

Journal Pre-proof

Redox resilience in skeletal muscle aging: cellular adaptations and exercise-mediated homeostasis

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PII: S0891-5849(26)01214-1

DOI: <https://doi.org/10.1016/j.freeradbiomed.2026.10.023>

Reference: FRB 18130

To appear in: *Free Radical Biology and Medicine*

Received Date: 11 August 2026

Revised Date: 1 October 2026

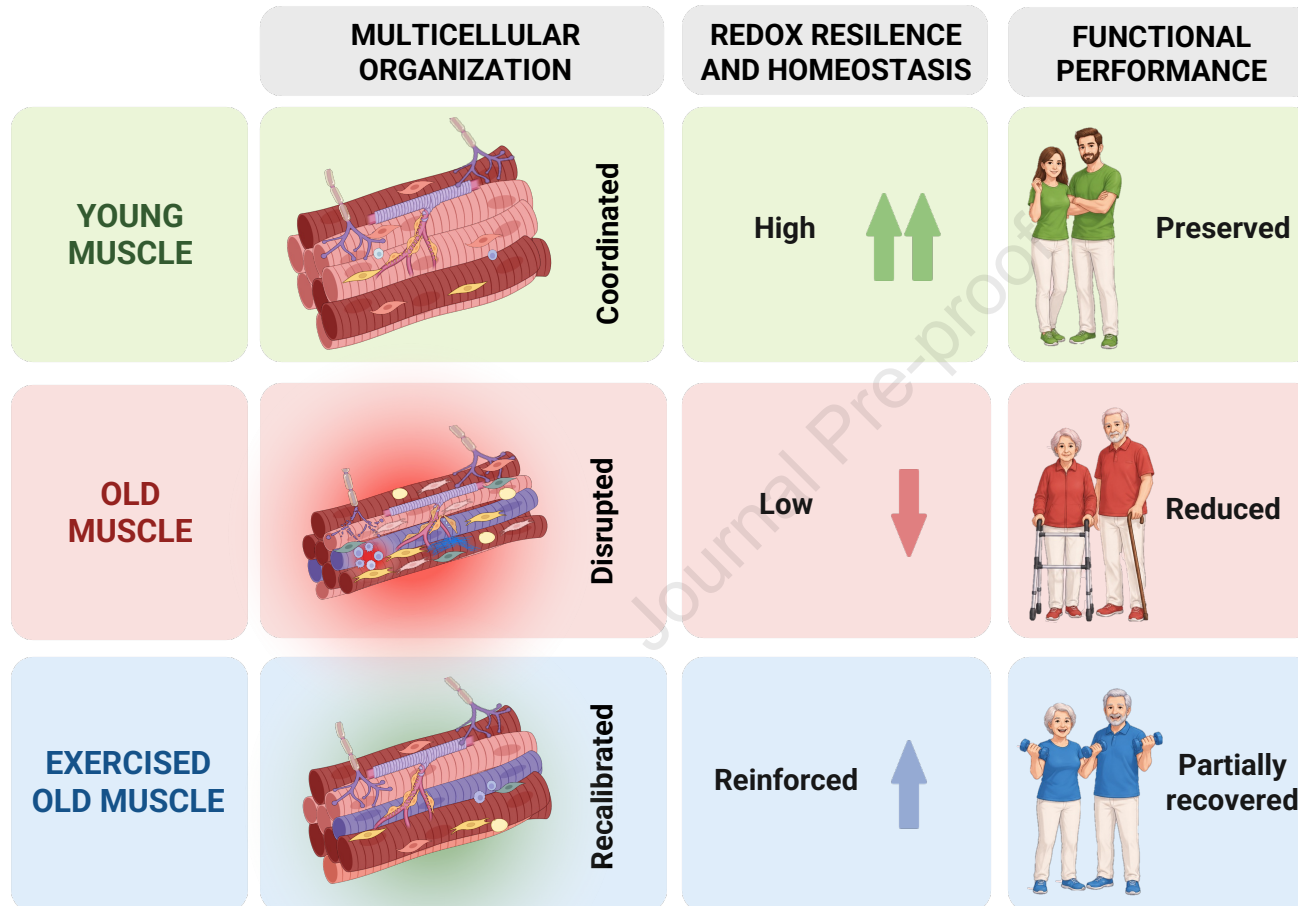
Accepted Date: 10 October 2026

Please cite this article as: E. Tamayo-Torres, M. Martinez-Canton, S. Soto-Rodriguez, A. Gorgori-Gonzalez, J. Carretero, J.I. Cervera-Miguel, O. Laosa, L. Rodriguez-Mañas, M.C. Gomez-Cabrera, Redox resilience in skeletal muscle aging: cellular adaptations and exercise-mediated homeostasis, *Free Radical Biology and Medicine*, <https://doi.org/10.1016/j.freeradbiomed.2026.10.023>.

