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Review Article

Intracellular and extracellular redox signals during exercise and aging

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A B S T R A C T

Regular physical activity enhances systemic health and resilience, partly through the generation of reactive oxygen species (ROS) that serve as key modulators of redox-sensitive signaling pathways. This review explores how redox signaling mediates both local and systemic responses to exercise, with particular focus on skeletal muscle and aging. We first examine the compartmentalized generation of ROS within myofibers, highlighting the distinct contributions of mitochondrial and NADPH oxidase systems and the context-dependent nature of oxidative eustress versus distress. We then detail how redox signals initiate adaptive responses that extend beyond muscle through the release of exerkines, cytokines, peptides, and metabolites, and their packaging within extracellular vesicles (EVs). These circulating factors facilitate interorgan communication and reinforce systemic redox homeostasis. Aging disrupts these processes, leading to impaired redox signaling, neuromuscular degeneration, and diminished responsiveness to exercise. Notably, animal models such as Sod1-deficient mice underscore the importance of neuronal redox control in sarcopenia. Finally, we highlight how exercise-induced EVs may counteract age-associated dysfunction by delivering redox-regulatory molecules to distant tissues. Understanding the molecular interplay between redox signals and systemic adaptation offers promising avenues for therapeutic strategies targeting metabolic and neuromuscular decline in aging.

1. Introduction

Physical activity is a cornerstone of preventive and therapeutic medicine, known to reduce risks of non-communicable diseases, including cardiovascular disease, diabetes, certain cancers, and neurodegenerative disorders [1]. In older populations, exercise effectively mitigates frailty, sarcopenia, and cognitive decline, while enhancing musculoskeletal integrity and metabolic health [2]. These systemic benefits arise from integrated molecular and systemic processes, many of which are rooted in redox biology [3–5].

Reactive oxygen species (ROS), long vilified for their potential to damage biomolecules, have been recontextualized within the exercise physiology field [6,7]. At moderate levels and activities, some ROS serve essential signaling functions, a phenomenon termed “oxidative eustress” [8]. These molecules, produced transiently during exercise, activate pathways that enhance antioxidant gene expression, promote mitochondrial biogenesis, and improve muscle contractility [9–13]. However, an imbalance between excessive chronic ROS production and/or scavenger capacity can lead to oxidative distress, contributing to cellular damage and disease-states, including insulin resistance and cardiovascular dysfunction. The dual role of ROS in physiology and pathology is determined by their type, concentration, activity and subcellular location [14,15].

Redox signaling is inherently compartmentalized, with eukaryotic cells maintaining distinct redox environments across organelles [16]. The secretory pathway is strongly oxidizing, supporting disulfide bond formation in proteins destined for export [17]. The cytoplasm is comparatively reducing, with redox signaling sustained by NADPH oxidases and nitric oxide synthases rather than metabolic oxidases [16]. Nuclear compartments also maintain a reduced redox potential but exhibit relative resistance to oxidation. Mitochondria represent one of the most reducing environments, characterized by high electron flux through the respiratory chain and pronounced sensitivity to oxidative perturbation. Skeletal muscle, which is structurally dominated by contractile myofibrils, the sarcoplasmic reticulum (SR), and transverse tubules, redox states exhibit marked subcellular heterogeneity [18]. Specific regions such as the subsarcolemmal, perinuclear, and neuromuscular junction regions, each may engage uniquely in redox signaling during and after exercise, ensuring that ROS effectively exert their signaling functions, avoiding widespread oxidative damage [19]. Understanding how organelle-specific redox dynamics coordinate during exercise stress is essential for elucidating mechanisms of muscle adaptation and performance.

Mounting research points to dysregulation of redox signaling and

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homeostasis as a fundamental mechanism underlying the gradual decline in skeletal muscle mass and function during aging, a condition known as sarcopenia [20,21]. Indeed, oxidized proteins, lipids, and DNA accumulate with age in human muscle, and this increase in damage is correlated with an age-dependent redox disruption [22]. Aging affects both the quantity and quality of skeletal muscle, involving muscle fiber atrophy, neuromuscular junction (NMJ) degeneration, and motor neuron loss associated with altered redox state [23]. This implies that loss of nerve-muscle connectivity could be a central mechanism in dysregulated redox signaling, compounding the functional decline in aged muscle [24].

Exercise remains a powerful intervention against age-related muscle decline [25], with programs tailored to older adults promoting substantial improvements in strength, mitochondrial function, and metabolic health, all partially mediated through redox-sensitive pathways [26,27]. Beyond local effects, exercise initiates a cascade of systemic adaptations mediated by various circulating factors collectively termed "exerkines" that facilitate inter-organ communication and coordinate systemic responses to exercise [28]. Exerkines include metabolites, cytokines, peptides, and nucleic acids secreted by skeletal muscle, adipose tissue, liver, brain, and other organs [29]. Many of these exerkines are released and transported via EVs, which protect labile cargo such as RNA and proteins from degradation and facilitate targeted delivery to recipient tissues [30]. The release and action of exerkines and EVs can be influenced by the modification of tissue redox environment, and, critically, exerkines and EVs can influence redox states in distant organs and enhance redox surveillance and systemic resilience against oxidative stress [31].

This review explores how intracellular and extracellular redox signals mediate the physiological effects of exercise and how these processes become dysregulated with aging. As we age, the balance between oxidative eustress and distress becomes harder to maintain, particularly in skeletal muscle. Yet, exercise training provides a potent non-pharmacological intervention that revitalizes redox signaling, promotes systemic communication via exerkines and extracellular vesicles, and counteracts age- and disease-related redox dysregulation.

2. Intracellular redox signaling during rest and exercise

Some of the earliest evidence that oxidants are generated during muscular activity originated from studies detecting elevated lipid peroxidation products in the exhaled air of exercising individuals [32]. This was followed by the seminal work of Davies and colleagues [33], who employed electron spin resonance (EPR) spectroscopy to demonstrate increased free radical content in skeletal muscle of rats subjected to treadmill running. Similar results were later reported by Jackson et al. [34] where intense muscle contraction increased the EPR signal in rat hind limbs. Collectively, these findings provided the foundation for the current consensus that oxidant molecules are produced in skeletal muscle both at rest and during contraction [34–36].

Among the ROS produced in skeletal muscle, superoxide anion ($O_2\bullet^-$) is a primary species, generated through the one-electron reduction of molecular oxygen. It is rapidly dismutated to hydrogen peroxide (H_2O_2), either spontaneously or by compartment-specific superoxide dismutase (SOD) isoforms [37]. Compared to $O_2\bullet^-$, H_2O_2 is more chemically stable and diffusible, making it the principal mediator of redox signaling in muscle cells [19,38,39]. However, its activity is spatially constrained by localized antioxidant systems that neutralize H_2O_2 near its site of production, resulting in distinct intracellular redox microdomains with tightly regulated oxidant–antioxidant dynamics [40,41].

