

REVIEW

An Overview of the Potential Impact of Physical Exercise on Cellular Aging Mechanisms: A Mini Review

Onur Oral¹, Iyanuloluwa Ojo², Naima Badid³, George Nomikos⁴, Evangelia Stavropoulou⁵

¹ Ege University, Faculty of Sports Sciences, Izmir, Turkey, ² University College Hospital, Ibadan, Oyo State, Nigeria, ³ Department of Biology, Faculty of Sciences of Nature and Life & Sciences of the Earth and the Universe, University of Tlemcen, Algeria, ⁴ Chios Hospital, Department of Orthopaedic Surgery, Chios, Greece, ⁵ Master of Research in Information and Communication, University of Lorraine, France

ABSTRACT

Background: This narrative review comprehensively synthesizes existing mechanistic and clinical evidence elucidating how physical exercise modulates fundamental cellular ageing processes. It also establishes critical priorities for translating these findings into effective health interventions.

Methods: Extensive literature searches were performed across PubMed, Scopus, Embase, Web of Science, and Google Scholar databases, focusing on English-language publications from 1985 to 2020. The search strategy incorporated terms related to cellular ageing, exercise physiology, oxidative stress, mitochondrial dynamics, inflammation, and telomere biology. Following rigorous screening criteria, 35 seminal studies were qualitatively analyzed for integration.

Results: Physical exercise initiates a complex interplay of coordinated intracellular signaling pathways, involving AMP-activated protein kinase (AMPK)-PGC-1 α , sirtuins, mammalian target of rapamycin (mTOR), and nuclear factor erythroid 2-related factor 2 (Nrf2). These pathways synergistically promote mitochondrial biogenesis and enhance mitochondrial quality control mechanisms, bolster endogenous antioxidant capacity, attenuate chronic low-grade inflammation, and preserve telomere integrity. Endurance training predominantly fosters mitochondrial and metabolic adaptations, resistance training facilitates proteostasis and skeletal muscle anabolism, while combined and high-intensity interval training (HIIT) protocols yield complementary and potentially synergistic cellular benefits. Effects on telomere length regulation and immune ageing are generally favorable but show heterogeneity, attributed largely to variability in assay methodologies and exercise protocols.

Conclusion: Regular physical activity robustly targets several hallmarks of cellular ageing. Bridging these mechanistic insights into practical clinical applications necessitates the development of standardized biomarkers, execution of well-powered long-term randomized controlled trials, tissue-specific multi-omic investigations, and inclusion of diverse populations across geographic and demographic spectra. Such integrative approaches will inform personalized exercise prescriptions to maximize health span extension.

Keywords: Cellular aging, exercise physiology, oxidative stress, mitochondrial dynamics, inflammation, and telomere biology

O. Oral, I. Ojo, N. Badid, G. Nomikos, E. Stavropoulou. An overview of the potential impact of physical exercise on cellular aging mechanisms: a mini review. *Scientific Chronicles* 2025; 30(4): 580-588

INTRODUCTION

Globally, ageing populations have placed unprecedented attention on interventions aimed at prolonging health span, the portion of life spent in good health, free from debilitating chronic diseases. Cellular ageing underpins many organismal ageing phenotypes and stems from an intricate network of interdependent molecular and cellular processes. These encompass genomic instability, telomere attrition, epigenetic dysregulation, loss of proteostasis, aberrant nutrient signaling, mitochondrial dysfunction, cellular senescence, stem cell depletion, and altered intercellular communication [1]. Each hallmark interlocks, contributing to the progressive functional decline seen across multiple organ systems.

Physical exercise represents a universally accessible, cost-effective, and nonpharmacologic strategy capable of influencing numerous cellular ageing pathways simultaneously. As a systemic intervention, it initiates adaptations at the molecular, cellular, and whole-body levels, mediating profound beneficial effects relevant to ageing biology.

During exercise, the generation of reactive oxygen species (ROS) is markedly increased. While excessive ROS can cause oxidative damage to lipids, proteins, and nucleic acids, transient bursts of ROS act as vital signaling molecules, initiating adaptive responses that enhance cellular defense capacity and resilience [2]. Mitochondrial dysfunction, which commonly accompanies advancing age, diminishes adenosine triphosphate (ATP) production efficiency and increases basal ROS output, thereby exacerbating oxidative stress and impairing energy-dependent cellular functions [3]. Concurrently, chronic low-grade

inflammation - termed inflammaging - represents a persistent, subclinical inflammatory state contributing to tissue degeneration and elevated chronic disease risk [4]. Telomeres, the protective nucleoprotein complexes capping chromosome ends, progressively shorten with replicative cycles and oxidative insults, making telomere length a sensitive biomarker reflecting cellular ageing and biological stress [5].