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Manuscript submitted to Free Radical Biology and Medicine**Review**

Title 1: Redox resilience in skeletal muscle aging: cellular adaptations and exercise-mediated homeostasis

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Abstract

Aging progressively impairs skeletal muscle function, leading to sarcopenia, frailty, and loss of independence. Although oxidative stress has long been considered a central driver of muscle aging, increasing evidence indicates that reactive oxygen species (ROS) also serve essential signaling functions that coordinate mitochondrial remodeling, proteostasis, metabolism, and tissue repair. Consequently, age-related muscle dysfunction is increasingly understood as reflecting impaired adaptive redox signaling rather than excessive oxidant production alone. In this review, we propose the concept of redox resilience as an integrative framework describing the capacity of skeletal muscle to preserve structural integrity and functional performance through the dynamic regulation of oxidant production, antioxidant defenses, and redox-

sensitive signaling in response to physiological challenges. We discuss how aging disrupts this resilience through impaired redox-sensitive signaling, including the attenuation of exercise-induced Nrf-2 activation, together with alterations in the multicellular organization of skeletal muscle.

Recent advances in single-cell and single-nucleus transcriptomics have revealed that muscle aging involves profound remodeling of specialized myonuclear populations, stromal cells, immune cells, and intercellular communication networks, highlighting the multicellular complexity of skeletal muscle aging and providing a framework to investigate how redox-dependent processes may interact with tissue-wide signaling networks.

We further examine how regular physical exercise reinforces redox resilience by promoting transient ROS-mediated signaling through NADPH oxidases, activation of Nrf-2 and PGC-1 α -dependent pathways, mitochondrial quality control, and metabolic remodeling. These adaptations enhance the capacity of skeletal muscle to respond to physiological stress while preserving tissue homeostasis. Finally, we discuss future perspectives for targeting adaptive redox networks to promote healthy muscle aging and propose that restoring redox resilience may preserve physiological ROS signaling while strengthening endogenous antioxidant responses and limiting excessive oxidative damage, thereby contributing to the maintenance of muscle function and health span.

1. Introduction

Skeletal muscle is one of the most plastic tissues in the human body, continuously adapting to fluctuations in mechanical load, metabolic demand, nutrient availability, and environmental stressors [1]. Throughout life, this adaptability preserves locomotion, metabolic homeostasis, and whole-body health. With advancing age, however, the capacity to maintain these adaptive responses progressively declines, resulting in impaired muscle regeneration, reduced functional performance, and an increased susceptibility to frailty and sarcopenia [2, 3]. Rather than being driven by a single molecular mechanism, skeletal muscle aging emerges from the progressive disruption of interconnected regulatory networks that coordinate cellular metabolism, tissue remodeling, and stress adaptation [4].

Among these regulatory systems, redox signaling has evolved from being considered merely a source of oxidative damage to becoming recognized as a fundamental component of cellular communication [5]. Reactive oxygen species (ROS) are now understood as context-dependent signaling molecules that coordinate metabolic remodeling, gene expression, and protein turnover.

Their signaling capacity depends on their transient production and precise subcellular compartmentalization, which confer specificity to redox-dependent signaling events. Thus, their biological effects are determined not only by their abundance but also by their temporal regulation, cellular origin, and interaction with endogenous antioxidant systems [6, 7].

This concept has shifted the classical view of oxidative stress toward a more dynamic model based on adaptive homeostasis [8]. Moderate and transient increases in ROS, such as those generated during muscle contractions, initiate signaling cascades that enhance mitochondrial biogenesis, antioxidant defenses, and tissue remodeling [9-11]. On the contrary, persistent or excessive oxidant exposure overwhelms adaptive mechanisms, leading to oxidative distress, chronic inflammation, and progressive functional decline [12]. The biological outcome of ROS generation is determined by the capacity of skeletal muscle to maintain a finely regulated redox balance rather than by oxidant production alone. Within this framework, aging is viewed not simply as the accumulation of molecular damage, but as the progressive decline in the capacity of adaptive mechanisms to restore and maintain homeostasis [6] [13].

Biological resilience has recently emerged as a central concept in aging research. Ferrucci and colleagues define resilience as the ensemble of biological mechanisms that preserve the identity, integrity, and autonomy of an organism in response to internal and external perturbations [14]. Extending this concept to skeletal muscle, we use the term redox resilience to describe the ability of muscle tissue to preserve structural integrity and functional performance through coordinated adaptive redox signaling despite the cumulative physiological challenges imposed by aging. Within the framework proposed here, mitochondrial dysfunction, impaired proteostasis, metabolic remodeling, disrupted intercellular communication, and chronic low-grade

inflammation can be viewed as interconnected processes that collectively contribute to the progressive loss of adaptive redox homeostasis during muscle aging [15].

Recent advances in single-cell and single-nucleus transcriptomics have transformed our understanding of skeletal muscle biology by revealing an extraordinary degree of cellular and nuclear heterogeneity [2]. Aging disrupts this multicellular ecosystem, promoting fiber type-specific vulnerabilities, inflammatory remodeling, fibrosis, and impaired regenerative potential [2]. These findings provide an opportunity to reinterpret redox regulation within the context of tissue-wide cellular communication instead of considering ROS signaling exclusively at the level of individual myofibers.

Among the interventions currently available, regular physical exercise, including endurance and resistance training, remains one of the most effective strategies for preserving skeletal muscle function throughout aging [16, 17].