Redox signaling conveys biological information through oxidation–reduction reactions or the formation of covalent adducts between redox-sensitive sensor proteins and second messengers [14]. However, not all redox reactions elicit signaling events; specificity is achieved through sensor proteins that undergo reversible oxidative modifications or form selective covalent interactions with target molecules [42]. One of the earliest redox-regulated responses to exercise identified was the induction of adaptive gene expression. Two landmark studies demonstrated that antioxidant supplementation impairs key molecular adaptations to endurance training in human skeletal muscle [13,43]. Gomez-Cabrera et al. [43] showed that oral vitamin C suppressed the exercise-induced expression of PGC-1α, mitochondrial biogenesis, and mRNA levels of antioxidant enzymes. Similarly, Ristow et al. [13] reported that combined antioxidant supplementation blunted improvements in insulin sensitivity and antioxidant gene expression. Collectively, these findings inaugurated the recognition of redox signaling as a fundamental driver of skeletal muscle adaptation to endurance exercise in humans.

2.1. Subcellular redox signaling controlling exercise responses

The intricate architecture of skeletal muscle fibers further enhances the specificity of redox signaling [18,19]. Each fiber contains a dense arrangement of organelles, including mitochondria, myofibrils, transverse (T)-tubules, and the sarcoplasmic reticulum (SR) [19]. This highly organized structure allows for the establishment of discrete intracellular compartments, within which redox-sensitive signaling proteins, such as kinases, phosphatases, and transcription factors, reside in proximity to ROS-producing sites.

Redox potential differs markedly between these compartments [44]. For instance, the cytosol, mitochondrial matrix, and peroxisomes are maintained in a reducing state, whereas the endoplasmic reticulum (ER) and mitochondrial intermembrane space (IMS) are comparatively oxidizing [44,45]. In their tissue-specific cysteine proteomics study, Xiao et al. [17] reported that in mouse skeletal muscle, ~40 % of secretory pathway proteins and 16 % of Golgi proteins contained oxidized cysteine residues, compared with only ~10 % in nuclear, cytosolic, and mitochondrial proteins. These gradients may define compartment-specific thresholds for cysteine reactivity: oxidative environments such as the ER favour disulfide bond formation and protein maturation, whereas reducing environments preserve cysteine thiols for reversible modifications central to redox signaling. As a result, H_2O_2-dependent signaling is not uniformly distributed but emerges within defined subcellular niches during exercise [19], insulin stimulation [46], and aging [17]. For detailed discussion of compartment-specific redox regulation in skeletal muscle, readers are referred to the following reviews [18,19].

2.2. Primary intracellular sources of ROS: mitochondria and NADPH oxidases

Mitochondria have long been considered a major source of ROS, primarily through electron leakage at Complexes I and III of the electron transport chain, which leads to the generation of $O_2\bullet^-$ [47]. This is rapidly converted to H_2O_2 by mitochondrial superoxide dismutases: SOD2 in the matrix and SOD1 in the IMS. Early estimates from studies using isolated mitochondria suggested that 1–2 % of consumed oxygen was converted into superoxide under specific in vitro conditions [48]. However, this value has been widely misapplied to in vivo settings. More recent analyses in intact cells reveal that only ~0.12–0.15 % of mitochondrial oxygen consumption results in H_2O_2 production, offering a more physiologically accurate estimate [49].

Fluorescent probes have enabled the determination of $O_2\bullet^-$ and H_2O_2 dynamics in intact contracting skeletal muscle fibers under both in vivo and in vitro conditions. Sakellariou et al. [36] added a key piece to this evolving understanding by demonstrating, through the use of the mitochondrial $O_2\bullet^-$ -sensitive probe MitoSOX, that mitochondrial $O_2\bullet^-$ levels do not increase during contractile activity. Building on this, subsequent investigations employing mitochondrial-targeted roGFP biosensors showed that neither muscle contraction nor endurance exercise increases H_2O_2 levels in the mitochondrial matrix, both in vitro [50] and in vivo [7]. These findings suggest that mitochondria may not be the

dominant source of ROS during exercise, as previously believed.

In fact, under physiological conditions, mitochondrial antioxidant systems consume H_2O_2 at rates exceeding production, so steady-state levels reflect a balance between these opposing processes [51]. During exercise, increased ADP levels resulting from elevated ATP turnover suppress mitochondrial ROS generation, while intracellular acidification during contractions may further shift mitochondrial redox status toward an antioxidant profile [52]. Accurate measurement of production requires inhibition of consumption pathways, for example using auranofin to block the thioredoxin/peroxiredoxin system and glutathione peroxidase inhibitors or GSH depletion to suppress the glutathione-dependent pathway [51]. Together, these data support the emerging view that mitochondrial H_2O_2 production is tightly regulated and likely not the principal driver of redox signaling during exercise.

2.2.1. Skeletal muscle NADPH oxidase 2

During the last decade, NADPH oxidase 2 (NOX2) has gained increasing recognition as a central enzymatic source of H_2O_2 in contracting skeletal muscle [53,54]. NOX2 is a multi-subunit complex consisting of a membrane-bound catalytic core (gp91phox and p22phox) and cytosolic regulatory components (p47phox, p67phox, p40phox, and Rac1), which assemble upon activation at specific subcellular sites such as the sarcolemma and transverse (T)-tubule [36,55]. In 2016, Henríquez-Olguín et al. [56] demonstrated that acute swimming exercise in mice stimulates NOX2 complex assembly in skeletal muscle, as evidenced by increased phosphorylation of p47phox, a key event that promotes its interaction with p22phox and facilitates the recruitment of gp91phox to the sarcolemma. Building on this, subsequent studies revealed that both continuous moderate-intensity [7] and high-intensity interval exercise [57] stimulate NOX2-dependent H_2O_2 production in mouse skeletal muscle, further confirming that NOX2 activation is a conserved feature across multiple exercise modalities.

Pharmacological inhibition of NOX2, using agents such as apocynin or the more specific gp91ds-tat peptide, reduced ROS production during muscle contraction [35,36,58]. Moreover, studies employing a NOX2-specific biosensor (p47phox-roGFP) have demonstrated real-time NOX2 activation in response to contraction, with signal loss in gp91phox- and p47phox-null muscles [7,59]. Although roGFP has a limited dynamic range, several studies using subcellularly targeted Orp1–roGFP constructs in p47phox (*Ncf1**) and Rac1 (Rac1 mKO) loss-of-function mouse models demonstrated that moderate-intensity exercise induces a cytosolic H_2O_2 signal in skeletal muscle, which is abolished in NOX2-deficient mice [7]. these findings were independently validated by Kano et al. [60], who expressed the ultrasensitive HyPer7 biosensor in tibialis anterior muscle fibers via in vivo electroporation. Electrically induced eccentric contractions were then performed in anesthetized mice, revealing a sustained increase in cytosolic H_2O_2 that was significantly attenuated by pharmacological inhibition of NOX2, confirming its role as a primary source of contraction-induced H_2O_2 in vivo.