This review integrates mechanistic and clinical evidence detailing how physical exercise modulates key cellular ageing processes, including oxidative stress, mitochondrial biology, inflammation, and telomere maintenance. Furthermore, it discusses how different exercise modalities and dosing regimens influence these outcomes, providing insight for future research and clinical translation.

MATERIALS AND METHODS:

A comprehensive search of the literature was conducted using a range of databases, including the US National Library of Medicine (PubMed), Scopus, EBSCO, MEDLINE, DRJI (Directory of Research Journal Indexing), Embase, Web of Science, Cochrane Library, Google Scholar, and SportDiscus. To gain a comprehensive understanding of the subject matter, some key search terms were selected for the search, including "cellular ageing", "exercise physiology", "mitochondrial dynamics", "oxidative stress", "inflammation" and "telomere biology". In addition, relevant literature was further identified through the examination of reference lists derived from the data searches. To focus on the most relevant results, the search was limited to peer-reviewed articles published in English between 1985 and 2020. To gain a

comprehensive understanding of the relationship among cellular ageing, exercise physiology, mitochondria, oxidative stress, and telomeres, it was necessary to meet certain criteria. Firstly, the relationship among cellular ageing, exercise physiology and telomeres had to be examined. Secondly, the studies had to be published in a peer-reviewed journal. Thirdly, the studies had to be in English. Following a rigorous selection process, 35 studies were chosen to be included in this review.

RESULTS

Exercise-Activated Molecular Pathways

Exercise engagement stimulates intricate cellular signalling networks that coordinate metabolic and stress adaptations. AMPK, a critical energy sensor kinase, is activated by rising AMP/ATP ratios and promotes mitochondrial biogenesis via upregulation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α), a principal transcriptional coactivator governing mitochondrial gene expression [6,7]. Sirtuins, particularly the NAD⁺-dependent deacetylase SIRT1, interface with PGC-1 α and modulate chromatin remodelling, mitochondrial function, and cellular stress responses, thereby working synergistically with AMPK [8]. The mammalian target of rapamycin (mTOR) pathway plays a nuanced role; acute, transient activation favors muscle protein synthesis and cellular growth, whereas chronic suppression is implicated in longevity-promoting mechanisms [9]. Exercise also robustly induces nuclear factor erythroid 2-related factor 2 (Nrf2), a master regulator orchestrating an array of antioxidant genes to

maintain redox homeostasis and mitigate oxidative damage [10].

Oxidative Stress and Hormetic Adaptations

Initial bouts of exercise induce a temporary surge in ROS levels, triggering hormesis—a process whereby low-level stress elicits adaptive cellular responses that ultimately strengthen antioxidant defenses and DNA repair capacity [11,12]. Repeated endurance or resistance exercise enhances endogenous antioxidant enzyme activities, including those of superoxide dismutase, catalase, and glutathione peroxidase, while concurrently reducing oxidative biomarkers such as lipid peroxidation products and oxidized DNA bases [13]. This induction of mitohormesis—adaptation to mitochondrial ROS—contributes to improved mitochondrial resilience and longevity-associated signaling [14]. Nrf2 activation mediates much of this adaptive antioxidant response, underscoring its central role in redox-sensitive transcriptional control [10].

Mitochondrial Biogenesis and Quality Control

Exercise triggers activation of the AMPK-PGC-1 α axis alongside downstream transcription factors nuclear respiratory factors 1 and 2 (NRF1/NRF2) and mitochondrial transcription factor A (TFAM), collectively driving mitochondrial biogenesis [15]. This cascade enhances not only mitochondrial quantity but also respiratory capacity and metabolic flexibility, enabling cells to meet

augmented energetic demands [16]. In addition, exercise promotes optimal mitochondrial dynamics by improving fusion and fission balance and stimulates mitophagy, the selective autophagic removal of dysfunctional mitochondria, thereby maintaining mitochondrial quality and reducing excessive ROS production relative to ATP output [17].

