Redox signaling-mediated muscle atrophy in ACL injury: Role of physical exercise (Review)

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Received September 13, 2024; Accepted February 3, 2025

DOI: 10.3892/mmr.2025.13484

Abstract. Muscle atrophy frequently occurs in patients with anterior cruciate ligament (ACL) injury, despite active participation in muscle strengthening programs. Without appropriate countermeasures such as exercise and pharmacological interventions, the atrophy may worsen. At the cellular and molecular levels, various protein synthesis-related pathways and redox-dependent molecules regulate processes associated with atrophy by activating or deactivating key signaling pathways. Muscle atrophy and the associated dysfunction can be reversed by physical exercise, which increases protein synthesis, thereby improving muscle strength and function around the ACL. However, the influence of different features of exercise protocols, including exercise type, intensity and duration, as well as the individual capacity of the patient, on the activity of the aforementioned pathways requires further investigation. Additionally, the mechanism by which redox-sensitive molecules attenuate atrophy in ACL injury remains to be fully understood. The present review discusses exercise, signaling pathways and muscle atrophy in ACL injury, and highlights potential therapeutic strategies. These findings may also have implications for other joint diseases associated with ACL-related injury.

Contents

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Key words: redox signaling, oxidative stress, physical exercise, anterior cruciate ligament injury, muscle atrophy

1. Introduction

Anterior cruciate ligament (ACL) injury is one of the most prevalent injuries among athletes, the incidence of which has doubled over the past two decades (1-5). However, the underlying mechanism remains poorly understood. Various risk factors, including age, sex and activity type, affect the recovery time and the degree of injury (1,2). The development of novel treatment strategies is crucial for improving the overcomes for athletes with this type of injury. Current treatment strategies, such as ACL reconstruction surgery, are often inadequate, as they may be unable to fully restore the stability and function of the knee when the injury is severe (3,4). This leads to increased healthcare costs, estimated at 1-2 billion dollars annually in the United States (4). Additionally, the pain level and extended recovery times may limit the ability of athletes to return to their sport. Treatment failure is often attributed to joint injury and post-traumatic osteoarthritis (1,2); however, the specific causes and mechanisms remain unclear. Several meta-analyses suggest that strength and plyometric training have the potential to prevent ACL injuries (2,6,7). However, once an athlete has sustained an ACL injury, these types of exercises are no longer effective. In addition, injury-related biological processes impact muscle protein synthesis and strength during the initial adaptation phase, contributing to muscle atrophy in the ACL region (8).

Oxidative stress-induced muscle atrophy is a major contributor to muscle weakness following ACL reconstruction. Studies have shown that increased reactive oxygen species (ROS) levels within muscle fibers increase the risk of injury and atrophy (8,9). However, it remains unclear

whether oxidative stress is the primary cause of injury or if ACL injury-induced muscle atrophy itself triggers oxidative stress. The ACL is composed of several proteins, including collagen, elastin and proteoglycans (10). These proteins are highly sensitive to oxidative modifications that can destabilize their scaffold structures; in particular, ROS have been reported to affect the transcription, translation and posttranslational modification of these proteins (11), thereby either impairing or enhancing muscle protein synthesis. These effects may ultimately lead to muscle atrophy or, in some cases, promote muscle protein synthesis following ACL reconstruction.

The use of exercise therapy during the rehabilitation of patients with ACL injury should be carefully considered, since exercise protocols are associated with increased ROS production (12). Understanding the risk factors, such as individual genetic makeups and molecular pathways that interact with redox molecules, may provide novel insights into ACL injury. In addition, it may help to expand the development of redox-based therapies for recovery.

2. Exercise-induced adaptation to prevent muscle atrophy in ACL injury: Role of thiol-based redox signaling

The production of ROS, particularly hydrogen peroxide (H_2O_2), during exercise affects the activation of various signaling pathways, enzymes and cell membranes (13), thereby influencing protein synthesis and muscle integrity. In particular, the sulfhydryl group of cysteine (Cys) is considered a key target of oxidation in several proteins across various tissues (14). For example, the oxidation of Cys-299 and Cys-304 on the a subunit of AMP-activated protein kinase (AMPK) has been shown to alter its kinase function (Fig. 1) (15). Notably, AMPK plays a crucial role in meniscal degeneration during ACL injury and may increase the risk of osteoarthritis (16).