2.2.2. NADPH oxidase 4

NADPH oxidase 4 (NOX4), another member of the NOX family expressed in skeletal muscle, is primarily localized to the SR and possibly the mitochondrial IMS [53]. Unlike NOX2, NOX4 is constitutively active and may function as a redox sensor regulated by intracellular oxygen tension and ATP availability. Evidence from cancer cells suggests that ATP produced via OXPHOS binds to a ATP-binding domain of NOX4, keeping ROS output low, whereas decreased mitochondrial ATP levels relieve this inhibition and enhance NOX4 activity [61]. Although less thoroughly characterized, NOX4-derived ROS are believed to participate in redox-regulated processes such as calcium release and transcriptional regulation, particularly during the post-exercise recovery phase [62,63].

2.3. Downstream mechanisms of H_2O_2 signaling induced by exercise

Among ROS produced in muscle, H_2O_2 is uniquely suited to act as a signaling molecule: it is stable enough to diffuse locally yet sufficiently reactive to oxidize specific cysteine residues on redox-sensitive proteins [64]. This selectivity reflects multiple factors, including thiols with low pKa and high nucleophilicity, stabilization by the surrounding microenvironment, solvent accessibility, and participation in redox relay mechanisms such as those mediated by peroxiredoxins [65]. During exercise, transient bursts of H_2O_2 function as second messengers that activate adaptive signaling pathways in skeletal muscle [19]. Key to this process is reversible cysteine oxidation, such as sulfenic acid formation, disulfide bond formation, or sulfenylamide linkages, which can modulate protein conformation, activity, or subcellular localization [65]. These modifications are reversible via thioredoxin and glutaredoxin systems, thereby restoring redox balance after signaling events have concluded. This mechanism enables H_2O_2 to specifically regulate transcription factors (e.g., Nrf2, FOXO), metabolic regulators like PGC-1α, and kinases involved in GLUT4 translocation during contraction [19]. Through selective oxidation of regulatory cysteines, H_2O_2 translates transient redox changes into robust cellular responses, including enhanced antioxidant defense, mitochondrial biogenesis, and insulin-independent glucose uptake, while preserving redox homeostasis post-exercise (Fig. 1). One of the key challenges in redox biology is achieving comprehensive mapping of cysteine oxidation events and elucidating their functional significance (Fig. 1).

3. Extracellular signals in the systemic response to exercise: the interplay of exerkines and EVs in the context of redox homeostasis

Adaptation to physical training results from long-term compensatory mechanisms aimed at preserving or restoring homeostasis disrupted by various exercise regimens. These adaptations occur across virtually all organ systems, highlighting the complexity and integrative nature of this multi-level biological process [66,67].

The concept of hormesis—whereby low doses of a stressor induce adaptive beneficial effects, applies well to exercise-induced systemic redox modulation [68]. Indeed, repeated exposure to moderate oxidative challenges via regular physical activity leads to upregulation of endogenous antioxidant systems, including SOD2, catalase, and glutathione peroxidase (GPx) [43]. This adaptive response improves systemic redox homeostasis and enhances the organism's ability to counteract oxidative insults.

Beyond localized effects in skeletal muscle, exercise serves as a powerful regulator of systemic redox homeostasis through a dynamic balance between ROS production and antioxidant defenses [69,70]. Physical activity enhances endothelial function, partly by reducing oxidative stress and increasing nitric oxide (NO) bioavailability [71]. Improved vascular redox balance contributes to the prevention of atherosclerosis and hypertension [67]. Additionally, exercise modulates systemic inflammation, a key driver of redox imbalance, by downregulating pro-inflammatory cytokines such as TNF-α and IL-6, and upregulating anti-inflammatory markers [72]. Furthermore, physical activity influences redox-sensitive pathways in metabolic tissues. In the liver and adipose tissue of cachectic tumor-bearing animals, exercise reduces lipid peroxidation and improves insulin sensitivity through enhanced antioxidant responses [73]. Exercise-induced ROS also play a role in muscle hypertrophy and repair by regulating satellite cell activation and gene expression related to growth [74,75].

The extent of this modulation depends on exercise variables such as intensity, duration, frequency, and the individual's training status. During moderate or well-calibrated intense exercise, ROS signaling—likely mediated by redox-sensitive thiol groups—plays a key role in numerous biological functions, including gene expression, vasodilation, cell growth, proliferation, and adaptation [76]. These processes