Inflammation, Myokines, and Immune Function

Contracting skeletal muscle fibers release a diverse suite of cytokines and peptides known as myokines, with interleukin-6 (IL-6) being a prototypical example. Despite IL-6's dual roles, muscle-derived IL-6 acts in an anti-inflammatory capacity, initiating cascades that enhance production of anti-inflammatory cytokines such as IL-10 and IL-1 receptor antagonist (IL-1ra) during and after exercise [18]. Regular physical training attenuates baseline levels of systemic proinflammatory biomarkers, including C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF- α), thereby dampening chronic inflammation associated with ageing and metabolic disease [19,20]. These anti-inflammatory effects support immune system rejuvenation by counteracting immunosenescence, which manifests as diminished immune surveillance and increased vulnerability to infections and malignancies [21].

Telomere Dynamics and Epigenetic Regulation

Observational investigations link greater physical activity levels and superior cardiorespiratory fitness with longer leukocyte telomere lengths and decreased rates of telomere attrition, especially in individuals engaging in vigorous aerobic exercise [22,23]. Interventional studies report that structured exercise programs in older adults increase telomerase activity—the enzyme responsible for telomere elongation—and reduce telomere shortening, accompanied by declines in cellular senescence markers in immune cells and vascular tissues [24]. Mechanistically, these effects likely result from concerted reductions in oxidative stress and inflammation, as well as direct regulation of telomerase via AMPK and sirtuin signaling pathways [25,26]. Meta-analyses confirm generally positive associations between physical activity and telomere maintenance, although heterogeneity in study design, participant demographics, and telomere measurement techniques produces variable outcomes [27].

Exercise Modality and Dose Considerations

Exercise modalities engage distinct, yet overlapping molecular cascades yielding different cellular outcomes. Endurance training predominantly activates AMPK-PGC-1 α signaling to enhance mitochondrial biogenesis and function [28]. High-intensity interval training (HIIT), characterized by alternating bursts of intense activity and recovery, simultaneously engages oxidative and anabolic

pathways, potentially combining the benefits of endurance and resistance exercise [29]. Resistance training strongly stimulates mTOR-mediated anabolic pathways, promoting muscle protein synthesis and maintenance of proteostasis [30]. Acute exercise bouts impose transient metabolic and oxidative stress, followed by adaptation phases that elevate basal antioxidant capacity and mitigate inflammation when training loads are appropriately dosed [31,32]. However, excessive or poorly regulated training may overwhelm adaptive mechanisms, elevating injury risk and inflammatory responses, emphasizing the need for personalized exercise dosing strategies [31]. Current guidelines by public health authorities recommend 150–300 minutes of moderate or 75–150 minutes of vigorous aerobic exercise per week, supplemented with resistance training twice weekly—levels generally consistent with cellular aging benefits observed in the literature [33].

DISCUSSION

Synthesis and Implications

The convergent evidence from molecular, physiological, and clinical studies robustly supports the concept that regular physical exercise modulates several interconnected hallmarks of cellular aging. Activation of key signaling pathways including AMPK–PGC-1 α , sirtuins, and Nrf2 underlies enhancements in mitochondrial function, antioxidant capacity, inflammation regulation, and telomere preservation [6–10]. Notably, exercise-induced adaptations differ by

modality, suggesting integrated exercise regimens combining endurance and resistance elements may provide the broadest spectrum of anti-ageing cellular benefits.

Clinical Translation and Public Health Relevance

Exercise constitutes a highly accessible, economically feasible intervention with multisystemic benefits extending across cardiovascular, metabolic, musculoskeletal, and immune domains. Individualized exercise prescriptions should integrate endurance and resistance training components tailored to personal health status, comorbidities, functional capacity, and patient goals to optimize cellular and systemic outcomes [20,33]. Policymakers and healthcare providers can leverage mechanistic data to reinforce and refine physical activity guidelines targeting extended health span and reduced chronic disease burden.

Limitations

This review recognizes several important constraints inherent in the current literature, including a predominance of observational and short-term randomized trials limiting causal inference and longitudinal insight [31]; considerable heterogeneity in exercise interventions, biomarker types and assay methodologies that obstruct synthesis [32,33]; underrepresentation of ethnic and sex-specific cohorts limiting generalizability; and insufficient investigation of sex-specific molecular responses to exercise [33,34]. Standardization of emerging biomarkers, such as telomere length assays and epigenetic clocks, is critically needed to enhance reproducibility

and comparability across studies [26]. Interindividual variability driven by genetics, epigenetics, and the microbiome further complicates extrapolation, underscoring the imperative for personalized exercise research [11].

