcium homeostasis, and redox signaling. With age, mitochondrial efficiency declines, leading to increased production of Reactive Oxygen Species (ROS), disrupted redox signaling, and oxidative damage to biomolecules, collectively contributing to cellular senescence and tissue deterioration.

The mitochondrion generates ATP *via* Oxidative Phosphorylation (OXPHOS), a process that simultaneously produces ROS as byproducts. Under physiological conditions, low levels of ROS act as signaling molecules, modulating gene expression, autophagy, and immune responses. However, aging is associated with increased electron leakage from the mitochondrial Electron Transport Chain (ETC), particularly at complexes I and III. This leads to excessive ROS accumulation, overwhelming the cell's antioxidant defense systems and shifting the redox environment toward a pro-oxidative state. The imbalance between ROS production and detoxification capacity-a condition termed "oxidative stress"-results in damage to mitochondrial DNA (mtDNA), proteins, and lipids, perpetuating a cycle of mitochondrial deterioration and redox imbalance.

Redox balance is maintained by a network of antioxidant enzymes and molecules, including Superoxide Dismutase (SOD), catalase, Glutathione Peroxidase (GPx), peroxiredoxins, and non-enzymatic antioxidants like Glutathione (GSH), vitamin C, and vitamin E. These components neutralize excess ROS and preserve cellular redox homeostasis. For instance, levels of reduced glutathione decline with age, impairing the cell's capacity to buffer oxidative stress. The transcription factor Nuclear factor erythroid 2-related factor 2 (*Nrf2*), a key regulator of antioxidant response, becomes less responsive in aged cells, resulting in attenuated induction of detoxifying enzymes and increased susceptibility to oxidative insults.

Mitochondrial dysfunction and redox imbalance are also intimately linked with the process of inflammaging-chronic, low-grade inflammation that characterizes aging. Damaged mitochondria release mitochondrial DNA and other Danger-Associated Molecular Patterns (DAMPs) into the cytosol or extracellular space, activating innate immune receptors such as Toll-Like Receptors (*TLRs*) and *NLRP3* inflammasomes. This triggers the production of pro-inflammatory cytokines like IL-1β and TNF-α, establishing a vicious cycle of inflammation and mitochondrial damage. Additionally, redox imbalance alters the function of redox-sensitive transcription factors such as *NF-κB* and *AP-1*, further promoting inflammatory gene expression.

Cellular senescence, a state of irreversible growth arrest, is another hallmark of aging exacerbated by mitochondrial dysfunction and oxidative stress. Senescent cells display a Senescence-Associated Secretory Phenotype (SASP), characterized by the release of inflammatory cytokines, chemokines, growth factors, and matrix-remodeling enzymes. Mitochondria in senescent cells are often enlarged, dysfunctional, and generate high levels of ROS. Neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's diseases exhibit marked mitochondrial abnormalities and oxidative damage. In Alzheimer's disease, for example, mitochondrial dysfunction precedes the formation of amyloid-β plaques, suggesting a causative role. ROS-mediated oxidation of mitochondrial proteins and lipids impairs synaptic function, disrupts calcium signaling, and promotes neuronal death. Therapeutic strategies targeting mitochondrial bioenergetics and redox homeostasis hold promise for mitigating cognitive decline in the elderly.

While the causal relationships between redox imbalance, mitochondrial failure, and aging are complex, accumulating evidence supports the hypothesis that targeting mitochondrial health could delay aging and mitigate age-related diseases. Antioxidant therapies have yielded mixed results in clinical settings, possibly due to poor bioavailability or non-specific ROS scavenging. However, emerging strategies that activate endogenous

Correspondence to: Robert Hofer, Department of Global Health Research, University of Geneva, Geneva, Switzerland, E-mail: Robert.hofer@uhst.ch

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antioxidant pathways or selectively target mitochondria-such as MitoQ, SkQ1, and SS-31-offer greater promise. These mitochondria-targeted antioxidants can cross the mitochondrial membrane and neutralize ROS at the source, thereby preserving mitochondrial integrity and function.

Caloric Restriction (CR), one of the most robust interventions for lifespan extension across species, enhances mitochondrial function and redox balance. CR stimulates *SIRT1*, and *PGC-1α*, promoting mitochondrial biogenesis and antioxidant defense. Similarly, exercise induces hormetic stress that upregulates endogenous antioxidant systems and improves mitochondrial efficiency. The concept of mitohormesis-whereby low levels of ROS trigger adaptive responses that enhance cellular resilience-is gaining traction as a framework for understanding the beneficial effects of lifestyle interventions on aging.

CONCLUSION

Redox imbalance and mitochondrial failure represent fundamental mechanisms in the biological aging process. Their interplay affects nearly every aspect of cellular physiology, from energy production and genome stability to inflammation and apoptosis. Understanding the molecular underpinnings of these processes provides valuable insights into the aging trajectory and highlights promising avenues for therapeutic intervention. As research continues to unravel the intricacies of mitochondrial biology and redox regulation, the prospect of modulating these pathways to promote healthy aging and extend healthspan becomes increasingly attainable.