The oxidation of insulin-like growth factor (IGF) decreases its binding affinity to its receptors, potentially affecting normal physiological processes such as meniscal repair and promoting musculoskeletal health (17,18). Furthermore, the oxidation of specific Cys residues on Src kinase influences ACL regeneration by modulating focal adhesions (19), which are essential for cell anchoring and migration in the ACL (20,21). Therefore, redox signaling involving thiol groups may play a key role in the recovery and healing of ACL injuries.

Thiol oxidation has been demonstrated to increase the generation of H_2O_2 via reoxidation of the active site of protein disulfide isomerase (22). This may increase the production of ROS in muscles, thereby improving adaptation to exercise. In addition, increased levels of H_2O_2 may activate AMPK and peroxisome proliferator-activated receptor γ coactivator-1 α (PGC-1α) to increase mitochondrial content, reduce muscle damage and prevent atrophy in the context of ACL injury (23).

3. Molecular pathways associated with the regulation of redox balance in ACL recovery

Exercise has been suggested to improve ACL repair by targeting redox-mediated molecular pathways. For example, the exercise-induced oxidation of Kelch-like ECH-associated protein 1 (KEAP1) has been shown to activate nuclear factor erythroid 2-related factor 2 (Nrf-2), a major antioxidant regulator that stimulates the transcription of antioxidant enzymes, including heme oxygenase-1 and thioredoxin 1, to combat oxidative stress in the ACL region (24). This effect prevents oxidative stress-mediated chondrocyte injury and cartilage degradation in the ACL, thereby reducing the risk of osteoarthritis following ACL injury (25).

As chondrocytes are rich in mitochondria, the increased oxygen demand induced by exercise may lead to hypoxic conditions in the tissue, which in turn activates hypoxia-inducible factor 1 and increases ROS production. However, this initial redox perturbation can be counteracted by exercise-induced Nrf-2 signaling, which delays cartilage degradation and prevents osteoarthritis in ACL-related injuries (26). Additionally, other pathways, such as cAMP response element-binding protein-induced acetylation and sirtuin 1-stimulated PGC-1α, have been demonstrated to contribute to the upregulation and nuclear retention of Nrf-2 during exercise (27).

The activation of Nrf-2 in fibroblasts can promote extracellular matrix (ECM) production to facilitate tissue repair in ACL injury (28). Furthermore, the nuclear factor k-light-chain-enhancer of activated B cells (NF-κB) pathway, another crucial pathway, has been suggested to either increase the production of ROS by cyclooxygenase-2, NADPH oxidase 2 (NOX2) and cytochrome p450, or reduce ROS levels via modulation of the c-Jun kinase pathway (29). High-intensity exercise has been shown to activate NF-κB signaling (29), leading to the increased production of antioxidant enzymes and potentially promoting ACL repair via calmodulin-dependent protein kinase II, mitogen-activated protein kinase (MAPK) and signal transducer and activator of transcription 3 (STAT3) signaling pathways (Fig. 2) (30).

Targeting NF-κB expression has been indicated to promote ACL repair by modulating the expression of various metalloproteinases that play key roles in inflammation, cell proliferation, differentiation and apoptosis in ACL fibroblasts (31). Furthermore, exercise-induced STAT3 signaling is critical for the regulation of skeletal muscle growth and regeneration. STAT3 signaling has been indicated to stimulate satellite cell expansion and facilitate the repair of skeletal muscles via IL-6 (32). This regulation changes satellite cell behavior and promotes myogenic lineage progression via myogenic differentiation 1, which ultimately improves ACL recovery (32).