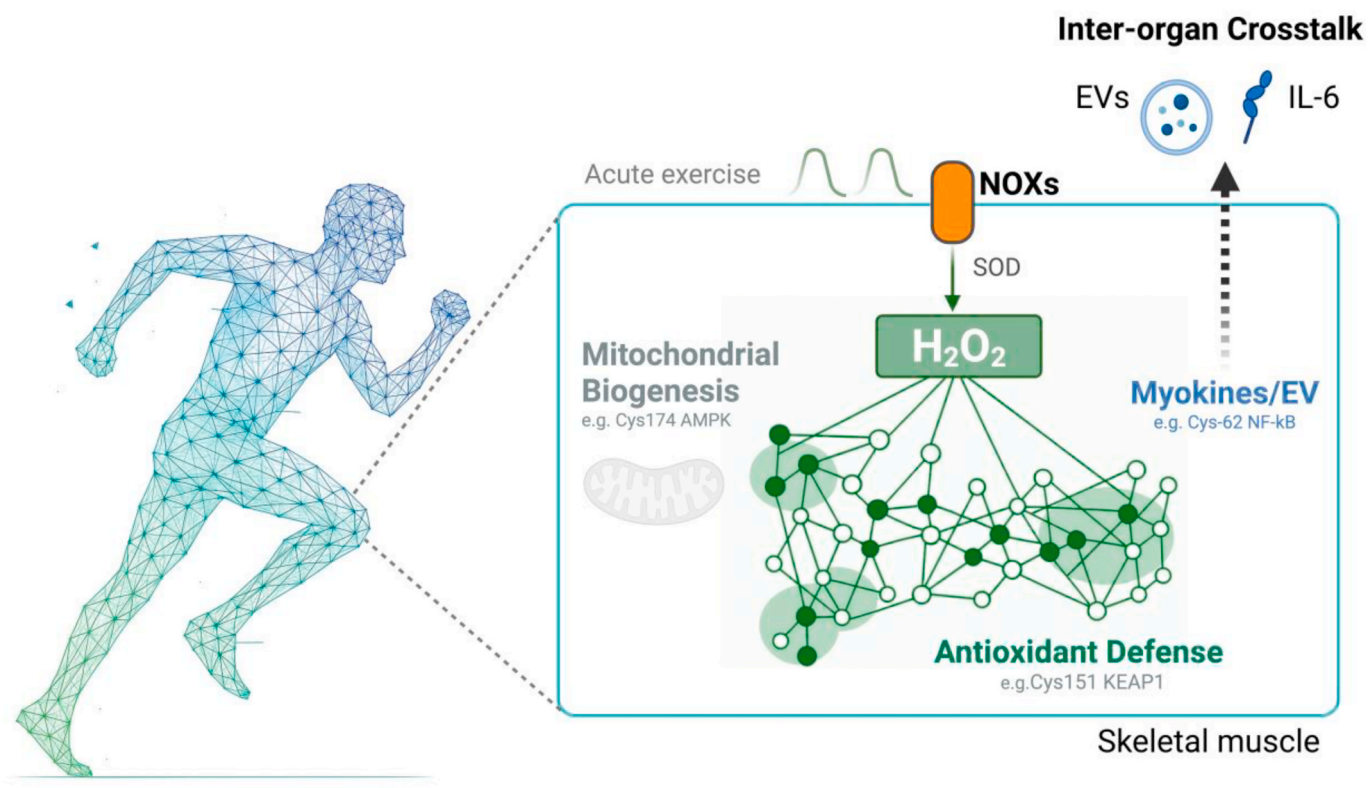

Fig. 1. Exercise Redox Signaling via Cysteine Oxidation Networks. Contractile activity activates NOX2, leading to transient H_2O_2 production, a key redox signal. H_2O_2 is proposed to regulate adaptive responses via site-specific cysteine oxidation on yet-to-be-fully-identified redox-sensitive proteins involved in mitochondrial biogenesis, antioxidant defense, and the release of myokines and extracellular vesicles (EVs). These processes are spatially and temporally coordinated within cysteine oxidation networks, enabling both local muscle remodeling and systemic inter-organ communication.

underpin exercise's beneficial effects on healthy aging and its preventive or therapeutic potential in various diseases [77–80]. Endurance training in particular has been shown to elevate antioxidant enzyme activity both in muscle and systemically. For instance, studies have found that trained individuals exhibit higher baseline levels of SOD and GPx compared to sedentary controls, indicating a chronic adaptive upregulation [10,81,82]. Resistance training also modulates redox status, though the mechanisms only partially overlap: while AMPK–PGC-1α–Nrf2 signaling shifts the balance toward metabolic resilience in endurance exercise, in resistance exercise the MAPK–NF-κB–mTOR signaling leads to a structural/functional resilience [66]. It appears to induce more localized muscle adaptations with modest systemic antioxidant effects compared to endurance exercise [83], although systemic beneficial effects have been reported [84,85]. In older adults, both aerobic and resistance training improve systemic oxidative markers and mitochondrial function [86].

During acute or exhaustive exercise, ROS production may surpass the cell's antioxidant capacity, leading to oxidative damage, impaired cellular function, and apoptosis through a pro-inflammatory, redox-sensitive response [33,87,88]. However, these responses are typically followed by a rebound increase in antioxidant enzyme expression during recovery. Additionally, contracting muscle generates nitric oxide (NO), primarily via nitric oxide synthase isoforms NOS1 and NOS2. While NO acts as an important signaling molecule, it can also react with superoxide to form peroxynitrite, which exacerbates oxidative stress by further depleting cellular thiol groups [89].

3.1. Redox signaling, exerkines, and exercise responses

Physical exercise induces widespread systemic adaptations that contribute to improved metabolic health, reduced inflammation, and enhanced resilience against chronic diseases. These adaptations are mediated not only by local responses in contracting skeletal muscles but also by endocrine and paracrine signals that orchestrate the cross-talk among organs such as the muscle, heart, brain, liver, and adipose tissue [90]. Emerging evidence points to exerkines and EVs as key mediators of this interorgan communication, with redox biology acting as a central regulator of their release and function [91,92].

Exerkines are a broad group of metabolites, hormones, and cytokines with endocrine, autocrine, and paracrine effects secreted into circulation during or after exercise and acting as signaling molecules. They include myokines (e.g., IL-6, irisin), hepatokines (e.g., FGF21), adipokines (e.g., adiponectin), and others released from various organs [93]. Exerkines can be grouped into two main categories based on their origin and function: 1) "metabolic exerkines", such as lactate, are by-products of macronutrient metabolism and energy pathways [94], and 2) "physiologic exerkines", that include hormones, growth factors, and cytokines, acting on specific tissues, cells, or organelles [95].

The term "myokines" has been introduced in 2003 by Pedersen et al. [96], who described IL-6 as one of the first identified myokines. IL-6 increases acutely in response to exercise and has systemic effects including enhanced glucose uptake and lipid oxidation [97]. IL-6, along with lactate and adiponectin, has been shown to support brain mitochondrial function, similarly to Brain Derived Neurotrophic Factor (BDNF) derived from immune cells [98–100]. Irisin, cleaved from FNDC5, promotes mitochondrial biogenesis, dynamics, and mitophagy in human adipocytes and is associated with upregulation of its receptor ITGA5 in human adipose tissue, which may serve as a compensatory response to enhance mitochondrial function and fat browning [101]. Though some controversy exists regarding irisin's detectability and function in humans, emerging evidence supports its role in metabolic regulation and neuroprotection, making it a critical mediator of the body's adaptation to exercise and a promising target for interventions in metabolic and neurodegenerative disorders [102,103]. Overall,

metabolic and physiologic exerkines interact to coordinate energy use, support mitochondrial health, and meet the body's adaptive demands during physical activity.

Many exerkines are sensitive to redox status. IL-6 expression in skeletal muscle is stimulated by ROS and regulated by NF-κB and redox-dependent p38 MAPK pathways [35,56,90]. NOX2 inhibitors [21] and antioxidant supplementation blunts IL-6 release, highlighting the essential role of redox signaling in its regulation [55]. IL-6 subsequently acts systemically to mobilize energy substrates and regulate inflammation, thus linking muscle oxidative stress to whole-body homeostasis [97]. ROS can also upregulate BDNF expression via CREB signaling pathways [104–106]. Exercise-induced oxidative eustress in the hippocampus and peripheral tissues may therefore enhance BDNF levels, contributing to cognitive and mood benefits [107]. Finally, the expression of Irisin is promoted by PGC-1α, a redox-sensitive transcriptional coactivator upregulated during mitochondrial ROS signaling, while FGF21 is modulated by AMPK and SIRT1 [108]. This positions irisin as a redox-dependent exerkine linking muscle oxidative status with systemic energy expenditure. For additional insight on this topic, the reader is referred to the recent article from Félix-Soriano and Stanford [109].