Beyond improving muscle strength and cardiorespiratory capacity, exercise induces highly coordinated redox-dependent adaptations [18, 19]. These responses illustrate that the beneficial effects of exercise arise not from suppressing oxidant production but from enhancing the adaptive capacity of skeletal muscle to respond appropriately to oxidative challenges [9, 20].

In this review, we examine current evidence supporting redox resilience as an integrative framework for understanding skeletal muscle aging. We discuss how age-associated alterations in cellular heterogeneity and redox signaling contribute to sarcopenia and frailty, and we highlight the molecular mechanisms through which exercise promotes adaptive homeostasis, ultimately preserving muscle function and extending health span.

2. Loss of redox resilience during skeletal muscle aging

Skeletal muscle aging is characterized by a progressive reduction in the capacity to preserve tissue homeostasis under physiological stress. While chronological aging is inevitably accompanied by cumulative molecular damage, the functional deterioration of skeletal muscle largely reflects the inability to maintain effective adaptive responses rather than the simple accumulation of cellular lesions [21]. This progressive loss of resilience underlies the development of sarcopenia, a syndrome

defined by the decline in muscle mass, strength, and physical performance, which substantially increases the risk of frailty, disability, and loss of independence [3, 22].

The age-associated deterioration of skeletal muscle is accompanied by profound structural remodeling.

Muscle fibers progressively reduce their cross-sectional area, while age-related motoneuron loss leads to denervation and motor unit remodeling. Although compensatory reinnervation can partially preserve neuromuscular function, this capacity becomes increasingly impaired with advancing age, contributing to the preferential denervation and atrophy of fast type fibers [2, 23]. These structural alterations are paralleled by functional impairments that become evident decades before advanced age. Muscle power begins to decline during early adulthood, followed by a progressive reduction in maximal strength after the fourth decade of life, compromising mobility, postural control, and the capacity to perform activities of daily living [24, 25] (Figure 1).

Although sarcopenia has traditionally been interpreted as a consequence of muscle atrophy, increasing evidence indicates that it represents a systems-level disorder involving coordinated alterations in metabolism, cellular communication, inflammation, and regenerative capacity [26, 27]. Among the multiple biological processes involved, mitochondrial dysfunction and disturbances in redox regulation consistently emerge as central drivers of muscle aging [28].

These mechanisms are closely interconnected. Impaired mitochondrial quality control can increase oxidant production, while disrupted redox signaling can further compromise mitochondrial function, proteostasis, and tissue remodeling [10, 28].

An important consideration is whether sarcopenia represents a distinct age-related muscle condition or largely reflects the consequences of physical inactivity. Although physical inactivity can reproduce several features of muscle aging and is a major contributor to sarcopenia, the two should not be considered synonymous. Sarcopenia is a multifactorial condition characterized by the progressive loss of muscle strength, mass, and physical performance, in which physical inactivity interacts with age-related biological changes affecting neuromuscular function, metabolism, inflammation, and regenerative capacity. Inactivity may therefore accelerate this

trajectory, whereas regular exercise can counteract many of these changes and preserve muscle homeostasis [29].

The contemporary view of redox biology challenges the traditional interpretation of ROS exclusively as toxic metabolic by-products. ROS are now recognized as indispensable signaling molecules whose biological activity depends on concentration, intracellular localization, chemical identity, and temporal dynamics [30, 31]. Under physiological conditions, localized ROS production regulates numerous adaptive processes, including mitochondrial biogenesis, antioxidant defense, autophagy, protein turnover, and even glucose uptake [10]. Consequently, the biological consequences of ROS are determined by the integrity of redox signaling networks rather than by oxidant production alone.

This dual nature of ROS is captured by the concepts of oxidative eustress and oxidative distress [6]. Oxidative eustress refers to the transient and spatially controlled oxidant signals that sustain physiological adaptations, whereas oxidative distress results from persistent or excessive oxidant exposure that disrupts redox signaling and promotes molecular damage. Importantly, these conditions should not be considered opposite states but rather different outcomes along a continuum determined by the adaptive capacity of the tissue. Healthy skeletal muscle continuously operates within this dynamic equilibrium, whereas aging progressively shifts the balance toward maladaptive responses as adaptive homeostasis deteriorates [21].

One of the clearest examples of oxidative eustress is physical exercise. Muscle contraction transiently increases ROS production, activating redox-sensitive signaling pathways that promote coordinated metabolic and structural adaptations [10, 11, 32]. By contrast, chronic oxidant accumulation, persistent inflammation, and impaired antioxidant regulation progressively shift redox signaling toward oxidative distress, contributing to mitochondrial dysfunction, impaired proteostasis, fiber atrophy, and reduced regenerative capacity [2, 12] (Figure 1).

The transition from adaptive redox signaling to maladaptive oxidative stress represents a critical biological event. Understanding the mechanisms responsible for this loss of resilience provides the conceptual basis for interpreting how cellular

heterogeneity influences muscle aging and why exercise remains the most effective intervention for preserving skeletal muscle homeostasis.