4. Redox signaling mediates muscle atrophy in ACL injury: Role of physical exercise

Although patients follow muscle strengthening programs, muscle atrophy generally occurs in ACL injury (2,5,6). Furthermore, the absence of countermeasures, such as exercise and pharmacological interventions, can further increase atrophy in the area affected by the ACL injury (7). Therefore, the identification of molecular signaling pathways that may be targeted to restore the health of muscles after ACL injury may help in the management of this injury and prevent the predisposition to osteoarthritis.

Redox molecules are key catalytic regulators of several molecular pathways during muscle strengthening. For example, the mammalian target of the rapamycin (mTOR) pathway plays a crucial role in protein synthesis, with ROS acting as the main

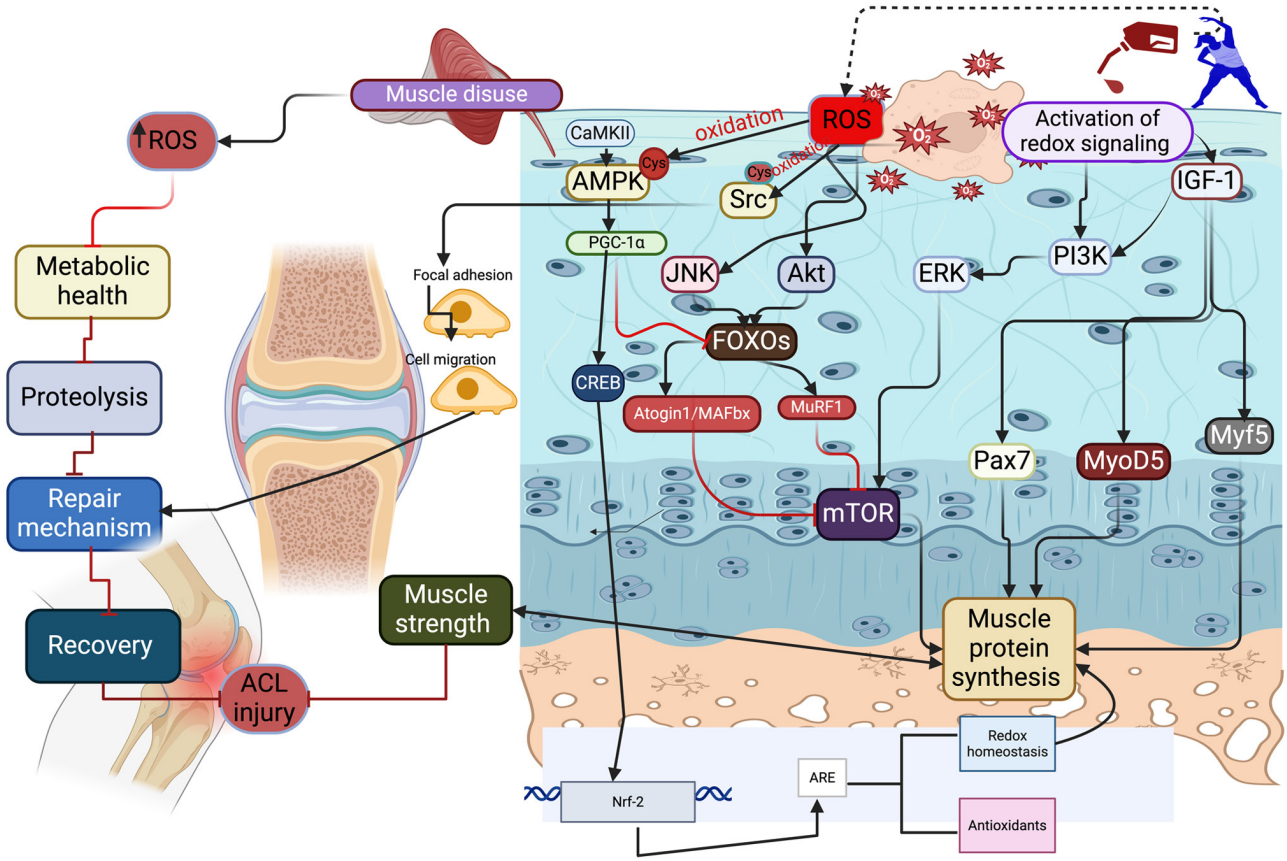

Figure 1. Muscle disuse due to ACL injury increases the levels of ROS, which in turn activate Akt, JNK and FOXO to inhibit mTOR signaling and subsequent protein synthesis. This affects metabolic health, increases proteolysis and inhibits repair. Exercise-induced redox modifications of AMPK and Src can improve tissue repair and remodeling, helping to prevent atrophy in ACL injury. Additionally, the redox modification of IGF-1 due to exercise can promote muscle protein synthesis via PI3K, ERK, mTOR, Pax7, MyoD5 and Myf5. Physical exercise also induces CaMKII, which in turn activates AMPK and PGC-1α, thus subsequently activating CREB to upregulate Nrf-2. ACL, anterior cruciate ligament; ROS, reactive oxygen species; JNK, c-Jun N-terminal kinase; FOXO, forkhead transcriptional factor O; mTOR, mammalian target of rapamycin; AMPK, AMP-activated protein kinase; IGF-1, insulin-like growth factor 1; PI3K, phosphoinositide 3-kinase; ERK, extracellular signal-regulated kinase; Pax7, paired box 7; MyoD5, myoblast determination protein 1; Myf5, myogenic factor 5; CaMKII, calmodulin-dependent protein kinase II; PGC-1α, peroxisome proliferator-activated receptor γ coactivator-1 α; CREB, cAMP response element-binding protein; Nrf-2, nuclear factor erythroid 2-related factor 2; MAFbx, F-Box/atrogin-1; MuRF1, muscle-specific RING finger protein 1.

regulators of mTOR signaling (33,34). In addition, ROS have been indicated to promote deactivation of the mTOR signaling pathway via the activation of F-Box/atrogin-1 (MAFbx) and muscle-specific RING finger protein 1 (MuRF1) (35).