Aging is generally associated with a blunted exerkine response to physical activity [28,110]. Furthermore, the signaling pathways downstream of exerkines—including those mediated by nuclear factor erythroid 2-related factor 2 (Nrf2), a key regulator of antioxidant gene expression—are frequently impaired in aged tissues, limiting the capacity for effective redox control [111]. Nevertheless, in aging populations, regular exercise can enhance mitochondrial efficiency, stimulate residual exerkine release, and activate antioxidant defenses, albeit often to a lesser degree than in younger subjects [112,113].

In summary, exerkines are key exercise-induced signaling molecules that link redox biology to systemic health by supporting mitochondrial function, energy balance, and cellular resilience. Although aging reduces exerkine responsiveness and antioxidant signaling, regular exercise can still enhance redox homeostasis and help counteract age-related decline, making exerkines a promising target for healthy aging and disease prevention.

3.2. *Extracellular vesicles in exercise responses*

EVs are broadly categorized into three major types based on their size and origin: exosomes (30–150 nm), microvesicles (100–1000 nm), and apoptotic bodies (>1000 nm). Exosomes originate from the endosomal system and are secreted upon fusion of multivesicular bodies with the plasma membrane, whereas microvesicles bud directly from the

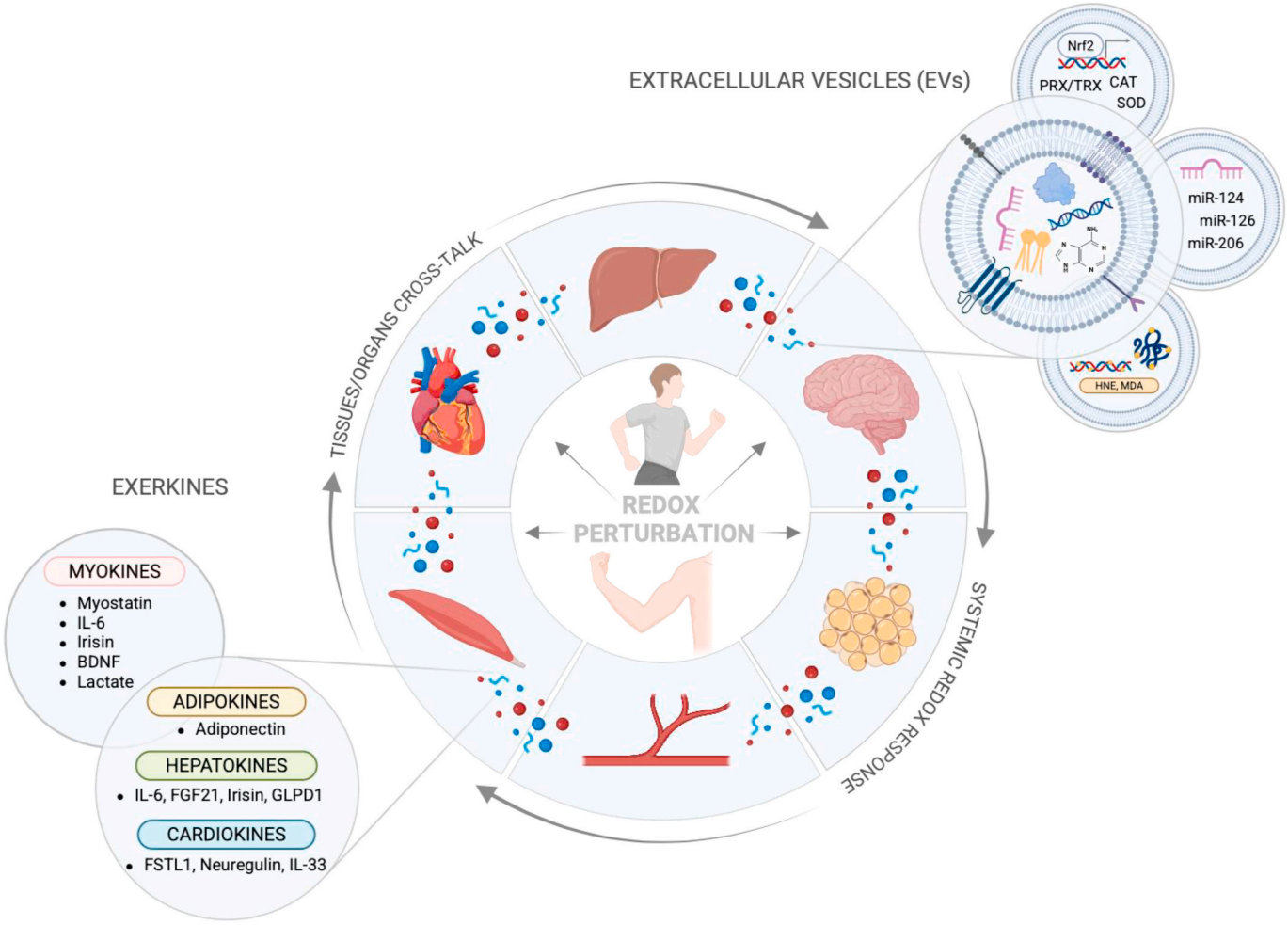

Fig. 2. Exerkines and exercise-induced EVs as key mediators of interorgan communication. Systemic effects of exercise are mediated not only by local adaptations within contracting skeletal muscle but also by endocrine and paracrine signaling that coordinates communication among the muscle, heart, brain, liver, and adipose tissue. Extracellular vesicles (EVs) and soluble or EV-associated exerkines constitute a key interorgan communication network, both dependent on and capable of modulating redox homeostasis. Exerkines, including myokines, hepatokines, adipokines, and other metabolites, hormones, and cytokines, regulate redox balance by influencing endoplasmic reticulum and mitochondrial stress responses, reactive oxygen species (ROS) signaling, and metabolic efficiency, collectively reducing oxidative stress. Likewise, exercise-modulated EV cargo (e.g., microRNAs, functional or post-translationally modified proteins) enhances antioxidant capacity, suppresses oxidative stress, and activates detoxification pathways, thereby contributing to the maintenance of systemic redox homeostasis.

plasma membrane [114]. Additional types of EVs have been described. For an exhaustive overview of EVs biology, the reader is directed to up-to-date, dedicated reviews [115–117].

The precise composition of EVs varies depending on the cell type and physiological condition, including exercise stimuli. In vivo studies from animal and human models have shown that acute and chronic exercise modulate the release, composition, and bioactivity of circulating EVs [93,118]. Both endurance and resistance exercises significantly increase the concentration of plasma EVs, with peaks occurring immediately post-exercise and gradually returning to baseline within a few hours [92].