3. Cellular heterogeneity shapes redox resilience in aging skeletal muscle

Skeletal muscle has traditionally been viewed as a relatively homogeneous tissue composed predominantly of contractile myofibers. Recent advances in single-cell and single-nucleus transcriptomics have challenged this concept, revealing skeletal muscle as a highly organized multicellular ecosystem in which specialized cell populations cooperate to preserve tissue homeostasis throughout life [2, 33]. This cellular complexity provides the structural basis for the remarkable adaptability of skeletal muscle but also explains why aging affects different cellular compartments unequally.

Although multinucleated myofibers account for most of the muscle volume, their maintenance depends on continuous interactions with an extensive network of resident mononuclear cells. Muscle stem cells, fibro-adipogenic progenitors, fibroblast-like stromal cells, adipocytes, smooth muscle cells, endothelial cells, pericytes, Schwann cells, motoneurons, macrophages, and lymphocyte populations collectively regulate regeneration, extracellular matrix remodeling, vascular homeostasis, metabolic communication, and inflammatory responses [2, 33]. Rather than functioning independently, these populations establish coordinated signaling networks that allow skeletal muscle to adapt efficiently to physiological stress.

Aging progressively disrupts this multicellular organization. Regenerative cell populations decline, whereas fibro-adipogenic progenitors, inflammatory myeloid cells, and fibrogenic stromal populations become increasingly prominent [2]. Consequently, the tissue microenvironment gradually shifts from one that favors regeneration and metabolic flexibility toward one characterized by chronic low-grade inflammation, extracellular matrix deposition, and impaired repair capacity [2]. These alterations compromise tissue regeneration and remodel the intercellular communication networks required to maintain skeletal muscle homeostasis (Figure 1).

The multinucleated compartment also undergoes extensive remodeling during aging. The myonuclei display a high degree of transcriptional specialization that reflects

their anatomical location, metabolic profile, and functional role within the myofiber. Distinct myonuclear subpopulations occupy specialized domains, including the neuromuscular and myotendinous junctions, while others are characterized by transcriptional programs linked to stress responses, denervation, or metabolic regulation. This functional compartmentalization indicates that individual myonuclei coordinate specific biological processes [2, 34].

Fiber type-specific remodeling is particularly relevant for understanding age-associated loss of redox resilience. Type II glycolytic fibers exhibit greater susceptibility to aging than oxidative type I fibers, undergoing preferential atrophy. The progressive decrease of ecto-NOX disulfide-thiol exchanger 1 (ENOX1)-positive myonuclear populations during aging, which are enriched in fast-contracting glycolytic fibers, is particularly interesting because ENOX1 is a plasma membrane-associated transmembrane redox enzyme involved in extracellular electron transfer. This observation suggests that aging selectively impairs nuclear programs involved in maintaining redox regulation [2]. Moreover, single-nucleus trajectory analyses have shown the emergence of stress-associated myonuclear populations together with progressive induction of oxidative stress response genes, including *NFE2L2*, *SOD2*, and *AP-1* family members (*FOS*, *JUN*), as well as inflammatory and proteostatic pathways, indicating that aging elicits a coordinated compensatory transcriptional response to increasing cellular stress rather than a passive accumulation of oxidative damage [2]. However, complementary functional studies indicate that this apparent activation of stress-responsive transcriptional programs does not necessarily translate into preserved adaptive redox signaling. Instead, aging is associated with a decline in skeletal muscle NOX4 abundance, impaired NOX4-dependent H₂O₂ signaling, reduced Nrf-2 stabilization and nuclear activity, diminished expression of canonical antioxidant enzymes, and increased oxidative protein damage, ultimately compromising the adaptive homeostatic responses normally induced by exercise [10]. Together, these findings suggest that although aging muscle attempts to mount compensatory redox responses at the transcriptional level, the progressive deterioration of the NOX4-Nrf-2 signaling axis limits the effectiveness of these adaptive programs, thereby contributing to the loss of redox resilience [10].

Metabolic remodeling accompanies these transcriptional changes. Here, metabolic remodeling refers to age-associated changes in the regulation and utilization of metabolic pathways, including oxidative phosphorylation, glycolytic metabolism, and pathways supporting cellular redox homeostasis. Aging type I fibers display reduced expression of genes involved in oxidative phosphorylation together with partial activation of glycolytic pathways, whereas type II fibers exhibit enhanced glycogen depletion, increased protein catabolism, and greater vulnerability to degeneration [2]. These divergent responses illustrate that skeletal muscle aging cannot be interpreted as a uniform decline but rather as the consequence of fiber type-specific adaptive programs with distinct capacities to maintain metabolic and redox homeostasis.

Another important aspect emerging from recent transcriptomic studies is the extensive remodeling of intercellular communication. Ligand-receptor interactions between myogenic and non-myogenic compartments increase markedly with aging, yet this expansion does not enhance tissue adaptation. Instead, signaling pathways involving IL-6, TGF- β , activins, and other inflammatory mediators progressively dominate the communication network, reinforcing fibrosis, chronic inflammation, and stem cell dysfunction while destabilizing regenerative programs [2]. Consequently, the decline in muscle function reflects not only intrinsic alterations within individual cells but also the progressive failure of coordinated communication across the entire tissue.