Forkhead transcriptional factor O (FOXO) protein, which is also activated by ROS, is the main mediator of protein turnover (33). Several signaling pathways, including the extracellular signal-regulated kinase, c-Jun N-terminal kinase, p38 MAPK and phosphoinositide 3-kinase (PI3K)/Akt/mTOR pathways, are involved in FOXO-mediated protein synthesis (36). These pathways may collectively contribute to the amelioration of muscle mass and strength in the ACL region following reconstruction.

Different aspects of exercise, such as its intensity and duration, affect muscle strength gain. This may be due to their impact on muscle protein synthesis and the associated molecular pathways (11). For example, studies have shown that the high intensity exercise-induced production of ROS, including H_2O_2 and $ONOO^-$, enhances protein synthesis via the activation of protein kinase B and mTOR, thus promoting muscle protein translation and hypertrophy (11,37). Consequently, this process may boost muscle strength during ACL injury. Conversely, ROS can disrupt ribosomal activity and reduce protein synthesis when muscles are not used sufficiently during ACL injury. For example, prolonged muscle disuse during ACL injury can increase ROS production, thereby inhibiting the proteolytic activity of mammalian target of rapamycin complex 1, Akt and FOXO3, and enhancing calpain activity to disrupt the contractile activity of the muscle (37-39).

The initial adaptation to exercise disturbs muscle protein synthesis and strength due to the elevation of ROS levels. This is crucial in ACL injury, as it may exacerbate inflammation and muscle degradation, and hinder recovery (39). In addition, other anabolic signaling molecules, such as IGF-1, have been indicated to accelerate protein synthesis through Akt activation during exercise (40,41). For example, it has been shown that 4 weeks of aerobic exercise upregulate IGF-1, thereby promoting protein synthesis and muscle growth via the PI3K/Akt signaling pathway (40,41). This involves upregulation of the expression of paired box 7, myoblast determination protein 1, myogenic factor 5 and mTOR, and downregulation of the expression of MuRF1 and MAFbx (42). As a result, muscle atrophy following ACL injury is reduced, leading to improved muscle strength. By contrast, extended exposure to low levels of oxidants, such as H_2O_2, reduces Akt phosphorylation and protein synthesis, thereby promoting proteolysis