Implications for future practice and research

Future investigations should prioritize the development and adoption of standardized biomarker protocols, execution of adequately powered, long-term randomized controlled trials, and employment of tissue-specific, integrative multi-omic methodologies to dissect complex aging processes. Recruitment of demographically and geographically diverse cohorts will address existing generalizability gaps. Dose-response trials directly comparing distinct exercise modalities and combinations are necessary to elucidate optimal individualized exercise prescriptions. Additionally, refinement of nutrient-sensing pathway understanding, particularly mTOR's dual role in anabolic adaptation and longevity, warrants focused exploration within exercise contexts [9]. Routine assessment and clinical monitoring of cardiorespiratory fitness should become integral to personalized exercise prescription development and public health initiatives [35].

CONCLUSION

This expanded narrative review highlights the multifactorial beneficial effects of physical exercise on fundamental cellular aging mechanisms, including mitigation of oxidative stress, enhancement of mitochondrial function, suppression of chronic inflammation, and maintenance of telomere length. These cellular-

level effects converge to support the well-documented role of exercise as a potent intervention for extending healthspan and reducing age-associated disease risk.

Exercise-induced activation of AMPK, sirtuins, PGC-1 α , and Nrf2 signaling pathways reinforces cellular stress resilience, metabolic efficiency, and genomic stability. Different exercise modalities distinctly influence cellular pathways, inviting the adoption of integrated regimens for comprehensive anti-aging benefits. While current physical activity guidelines appear adequate to confer significant cellular advantages, optimal dosing strategies may require adjustment based on individual genetic, epigenetic, and health profiles.

Nonetheless, critical knowledge gaps remain—including specific molecular interactions, dose-response curves, and personalized modifiers of exercise efficacy—all meriting longitudinal, multi-modal, and diversified research efforts. Customized exercise prescriptions harnessing genetic and environmental data promise to enhance therapeutic potential.

In sum, regular physical exercise remains a cornerstone of healthspan extension strategies. Advancements in understanding the molecular nexus between exercise and aging will enable refinement of intervention paradigms to maximize functional longevity and alleviate aging-related morbidity. Clinicians and public health practitioners must emphasize exercise as a foundational nonpharmacologic modality for modulating the fundamental biology of aging.

Acknowledgment: We would like to express our sincere gratitude to Dr. George N. Nomikos for his invaluable contributions to the literature research process and for his

unique academic guidance during the preparation of this review article.

Conflict of Interest: The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Funding: The authors certify that no specific funding was received from any financial organization for this work.

Author Contributions:

All authors contributed to the conceptualization, literature review, analysis, and writing of this manuscript. All authors read and approved the final version.

ΒΙΒΛΙΟΓΡΑΦΙΑ

1. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell*. 2013;153(6):1194-1217.
2. Halliwell B, Gutteridge JMC. *Free Radicals in Biology and Medicine*. 5th ed. Oxford University Press; 2015.
3. Wallace DC. A mitochondrial bioenergetic etiology of disease. *J Clin Invest*. 2005;115(4):1013-1020.
4. Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *J Gerontol A Biol Sci Med Sci*. 2014;69 Suppl 1:S4-S9.
5. Blackburn EH, Epel ES, Lin J. Human telomere biology: a contributory and interactive factor in aging, disease risks, and protection. *Science*. 2015;350(6265):1193-1198.
6. Hardie DG. AMP-activated/SNF1 protein kinases: conserved guardians of cellular energy. *Nat Rev Mol Cell Biol*. 2007;8(10):774-785.
7. Jäger S, Handschin C, St Pierre J, Spiegelman BM. AMP-activated protein kinase (AMPK) action in skeletal muscle via direct phosphorylation of PGC-1 α . *Proc Natl Acad Sci USA*. 2007;104(29):12017-12022.
8. Cantó C, Auwerx J. PGC-1 α , SIRT1 and AMPK, an energy sensing network that controls energy expenditure. *Curr Opin Lipidol*. 2009;20(2):98-105.
9. Saxton RA, Sabatini DM. mTOR signaling in growth, metabolism, and disease. *Cell*. 2017;169(2):361-371.
10. Muthusamy VR, Kannan S, Sadhaasivam K, et al. Acute exercise stress activates Nrf2/ARE signaling and promotes antioxidant mechanisms in the myocardium. *Free Radic Biol Med*. 2012;52(2):366-376.
11. Ristow M, Schmeisser K. Mitohormesis: promoting health and lifespan by increased levels of reactive oxygen species. *Dose-Response*. 2014;12(2):288-341.
12. Radak Z, Chung HY, Goto S. Systemic adaptation to oxidative challenge induced by regular exercise. *Free Radic Biol Med*. 2008;44(2):153-159.
13. Powers SK, Jackson MJ. Exercise-induced oxidative stress: cellular mechanisms and impact on muscle force production. *Physiol Rev*. 2008;88(4):1243-1276.
14. Scarpulla RC. Transcriptional paradigms in mammalian mitochondrial biogenesis and function. *Physiol Rev*. 2011;88(2):611-638.