These EVs are derived from various tissues, including skeletal muscle, endothelium, platelets, immune cells, and even the central nervous system (Fig. 2) [93]. One of the first studies to report exercise-induced EVs found elevated levels of circulating exosomes carrying skeletal muscle-specific proteins and microRNAs (miRNAs) after acute treadmill running in mice and humans [119]. These findings support the notion that muscle-derived EVs act as messengers in muscle-to-organ communication, especially under physical stress [92]. Nevertheless, the tissue origin of exercise-induced EVs is diverse, reflecting the multi-systemic nature of exercise-induced adaptations [120]. Studies utilizing proteomic, transcriptomic, and surface marker profiling have identified several tissues involved in EVs release in the human bloodstream, such as skeletal muscle [119], endothelial cells [121], platelet and blood cells [122], adipose tissue [123], brain and neural tissues [124].

The cargo of exercise-induced EVs includes a rich repertoire of proteins, lipids, and RNAs, notably miRNAs that modulate gene expression in target cells (Fig. 2). For instance, skeletal muscle-derived EVs carrying IL-6 mRNA or protein can activate immune cells and modulate inflammation in subjects, supporting the anti-inflammatory role of regular exercise [122]. Specific miRNAs such as miR-1, miR-133a, and miR-206, all involved in muscle development and regeneration, are enriched in muscle-derived EVs post-exercise in a mice model of type 2 diabetes [125]. These miRNAs influence not only muscle repair and adaptation but also systemic metabolic pathways.

EVs have been shown to mediate the transfer of mitochondrial components, and in some cases intact mitochondria, between cells, a process that can profoundly influence redox homeostasis by altering mitochondrial ROS production, antioxidant capacity, and metabolic coupling in recipient cells [114]. Although antioxidant enzymes have been identified in exercise-induced EVs, suggesting a role in modulating oxidative stress [93,126]. EVs from exercised muscle have been shown to stimulate endothelial cells, thereby enhancing angiogenesis, likely through VEGF-associated signaling pathways [127]. This intercellular communication may contribute to the well-known vascular benefits of physical activity. EVs released during exercise also play crucial roles in cardiovascular health. Endothelial cell-derived EVs contribute to nitric oxide signaling, improve endothelial function, and reduce arterial stiffness [128]. Furthermore, EVs from exercised individuals are enriched in cardioprotective antioxidants [31,126] and miRNAs such as miR-126 and miR-222 [129], which protect cardiac cells from oxidative stress damage and regulate vascular integrity and angiogenesis.

In metabolic tissues, EVs have been shown to enhance insulin sensitivity and glucose uptake. For example, EVs from exercised mice improved insulin signaling in adipocytes and hepatocytes in vitro, an effect attributed to the delivery of AMPK-activating components [130]. This supports the growing consensus that EVs are key mediators of the anti-diabetic effects of exercise [131]. The central nervous system is also a target of the exercise benefits mediated by EVs. Exercise increases the release of neuronal and astrocytic EVs, which contain neurotrophic factors such as BDNF and miR-124—both known to support neurogenesis and synaptic plasticity [132,133]. These EVs may cross the blood-brain barrier or exert peripheral actions that indirectly influence brain health. Moreover, exercise-induced EVs are implicated in modulating systemic inflammation [30]. They can suppress the activation of pro-inflammatory macrophages and promote the expansion of anti-inflammatory Tregs, contributing to the systemic anti-inflammatory profile observed in physically active individuals [72].

Thus, exercise-induced EVs emerge as versatile mediators of inter-organ communication, carrying molecular cargo that supports metabolic regulation, vascular and cardiac protection, neuroplasticity, and redox homeostasis. While evidence for mitochondrial transfer remains limited, the diverse bioactive contents of these vesicles highlight their central role in translating physical activity into systemic health benefits.

4. Redox signaling in age-related muscle decline

The progressive decline in skeletal muscle mass and functional capacity with age, referred to as sarcopenia, poses significant health challenges, contributing to instability, increased susceptibility to falls, and the eventual loss of independence in older adults [134]. By the seventh decade of life, reductions in muscle cross-sectional area and strength reach 25–30 % and 30–40 %, respectively [135]. This deterioration arises not only from a reduction in the number of muscle fibers but also from the atrophy and weakening of those that remain [136,137].

This phenomenon is well-documented in both humans and animal models. Rodent studies mirror the age-related muscle deterioration seen in humans, validating their use in ageing research [138,139]. Age-associated neuromuscular degradation occurs concurrently with a loss of motor neurons, further exacerbating muscle weakness. In both humans and rodents, aging results in the degeneration of 25–50 % of motor neurons [140,141]. Disruption in the integrity of NMJs and fiber denervation are common findings in aged muscle tissue, with studies reporting that nearly 15 % of muscle fibers in older mice are fully denervated and that over 80 % of NMJs exhibit morphological impairments [142].

4.1. Oxidative damage and lifespan considerations

At the cellular level, ageing is accompanied by an accumulation of oxidative damage to macromolecules such as lipids, proteins, and DNA [143,144]. Although early investigations in non-mammalian species demonstrated that reducing ROS extended lifespan [145,146], more recent mammalian studies suggest that oxidative damage is not the sole determinant of longevity [147,148]. However, increased ROS activity and oxidative stress are implicated in the pathophysiology of many age-related diseases and dysfunctions [149].

Ageing also impairs the body's ability to adapt to physiological stressors, particularly those involving redox signaling [150]. In skeletal muscle, aging leads to diminished exercise-induced adaptations, including reduced acute stress responses [151], compromised mitochondrial biogenesis [152,153], and blunted anabolic responses [154]. The mechanisms underlying these impairments are unclear but functionally they decrease the effectiveness of physical activity in preserving muscle mass and strength. Notably, genetic interventions targeted at some of the specific attenuated pathways have shown promise in counteracting these age-related deficiencies [155–157].

4.2. Genetic manipulation and the role of Sod1

In mammalian models, the role of oxidative stress in aging has been investigated through various genetic manipulations. A landmark study by Pérez et al. (2009) [147] examined 18 mouse models with altered antioxidant gene expression. Despite significant variations in tissue oxidative damage, these manipulations did not influence lifespan, challenging the oxidative damage theory of aging. Nonetheless, further analyses revealed that under chronic stress conditions, such as those leading to pathological phenotypes, enhanced antioxidant defences mitigated some age-associated deteriorations [158].

Among the models studied, mice lacking Cu/Zn superoxide dismutase (Sod1) showed a unique phenotype. Sod1-deficient mice exhibited a

20 % reduction in lifespan and accelerated skeletal muscle aging, making them a valuable model for studying sarcopenia [159]. In-depth characterization of these Sod1KO mice revealed mitochondrial abnormalities, NMJ degeneration, and a loss of muscle strength that resembled aging-associated phenotypes in wild-type mice [160–162].