Within this multicellular framework, redox regulation should be considered an emergent property of tissue organization rather than the product of isolated intracellular reactions. ROS generated in one cellular compartment may influence neighboring cell populations through redox-sensitive mechanisms, contributing to intercellular communication across the tissue [35]. The preservation of redox resilience may therefore depend on maintaining the functional integrity of this cellular ecosystem rather than simply regulating oxidant production within individual myofibers.

This systems-level perspective provides a new framework for understanding skeletal muscle aging. The progressive loss of specialized cellular populations, disruption of intercellular communication, and decline in nuclear specialization collectively reduce

the adaptive capacity of the tissue. These changes create the biological context in which redox signaling gradually shifts from promoting physiological adaptation to driving maladaptive remodeling, thereby increasing susceptibility to sarcopenia and frailty.

4. Exercise reinforces redox resilience through adaptive molecular networks

Physical exercise represents the most effective non-pharmacological intervention for preserving skeletal muscle function throughout aging [3, 16, 17]. Although traditionally viewed to improve strength, endurance, or body composition, its biological effects extend far beyond mechanical adaptations. Exercise acts as a systemic regulator of cellular homeostasis, eliciting coordinated molecular responses that improve tissue remodeling.

Exercise constitutes a complex physiological challenge that simultaneously exposes skeletal muscle to multiple forms of stress [36]. Repeated muscle contractions generate mechanical strain, metabolic perturbations associated with high ATP turnover, fluctuations in calcium homeostasis, transient ischemia and reperfusion, local increases in temperature, and the production of reactive oxygen and nitrogen species. Rather than acting independently, these stimuli converge to activate highly coordinated signaling networks that promote cellular adaptation. Within this integrated stress response, oxidative stress occupies a unique position because ROS not only arise because of the increased metabolic demand but also function as essential second messengers that coordinate some of the adaptive responses elicited by exercise. Rather than suppressing ROS production, exercise repeatedly exposes skeletal muscle to transient oxidative challenges that strengthen its capacity to maintain redox balance during subsequent physiological stress (Figure 2).

This adaptive response exemplifies the principle of hormesis, whereby moderate biological stress induces protective mechanisms that increase tissue resilience [5, 37]. In the context of exercise, transient increases in ROS act as hormetic signals that activate redox-sensitive pathways and stimulate endogenous antioxidant defenses, mitochondrial remodeling, and cellular quality-control mechanisms. Repeated exposure to these transient redox challenges enhances the capacity of skeletal muscle

to respond to subsequent physiological stress, whereas excessive or sustained ROS production may overwhelm these adaptive mechanisms and promote oxidative damage. Consequently, the beneficial effects of exercise arise not despite ROS production but because these transient oxidant signals coordinate adaptive remodeling [38].

The molecular origin of these signals has been substantially redefined over the past decade. Although mitochondria contribute to basal oxidant production, accumulating evidence indicates that NADPH oxidases are important sources of exercise-induced ROS signaling [38]. NOX2 becomes rapidly activated during muscle contraction, promoting glucose uptake and metabolic adaptation, whereas NOX4 contributes to mitochondrial remodeling and long-term maintenance of oxidative metabolism through Nrf-2-dependent pathways [10, 39]. Rather than functioning as pathological oxidant sources, these enzymes establish localized redox microdomains that regulate intracellular signaling while preserving molecular specificity. Xanthine oxidoreductase, particularly its oxidase form (XO), also contributes to the transient ROS burst generated during muscle contraction, primarily within the extracellular compartment and vascular endothelium. Importantly, inhibition of XO-derived ROS with allopurinol attenuates exercise-induced activation of MAPK and NF- κ B signaling and prevents the upregulation of adaptive genes such as MnSOD, eNOS and iNOS, demonstrating that XO-derived oxidants participate in the molecular programs underlying exercise adaptation rather than simply promoting oxidative damage [40-42].

Consistent with this concept, extracellular superoxide generated by XO during muscle contractions has been shown to support normal force production, further emphasizing that localized ROS production contributes to physiological muscle function [43].

Thus, the biological effects of ROS depend not only on their abundance but also on their source and subcellular localization, as distinct ROS-generating systems produce spatially confined redox signals that engage specific molecular targets and downstream adaptive responses.

Activation of redox-sensitive transcription factors constitutes a central component of this adaptive response. Exercise-induced ROS stimulate Nrf-2 signaling, increasing the expression of endogenous antioxidant enzymes including superoxide dismutase, catalase, glutathione peroxidase, heme oxygenase-1, and NAD(P)H quinone oxidoreductase-1, thereby strengthening intrinsic antioxidant defenses without abolishing physiological oxidant signaling [38, 44]. Simultaneously, PGC-1 α coordinates mitochondrial biogenesis and oxidative metabolism, improving respiratory efficiency while reducing electron leakage and enhancing ATP production [45, 46]. Together, these pathways reinforce adaptive homeostasis rather than simply increasing antioxidant capacity.