15. Holloszy JO. Mitochondrial biogenesis and metabolic memory. *J Appl Physiol* (1985). 2008;104(3):475-481.
16. Drake JC, Wilson RJ, Yan Z. Molecular mechanisms for mitochondrial adaptation to exercise training in skeletal muscle. *FASEB J*. 2016;30(1):13-22.
17. Menshikova EV, Ritov VB, He J, et al. Effect of exercise on mitochondrial content and function in aging human skeletal muscle. *J Gerontol A Biol Sci Med Sci*. 2006;61(6):534-540.
18. Pedersen BK, Febbraio MA. Muscle as an endocrine organ: focusing on muscle-derived interleukin-6. *Physiol Rev*. 2008;88(4):1379-1406.
19. Beavers KM, Brinkley TE, Nicklas BJ. Effect of exercise training on chronic inflammation. *Clin Chim Acta*. 2010;411(11-12):785-793.
20. Pedersen BK, Saltin B. Exercise as medicine—evidence for prescribing exercise as therapy in 26 different chronic diseases. *Scand J Med Sci Sports*. 2015;25 Suppl 3:1-72.
21. Simpson RJ, Kunz H, Agha N, Graff R. Exercise and the regulation of immune functions. *Prog Mol Biol Transl Sci*. 2012;135:355-380.
22. Ludlow AT, Zimmerman JB, Witkowski S, et al. Relationship between physical activity level, telomere length, and telomerase activity. *Med Sci Sports Exerc*. 2008;40(10):1764-1771.
23. Tucker LA. Physical activity and telomere length in adults: a systematic review. *J Phys Act Health*. 2017;14(2):195-206.
24. Werner C, Fürster T, Widmann T, et al. Physical exercise prevents cellular senescence in circulating leukocytes and in the vessel wall. *Circulation*. 2009;120(24):2438-2447.
25. Opresko PL, Shay JW. Telomere-associated aging disorders. *Ageing Res Rev*. 2017;33:52-66.
26. Montpetit AJ, Alhareeri AA, Montpetit M, et al. Telomere length: a review of methods for measurement. *Nurs Res*. 2014;63(4):289-299.
27. Mundstock E, Zatti H, Louzada FM, et al. Effects of physical activity on telomere length: systematic review and meta-analysis. *Ageing Res Rev*. 2015;22:72-80.
28. Naci H, Salcher-Konrad M, Dias S, et al. How does exercise treatment compare with antihypertensive medications? A network meta-analysis of randomized controlled trials. *Br J Sports Med*. 2019;53(14):859-869.
29. Opresko PL, Shay JW. Telomere maintenance and disease. *EMBO J*. 2017;36(11):1227-1248.
30. Phillips SM, Tipton KD, Aarsland A, Wolf SE, Wolfe RR. Mixed muscle protein synthesis and breakdown after resistance exercise in humans. *Am J Physiol Endocrinol Metab*. 1997;273(1 Pt 1):E99-E107.
31. Piercy KL, Troiano RP, Ballard RM, et al. The physical activity guidelines for Americans. *JAMA*. 2018;320(19):2020-2028.

32. Powers SK, Deminice R, Ozdemir M, et al. Exercise-induced oxidative stress: friend or foe? *J Sport Health Sci.* 2020;9(5):415-425.
33. Radak Z, Chung HY, Koltai E, Taylor AW, Goto S. Exercise, oxidative stress and hormesis. *Ageing Res Rev.* 2008;7(1):34-42. Radak Z, Zhao Z, Koltai E, Ohno H, Atalay M. Oxygen consumption and usage during physical exercise: the balance between oxidative stress and ROS-dependent adaptive signaling. *Antioxid Redox Signal.* 2013;18(10):1208-1246.
34. Ross R, Blair SN, Arena R, et al. Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign. *Circulation.* 2019;134(24):e653-e699.