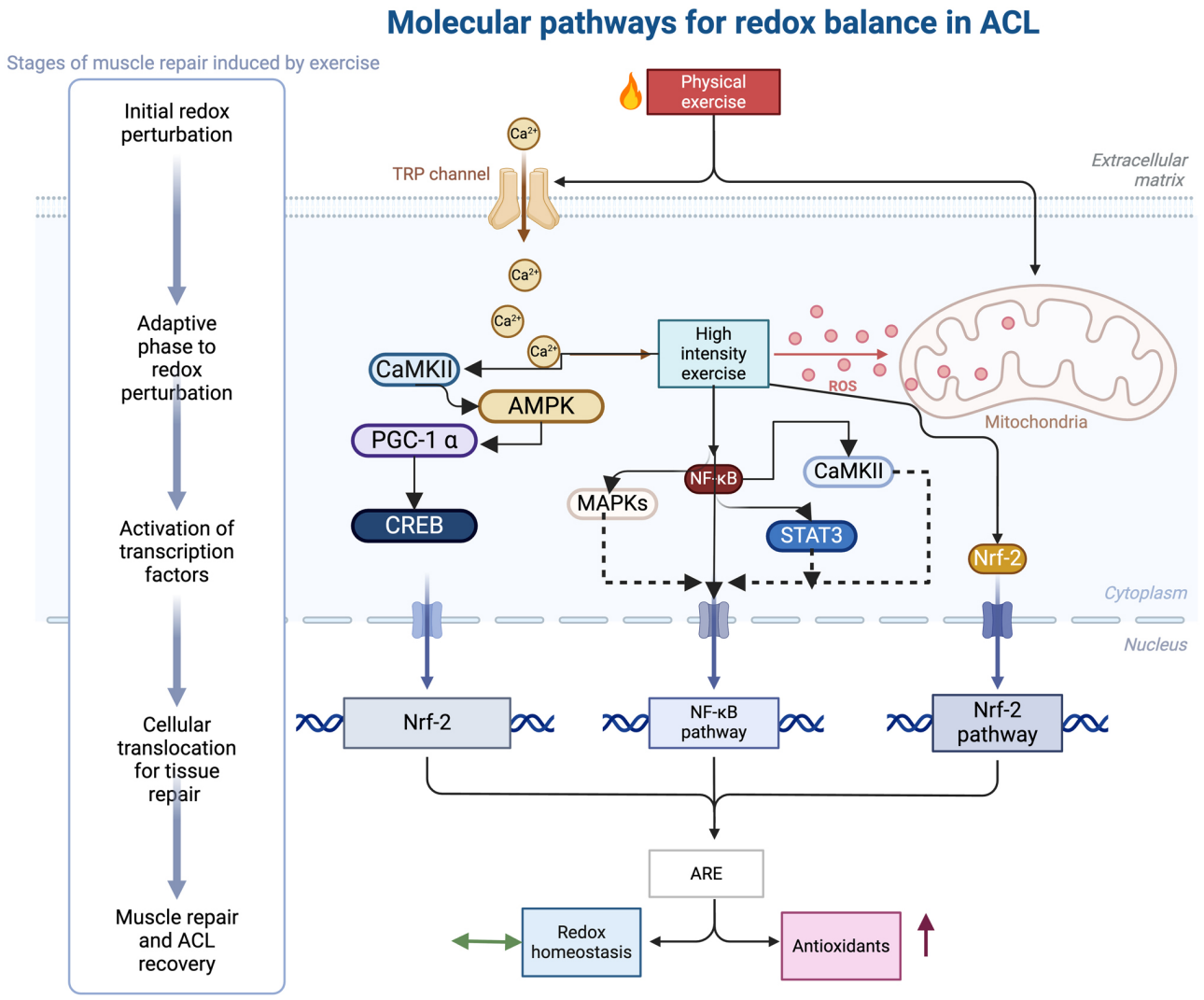

Figure 2. Molecular pathways regulating the redox system in ACL injuries during exercise. Physical exercise induces CaMKII, which in turn activates AMPK and PGC-1α. The subsequent activation of CREB upregulates Nrf-2. High-intensity exercise promotes the production of ROS, which in turn activates NF-κB signaling through MAPKs STAT3, thus triggering the Nrf-2 response. This results in an increased production of AREs and antioxidants. An upward arrow (↑) indicates an increase in antioxidants, while equivalence arrow (↔) represents a redox balance. ACL, anterior cruciate ligament; CaMKII, calmodulin-dependent protein kinase II; AMPK, a subunit of AMP-activated protein kinase; PGC-1α, peroxisome proliferator-activated receptor γ coactivator-1 α; CREB, cAMP response element-binding protein; Nrf-2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; MAPKs, mitogen-activated protein kinases; STAT3, signal transducer and activator of transcription 3; ARE, antioxidant response elements; TRP, transient receptor potential.

and muscle wasting (41). Furthermore, oxidative stress is the main regulator of muscle atrophy after ACL injury (43,44). Therefore, the upregulation of antioxidants, such as manganese superoxide dismutase, may help to attenuate atrophy and muscle weakness following ACL injury (44).

5. Factors causing muscle atrophy in ACL injury and the role of exercise-mediated redox signaling

Exercise is commonly prescribed to improve ACL injuries. However, muscle atrophy can still occur, indicating that an exercise program alone may not be sufficient to prevent muscle atrophy after ACL injury. Other factors, such as age, sex, genetic makeup and the molecular crosstalk induced by particular exercise protocols, also require consideration (1,2) (Fig. 3). Poor muscle regrowth following ACL injury has been identified as a common factor that delays the healing of an ACL injury (45). However, particular types of exercise and the resulting fiber-type transitions have been indicated to ameliorate this (45). For example, certain exercise types, such as eccentric exercises, have been found to be particularly effective in restoring muscle function after ACL injury, with ACL rehabilitation programs involving eccentric exercises increasing muscle strength by 30% compared with that achieved using concentric exercises (45,46). Notably, one study demonstrated that just 15 min of acute eccentric exercise improved muscle growth without inducing muscle fiber injury (45). This may be due to the elastic characteristics of the tendon unit, which protects the muscle from damage (47).

Redox-mediated signaling, such as that involving the mTOR pathway, is associated with muscle growth through the phosphorylation of downstream targets, including $p70^{S6k}$ (45). By contrast, over-training may result in redox collapse, potentially reducing $p70^{S6k}$ phosphorylation, inhibiting muscle