An equally important component of exercise-induced redox resilience involves metabolic remodeling. The pentose phosphate pathway has emerged as a critical interface between energy metabolism and antioxidant defense through its capacity to generate NADPH required for glutathione recycling and multiple reductive biosynthetic reactions. The rate-limiting enzyme glucose-6-phosphate dehydrogenase (G6PD) is consistently upregulated following acute and chronic exercise, supporting tissue repair, mitochondrial maintenance, and antioxidant regeneration [47-49]. These observations highlight that exercise modifies not only signaling pathways but also the metabolic infrastructure necessary to sustain long-term redox homeostasis.

The preservation of redox resilience also depends on efficient mitochondrial quality control. Repeated exercise stimulates mitochondrial turnover through coordinated activation of biogenesis, mitophagy, and mitochondrial dynamics, preventing the accumulation of dysfunctional organelles that otherwise become major contributors to chronic oxidative stress during aging. Improvements in mitochondrial efficiency are accompanied by enhanced proteostasis, heat shock protein expression, and autophagic activity, collectively maintaining cellular integrity under repeated physiological stress [50, 51].

Importantly, these adaptations differ according to exercise modality. Endurance training predominantly enhances oxidative metabolism, mitochondrial density, and aerobic efficiency through sustained activation of mitochondrial signaling pathways.

Resistance exercise, in contrast, preferentially stimulates mechanosensitive pathways involved in muscle hypertrophy, cytosolic antioxidant defenses, and regenerative remodeling. Concurrent training integrates many of these adaptations, providing complementary improvements in metabolic health, muscle function, and vascular physiology [45, 52]. Despite these modality-specific differences, all forms of regular exercise share a common biological outcome: the reinforcement of adaptive redox signaling and the preservation of tissue homeostasis.

One of the strongest arguments supporting this interpretation derives from studies evaluating antioxidant supplementation during exercise training. Pharmacological attenuation of ROS generation through vitamins C and E consistently blunts many exercise-induced adaptations, including mitochondrial biogenesis, improvements in insulin sensitivity, and endogenous antioxidant responses [19, 53-55]. These findings demonstrate that physiological oxidant signaling is not an undesirable by-product of exercise but an essential mediator of adaptation. Interfering with these signals may therefore compromise the very mechanisms responsible for maintaining muscle resilience throughout aging [10].

Collectively, current evidence indicates that exercise does not simply reduce oxidative stress. Instead, it repeatedly recalibrates the molecular networks responsible for maintaining adaptive redox homeostasis. By coordinating mitochondrial remodeling, metabolic flexibility, endogenous antioxidant defenses, and intercellular communication, regular physical activity preserves the capacity of skeletal muscle to respond effectively to physiological challenges. In this context, exercise should be regarded as the primary biological stimulus capable of reinforcing redox resilience and delaying the functional decline associated with aging.

5. Future perspectives: targeting redox resilience for healthy muscle aging

Despite remarkable advances in our understanding of skeletal muscle aging, many fundamental questions remain unresolved. Recent technological advances, including single-cell and single-nucleus transcriptomics, spatial transcriptomics, high-dimensional proteomics, and metabolomics, provide unprecedented opportunities to investigate how individual cellular populations contribute to tissue adaptation during

aging. Future studies integrating these technologies with functional analyses of redox signaling will be essential for defining the cellular networks that preserve tissue resilience or drive susceptibility to age-related decline. In particular, understanding how ROS signaling is spatially compartmentalized, how distinct oxidant sources interact, and how these signals are integrated across multiple cell populations represents one of the major challenges for redox biology in the coming years. Such knowledge will help explain why physiological oxidant signaling promotes adaptation whereas chronic dysregulation accelerates degeneration.

Exercise remains the strongest physiological stimulus capable of promoting integrated adaptation. However, significant questions remain regarding how exercise prescriptions should be optimized according to biological age, sex, genetic background, disease status, and individual responsiveness. Future research should move beyond comparing exercise modalities and instead identify the molecular signatures that define successful adaptation. Such an approach may facilitate the development of precision exercise interventions capable of maximizing redox resilience while minimizing functional decline in diverse populations.

Beyond exercise, several emerging therapeutic strategies warrant further investigation.

Pharmacological and nutraceutical approaches targeting specific components of redox resilience may complement exercise-based interventions by reinforcing endogenous adaptive mechanisms. Compounds such as urolithin A, which promotes mitochondrial quality control; sulforaphane, an activator of Nrf-2 signaling; resveratrol, which modulates SIRT1/PGC-1 α -related pathways; and NAD⁺ precursors have been investigated for their potential to improve mitochondrial and metabolic homeostasis during aging [56]. Additional strategies include pharmacological activation of redox-sensitive transcription factors, modulation of NADPH oxidase signaling, enhancement of mitochondrial quality control, and targeting metabolic pathways that support redox homeostasis, such as the pentose phosphate pathway [57].

However, these interventions target only selected components of the adaptive response and are unlikely to reproduce the coordinated, multisystem adaptations

elicited by physical exercise. Thus, rather than representing true “exercise mimetics,” they may be better considered complementary strategies, particularly when the capacity to exercise is limited. Nevertheless, these approaches should be designed to preserve physiological redox signaling rather than indiscriminately suppress oxidant production, recognizing that adaptive ROS signaling is indispensable for tissue remodeling and long-term muscle function [57].