To delineate the tissue-specific impact of Sod1 loss, researchers created mouse models with targeted deletions. Muscle-specific deletion of Sod1 (mSod1KO) had minimal effects on muscle mass and function, suggesting that muscle-intrinsic ROS dysregulation alone is insufficient to induce sarcopenia [163]. Conversely, neuron-specific Sod1 expression in a Sod1KO background (SynTgSodKO) prevented NMJ degeneration and muscle atrophy, underscoring the importance of neuronal redox balance [164]. Additional studies using embryonic neuron-specific Sod1 knockouts [165] did not recapitulate the severe phenotype, possibly due to developmental compensations. However, inducible neuron-specific Sod1 deletions in adulthood (i-mn-Sod1KO) led to a premature onset of muscle atrophy and NMJ disintegration in older mice, reinforcing the central role of motor neurons in age-related muscle decline [162].

Research has consistently shown that mitochondrial hydrogen peroxide production increases with age in skeletal muscle [166,167]. In Sod1KO mice, this elevated ROS production is linked to NMJ deterioration and fiber denervation [164,168]. Nerve transection experiments demonstrated that denervation also significantly increased mitochondrial peroxide generation, both in denervated and adjacent innervated fibers, suggesting a non-cell autonomous mechanism [169]. Proteomic analyses comparing Sod1KO and mSod1KO mice show distinct molecular changes in nerves and muscles, implicating disrupted redox signalling in the peripheral nervous system as a major factor in the muscle loss that occurs in this model of accelerated age-related muscle aging [168]. These findings challenge the notion that oxidative damage per se drives sarcopenia, pointing instead to impaired signalling pathways (Fig. 2).

The effects of a specific lack of Sod1 to accelerate muscle ageing are somewhat surprising and have been attributed to an increase in oxidative damage in these mice. While the function of Sod1 is the dismutation of superoxide to hydrogen peroxide in the cytosol and mitochondrial IMS, these mice also show an increase in muscle mitochondrial hydrogen peroxide generation which appears to contribute to the muscle degeneration [165,167]. An additional mechanism by which Sod1 deficiency may contribute to muscle loss involves peroxynitrite, a reactive nitrogen species formed by the interaction of superoxide and nitric oxide. Elevated peroxynitrite levels in Sod1KO mice have been shown to nitrate essential proteins in motor neurons, such as nerve growth factors, compromising neuromuscular communication [170, 171]. Comparative studies with mitochondrial matrix-localized MnSOD (Sod2) further emphasize the tissue-specific role of Sod1. While Sod2 deletion impairs oxidative metabolism, it does not trigger premature muscle aging [172].Thus the effect of Sod1 deficiency to cause premature muscle loss is highly specific and appears related to location of the protein in the cytosol and IMS and additionally a key role for this protein in ROS regulation in motor neuron health [172].

Given the similarities between Sod1KO mice and aged wild-type animals, including the occurrence of markers of frailty such as weight loss, reduced activity, and systemic inflammation, these models may provide a relevant platform for aging studies [173]. Recent analyses of i-mnSod1KO mice confirmed accelerated aging features, including reduced axonal caliber and simplified NMJ architecture, mimicking advanced aging in wild-type controls [24].

4.3. Redox adaptations to exercise and the role of local denervation

The diminished capacity for redox-mediated adaptations to exercise in both aged and Sod1-deficient mice further implicates dysregulation of ROS signalling in muscle decline. Sod1KO mice fail to exhibit normal transcriptional responses to contractile activity, resembling old wild-type mice [174]. Elevated ROS production, particularly H_2O_2, likely drive increased expression of antioxidant enzymes, which may buffer critical cysteine oxidation events necessary for signalling [175].

It has been proposed that recurrent cycles of localized denervation and re-innervation throughout life create redox fluctuations that impair mitochondrial function and inhibit redox-sensitive adaptation mechanisms [176] (Fig. 3). The ensuing suppression of exercise-induced signaling responses in aging muscle could be a direct consequence of this denervation-induced elevation of mitochondrial ROS generation [175].

In conclusion ageing-associated muscle loss is a multifactorial process, driven by the convergence of motor neuron degeneration, impaired redox signalling, mitochondrial dysfunction, and disrupted muscle adaptation mechanisms. While oxidative damage is a hallmark of ageing tissues, current evidence suggests that it is the dysregulation of redox signalling that plays a more critical role in sarcopenia. The Sod1KO mouse model and its tissue-specific variants have been instrumental in uncovering these mechanisms. Going forward, therapeutic strategies that target neuronal redox homeostasis and support mitochondrial integrity hold promise in mitigating muscle degeneration and preserving physical function in the elderly.

5. Redox modulation of EVs during exercise and aging

Recent evidence suggests that ROS and redox signaling also plays a pivotal role in the biogenesis, release, cargo composition, and functional properties of EVs [177]. This relationship is bidirectional: redox modulation and oxidative stress influence both the number and content of exosomes and microvesicles produced by cells. At the same time, EVs can directly or indirectly modulate ROS types in both the extracellular and intracellular compartments [178]. Understanding how redox balance influences EV biology provides insight into physiological and pathological states, particularly those characterized by oxidative stress, such as cancer, cardiovascular disease, neurodegeneration, and responses to exercise [126].

Studies have demonstrated that oxidative stress can upregulate EV release by promoting intracellular calcium influx and cytoskeletal rearrangement, key processes required for vesicle budding and exocytosis [179]. For instance, H_2O_2 has been shown to enhance exosome secretion in various cell types, including endothelial and cancer cells [180]. At the molecular level, redox-sensitive proteins such as thioredoxins, peroxiredoxins, and glutathione peroxidases modulate the machinery involved in EV formation, including the ESCRT complex and small GTPases [181]. This suggests that the intracellular redox state can act as a switch, controlling the intensity and quality of EV-mediated communication.

The redox environment also significantly influences the composition of EV cargo. Cells exposed to oxidative stress selectively load stress-responsive molecules into EVs, including damaged proteins, mitochondrial DNA (mtDNA), oxidized lipids, and microRNAs that regulate redox-sensitive pathways [182,183]. For example, EVs from oxidative-stressed endothelial cells carry miR-210 and miR-34a, which modulate mitochondrial function and angiogenesis in recipient cells [184]. Similarly, exercise-induced EVs, released under transient redox imbalance, often contain antioxidant enzymes such as SOD1 and SOD2, glutathione S-transferase, and peroxiredoxin-1, suggesting a mechanism for systemic redox buffering [31,93,126,185]. This adaptive transfer of antioxidant defense components via EVs highlights their role in maintaining redox homeostasis across tissues.

