Perspective

iMedPub Journals
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Chronic Obstructive Pulmonary Disease: Open Access
ISSN 2572-5548

2025
Vol.10 No.01: 04

Cellular Senescence and Mitochondrial Dysfunction as Central Players

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Rec date: January 06, 2025; **Acc date:** January 08, 2025; **Pub date:** January 31, 2025

Citation: Hougaard M. (2025) Cellular Senescence and Mitochondrial Dysfunction as Central Players. Chron Obstruct Pulmon Dis 10.01: 04.

Introduction

Aging and age-related diseases are driven by a complex interplay of molecular and cellular processes that gradually impair tissue function and resilience. Among the most significant mechanisms identified in recent decades are cellular senescence and mitochondrial dysfunction, both of which are widely regarded as hallmarks of aging. Cellular senescence refers to a state of stable and irreversible cell cycle arrest that cells enter in response to various stressors, including DNA damage, oxidative stress, and oncogenic signaling. Although initially protective-preventing uncontrolled proliferation of damaged cells-senescent cells accumulate with age and secrete a pro-inflammatory milieu known as the senescence-associated secretory phenotype (SASP). This microenvironment promotes chronic inflammation, tissue remodeling, and the disruption of normal cellular communication. On the other hand, mitochondria, the energy powerhouses of the cell, undergo progressive functional decline during aging, characterized by reduced bioenergetic efficiency, impaired dynamics (fusion and fission), accumulation of mutations in mitochondrial DNA (mtDNA), and heightened production of Reactive Oxygen Species (ROS) [1].

Description

Cellular senescence is triggered by multiple intrinsic and extrinsic signals. Key inducers include telomere shortening-a consequence of the end-replication problem in somatic cells-persistent DNA damage, oxidative stress, and aberrant oncogene activation. Once senescence is established, cells adopt a distinct phenotype characterized by growth arrest, morphological changes such as enlargement and flattening, altered chromatin organization, and metabolic reprogramming. Central to senescence induction are the p53/p21 and p16^INK4a/Rb tumor suppressor pathways, which converge to halt cell cycle progression. Although initially protective, the persistence of senescent cells has deleterious effects on tissue microenvironments [2].

Mitochondria, meanwhile, play a central role in energy metabolism, generating Adenosine Triphosphate (ATP) through oxidative phosphorylation. They are also hubs of redox signaling, calcium homeostasis, apoptosis regulation, and biosynthesis of metabolic intermediates. With advancing age, mitochondrial function progressively deteriorates. Structural changes such as mitochondrial swelling, cristae disorganization, and fragmentation are commonly observed. Functionally, aged mitochondria exhibit reduced respiratory capacity, lower ATP output, and increased ROS production. ROS, when produced at physiological levels, act as signaling molecules that regulate cellular adaptation. However, excessive ROS lead to oxidative damage of proteins, lipids, and nucleic acids, including mtDNA. Because mitochondria lack robust repair mechanisms compared to nuclear DNA, mtDNA mutations accumulate over time, further impairing respiratory chain activity. Moreover, defective mitochondria can escape clearance due to impaired autophagy and mitophagy, leading to their accumulation and perpetuation of cellular stress [3,4].

The link between mitochondrial dysfunction and cellular senescence is profound and reciprocal. On one hand, mitochondrial dysfunction is a key driver of senescence. ROS generated by dysfunctional mitochondria induce persistent DNA damage, activating DNA Damage Response (DDR) pathways that trigger senescence. Altered mitochondrial dynamics, including excessive fission or impaired fusion, disrupt energy metabolism and promote the activation of pro-senescent pathways such as p53 and p16^INK4a. Defective mitochondria also impair NAD^+ homeostasis, limiting the activity of sirtuins-NAD^+-dependent deacetylases that regulate genomic stability, mitochondrial biogenesis, and stress resistance. On the other hand, senescent cells exacerbate mitochondrial dysfunction. Senescence-associated metabolic reprogramming skews cells toward glycolysis but also leaves mitochondria hyperactive and inefficient, producing higher levels of ROS. Moreover, SASP factors can induce mitochondrial stress in neighboring cells, amplifying tissue-level dysfunction. Thus, senescence and mitochondrial dysfunction create a feed-forward loop that accelerates aging and contributes to age-related pathologies [5].

Conclusion

Cellular senescence and mitochondrial dysfunction stand as central players in the biology of aging, intricately linked in a feedback loop that drives tissue decline, systemic inflammation, and age-related disease. Senescence arrests damaged cells but imposes chronic harm through SASP and metabolic reprogramming, while mitochondrial dysfunction disrupts energy homeostasis and generates excessive ROS that trigger and sustain senescence. Together, they shape the landscape of aging and underlie diverse chronic diseases ranging from cardiovascular dysfunction to neurodegeneration. Advances in senolytics, mitochondrial therapeutics, and systems-level approaches are illuminating new strategies to break the vicious cycle between senescence and mitochondria, offering unprecedented opportunities to extend healthspan and improve late-life resilience. By targeting these central hallmarks, biomedical science moves closer to the ultimate goal of precision longevity medicine-treating aging not as an inevitable decline but as a modifiable, biological process.

Acknowledgment

None.

Conflict of Interest

None.

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