In conclusion, skeletal muscle aging should be understood not simply as the accumulation of oxidative damage but as the progressive erosion of adaptive capacity across an increasingly complex cellular ecosystem. The integration of redox biology, cellular heterogeneity, exercise physiology, and systems biology offers a new perspective for understanding the mechanisms underlying sarcopenia and frailty. We propose that redox resilience provides a unifying conceptual framework linking these processes, placing adaptive homeostasis at the center of healthy muscle aging. Future studies designed within this framework may facilitate the development of more effective strategies to preserve muscle function, extend health span, and improve quality of life in the aging population.

Disclaimer

This work was supported by the following grants: Instituto de Salud Carlos III CB16/10/00435 (CIBERFES); (PID2022-142470OB-I00) from the Spanish Ministry of Innovation and Science; PROMETEO (CIPROM/2022/56) de "Consellería de Educación, Universidades, y Empleo de la Generalitat Valenciana"; EU Funded H2020- DIABFRAIL-LATAM (Ref: 825546); Red EXERNET-RED DE EJERCICIO FISICO Y SALUD (RED2022-134800-T) Agencia Estatal de Investigacion (Ministerio de Ciencias e Innovación). Part of the equipment used in this work has been funded by Generalitat Valenciana and co-financed with FEDER funds (OP FEDER of Comunitat Valenciana 2014-2020). M. M-C is a beneficiary of the APOSTD postdoctoral grant (Ref. CIAPOS/2024/038), funded by the Generalitat Valenciana and the European Social Fund Plus (ESF+). S.S-R (PREP2022-000563) and A.G-G (FPU22/02539) received a predoctoral grant financed by the Spanish Ministry of Universities.

The authors used AI language model developed by OpenAI to improve the clarity and readability of parts of the manuscript. The authors reviewed and edited the content and take full responsibility for the final version of the manuscript.

Authors' contributions

E.T-T, M.M-C, S.S-R, A.G-G, J.C., J.I.C-M, O.L. writing and review; L. R-M and M.C.G-C writing-review & editing

Declaration of interests

The authors declare no competing interests.

FIGURE LEGENDS

Figure 1. Multicellular remodeling and redox resilience in young and old skeletal muscle. Role of exercise.

Young skeletal muscle maintains coordinated interactions within a multicellular ecosystem comprising myofibers, muscle stem cells (MuSCs), stromal cells (fibroblast-like cells, fibro-adipogenic progenitors (FAPs), and adipocytes), vascular cells (smooth muscle cells (SMCs), endothelial cells (ECs), and pericytes), neural cells (Schwann cells and motor neurons), and immune cells (lymphocytes, macrophages, and other myeloid cells). Aging disrupts intercellular communication and regenerative coordination, leading to preferential type II myofiber atrophy, chronic low-grade inflammation, extracellular matrix deposition, fibrosis, denervation and degenerative remodeling. These alterations reduce adaptive capacity and shift redox regulation toward oxidative distress, resulting in a loss of redox resilience. Exercise partially recalibrates these signaling networks, improving multicellular coordination, tissue remodeling, and regenerative capacity, thereby reinforcing redox resilience and preserving muscle function. Created with BioRender.com.

Figure 2. Exercise-induced hormetic redox signaling reinforces skeletal muscle redox resilience.

Exercise-induced mechanical strain, metabolic perturbation, Ca^{2+} signaling, and transient hypoxia/reperfusion stimulate localized oxidant production by the NADPH oxidases NOX2 and NOX4, xanthine oxidase (XO), and mitochondria. These transient oxidant signals (oxidative eustress) activate coordinated adaptive molecular pathways involving Nrf-2-dependent antioxidant defenses, PGC-1 α -mediated mitochondrial biogenesis and oxidative metabolism, G6PD-dependent pentose phosphate pathway activity and NADPH generation, MAPK/NF- κ B signaling, proteostasis, and mitochondrial quality control. These responses reinforce redox resilience and contribute to delaying age-related functional decline. Created with BioRender.com.