EV biogenesis, cargo composition, and release dynamics are significantly altered during aging, contributing to age-associated tissue dysfunction and systemic inflammation [186,187]. Senescent cells release EVs enriched in pro-inflammatory cytokines, matrix-modifying enzymes, and microRNAs that promote tissue degeneration and immune dysregulation [188,189]. Notably, aged individuals often exhibit elevated levels of EVs carrying inflammatory markers, which have been

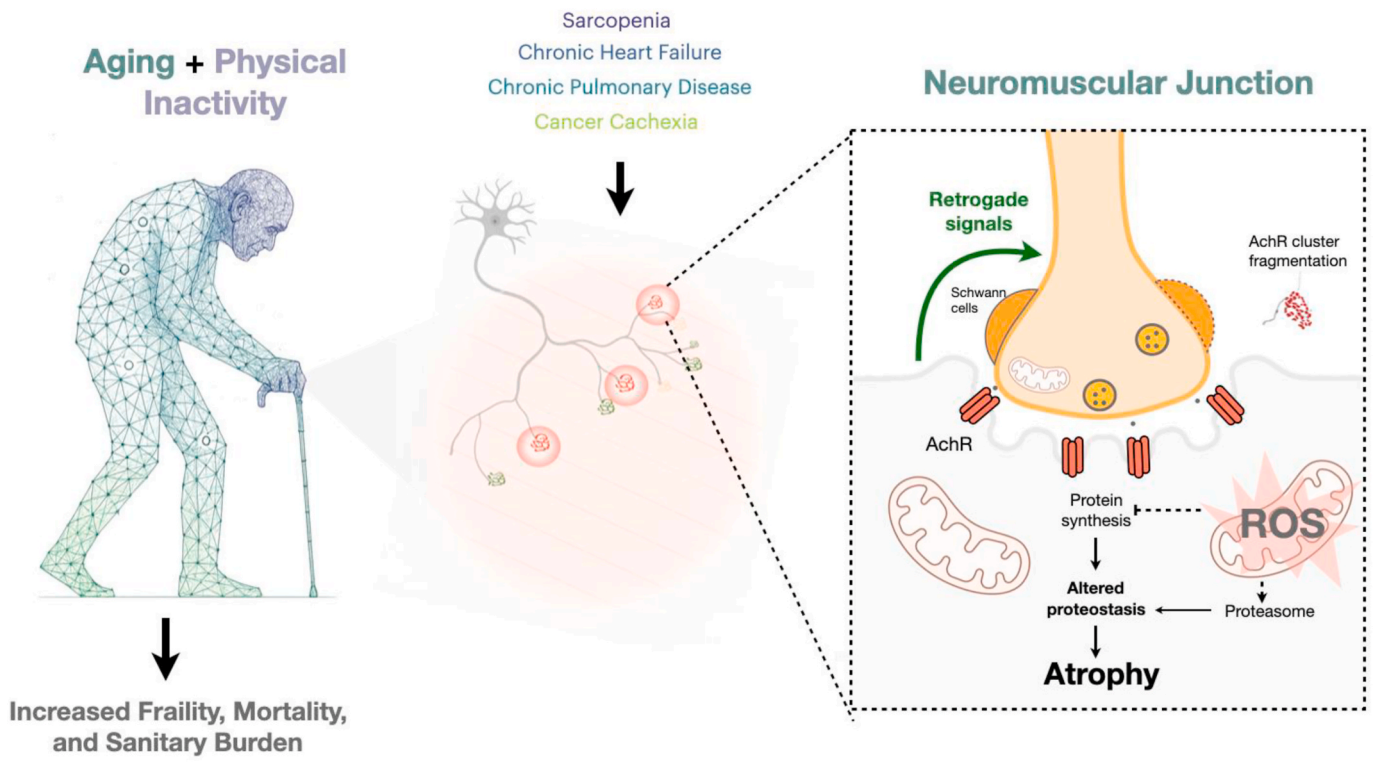

Fig. 3. NMJ Dysfunction Links Aging and Inactivity to Muscle Atrophy. Aging and physical inactivity contribute to neuromuscular junction (NMJ) dysfunction, marked by disrupted retrograde signaling, AChR fragmentation, and increased ROS. These changes impair proteostasis and promote muscle atrophy, contributing to frailty and disease progression in conditions such as sarcopenia and chronic illness.

linked to frailty and metabolic disturbances [190,191]. As indicated above, physical exercise is a potent modulator of EV release and composition, representing a possible countermeasure against aging-related changes in EV biology [190,191]. Besides this premise, experimental results are still minimal. Using in vitro and in vivo complementary studies, Kim et al. demonstrated in 2015 that aerobic exercise reduces the release of endothelial microparticles in prehypertensive individuals and that these beneficial effects are, in part, mediated by shear stress-induced mitochondrial biogenesis [192]. Recently, Radak's group [193] found that the proteomic profile of EV cargo from older adults is associated with the acceleration of the biological age estimator DNAmFitAge (AgeAccelFit). On the contrary, old mice treated with small EVs derived from adipose mesenchymal stem cells (ADSCs) of young animals show an improvement in several parameters usually altered with aging, including, among others, pro-regenerative effects and a decrease in oxidative stress, inflammation, and senescence markers in muscle and kidney [194]. Finally, in mice and humans, Abdelsaid et al. [131] demonstrated that exercise improves the angiogenic potential of circulating exosomes in type 2 diabetes in a SOD3-dependent manner, introducing the possibility that exercise-induced EVs might deliver bioactive cargo that modulates redox homeostasis signaling, thereby reducing oxidative stress and preserving cellular function during aging [195].

6. Conclusions

Redox signaling is a key mediator of exercise-induced adaptations in skeletal muscle and across organ systems. Controlled ROS production, especially H_2O_2 from sources like NOX2, drives beneficial responses such as mitochondrial biogenesis, antioxidant defense, and metabolic regulation. Exercise also promotes systemic resilience via redox-sensitive exerkines and EVs, which mediate inter-organ communication.

With aging, redox signaling becomes dysregulated, contributing to sarcopenia and neuromuscular decline. However, regular exercise can restore redox balance, enhance stress responses, and slow muscle degeneration. Targeting redox-regulated pathways and EV signaling offers promising strategies to support muscle health and systemic function during aging.

Despite these advances, important gaps remain. The functional significance of cysteine oxidation networks in exercise and aging is still incompletely defined, particularly in linking site-specific modifications to physiological outcomes. In addition, the pharmacological potential of targeting redox-dependent interorgan communication, for example between skeletal muscle, liver, adipose tissue, and brain, remains largely unexplored in the context of metabolic and aging-related diseases. Finally, while neuronal redox control has been implicated in sarcopenia, the mechanisms of neuron to muscle redox communication are only beginning to be uncovered and require further study.

CRediT authorship contribution statement

Daniela Caporossi: Writing – review & editing, Writing – original draft, Conceptualization. **Malcolm J. Jackson:** Writing – original draft, Investigation. **Carlos Henriquez-Olguin:** Writing – review & editing, Writing – original draft, Visualization, Methodology.

Conflicts of interest

The authors have no conflicting interests to disclose.

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