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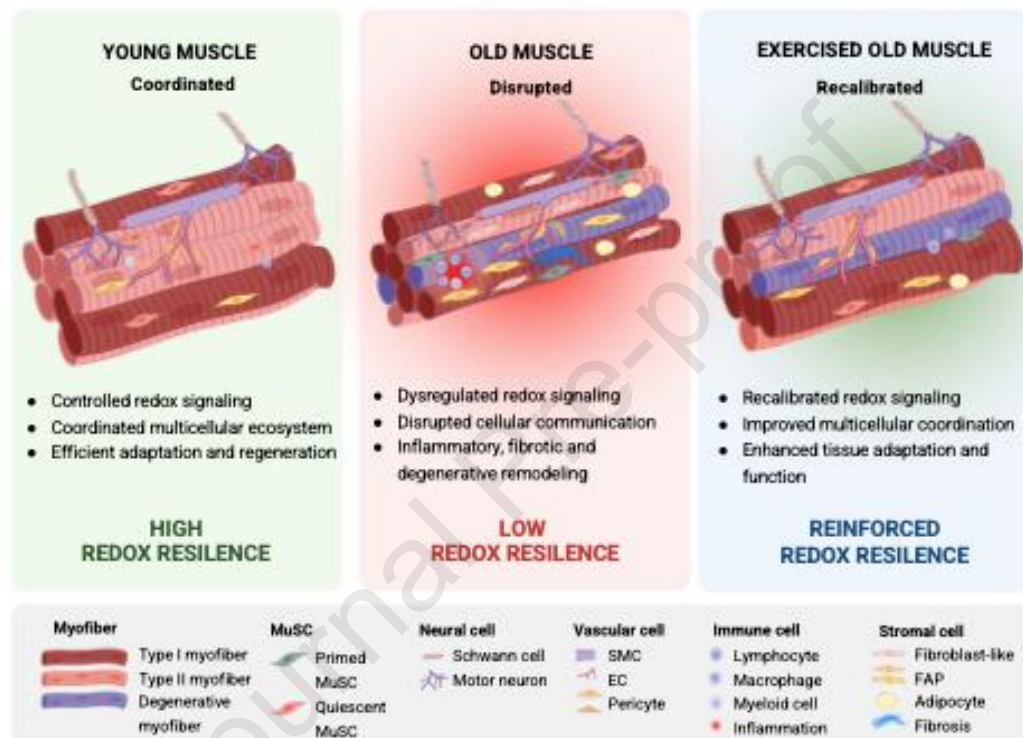
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687 FIGURE 1.



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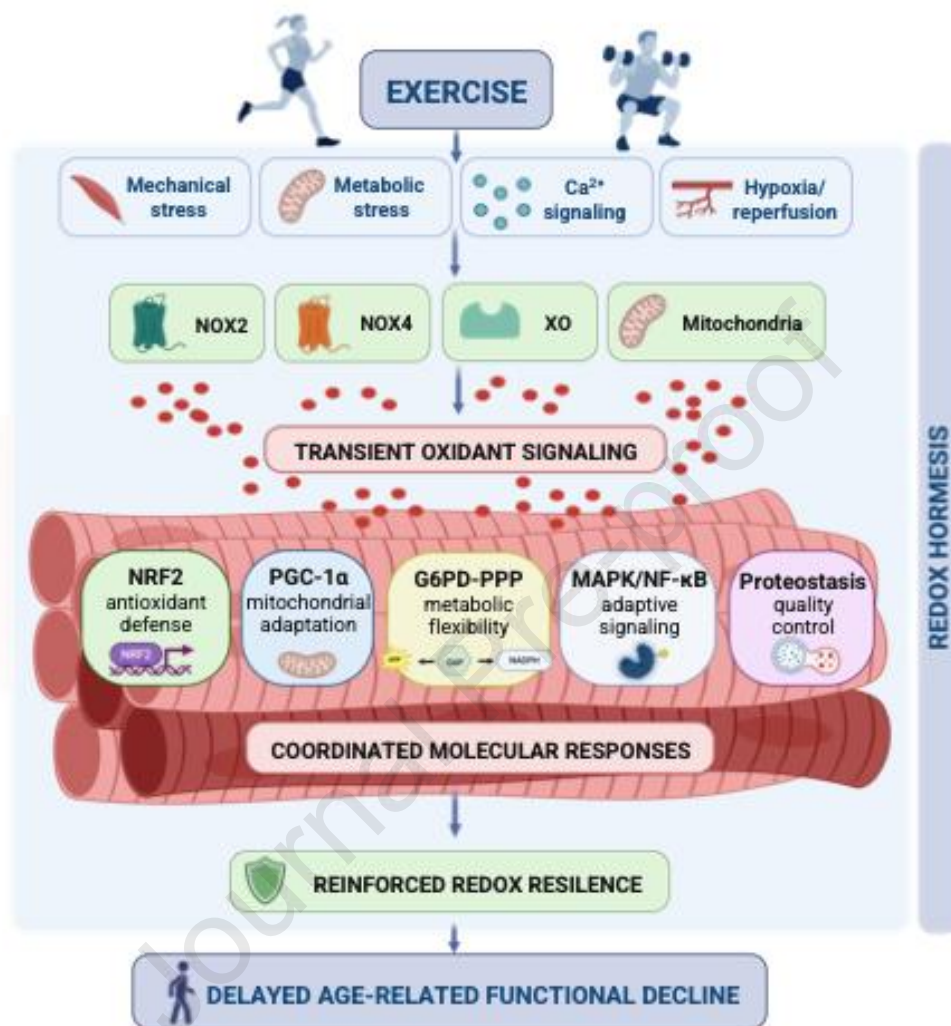
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695 FIGURE 2:



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Highlights

- Redox resilience provides an integrative framework for skeletal muscle aging.
- Aging impairs adaptive redox signaling and disrupts muscle cellular networks.
- Cellular heterogeneity shapes redox homeostasis and age-related muscle decline.
- Exercise reinforces redox resilience through coordinated adaptive signaling.
- Nrf-2, PGC-1 α and mitochondrial quality control contribute to exercise adaptation.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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