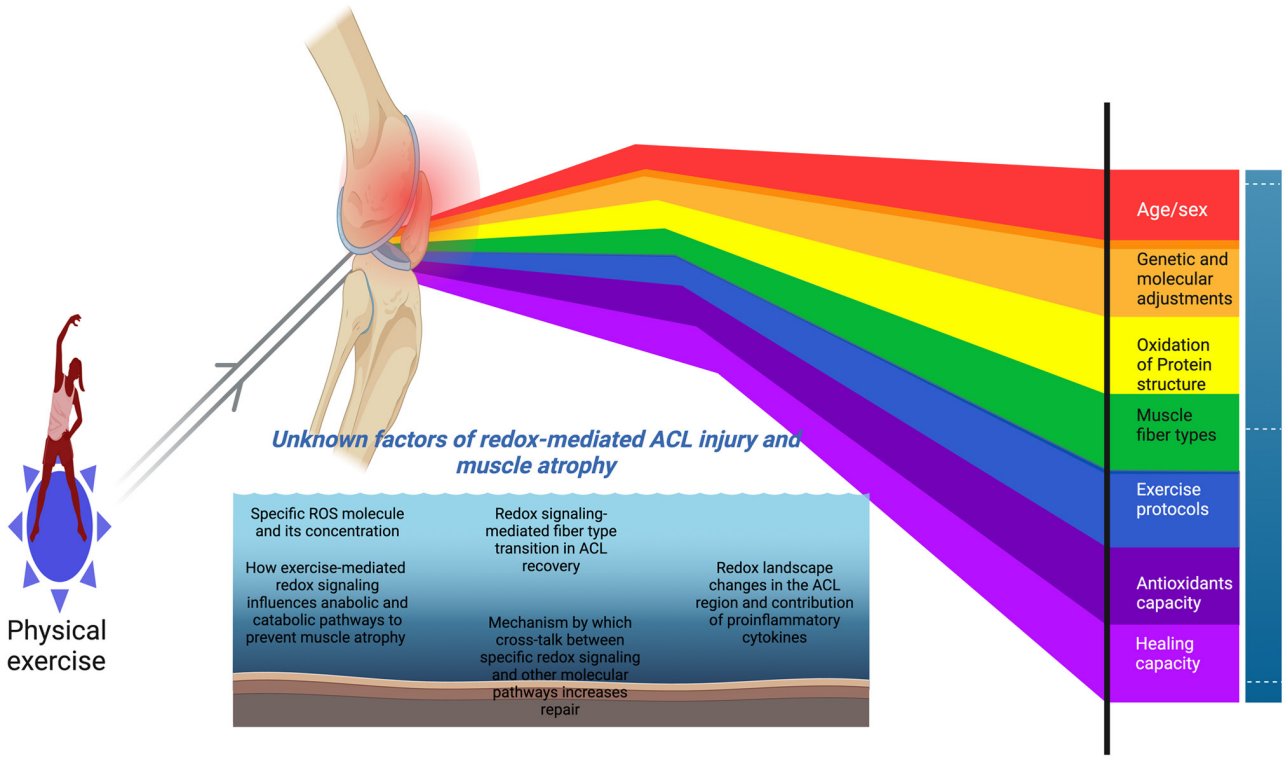

Figure 3. ROS-mediated factors affecting muscle atrophy in the ACL region following injury. Physical exercise induces redox modifications that influence signaling in ACL injury. These modifications are regulated by factors such as the sex and genetic and molecular makeup of the individual. These factors can alter the protein structure of the ACL region and affect its healing capacity. ACL, anterior cruciate ligament; ROS, reactive oxygen species.

growth and contributing to the loss of muscle (48). In addition, elevated levels of ROS and oxidative stress contribute to protein translation by activating eukaryotic translation initiation factor 4E-binding protein, a process possibly induced by $p70^{S6k}$ (48,49). The phosphorylation levels of molecules from these pathways have been indicated to vary during exercise according to its duration, thereby affecting protein synthesis; for example, the activation of $p70^{S6k}$ has been found to be elevated 6 h post-exercise (50). However, other studies found that protein synthesis was increased 24 h after a single bout of exercise, suggesting that the type of exercise and the experimental environment can affect muscle protein synthesis (51,52).

Exercise-induced redox alterations have been indicated to induce changes in fiber types. For example, a study revealed that endurance performance shifts muscle fibers to a more oxidative phenotype with higher oxygen consumption, thereby helping to prevent atrophy in ACL injury (53). However, higher oxygen consumption may disturb the oxidative environment and induce oxidative stress and further injury (54). As a result, a proteolytic event could be initiated, potentially affecting muscle mass growth. Therefore, careful consideration of the duration and intensity of endurance exercise is essential, particularly following ACL injury.

Metabolic health in the ACL region is important in promoting rapid recovery after ACL injury (55). In this context, exercise-induced redox molecules, such as NAD^+/NADH, can improve mitochondrial respiration and muscle health by regulating nicotinamide phosphoribosyltransferase (56). In addition, the exercise-mediated activation of AKT and mTOR promotes the effective distribution of glucose into the muscles around the ACL, aiding its recovery (57). Furthermore, the redox status of specific muscle fibers, influenced by different exercise protocols, may improve muscle functions in the ACL region by enhancing mitochondrial respiratory capacity, increasing muscle capillarization and boosting maximal oxygen consumption (57). For example, performing aerobic exercise for 2 weeks, ~30 min, has been indicated to alter the redox status of muscle, resulting in improved muscle mass and strength (57). In addition, resistance-type exercises, comprising a 45-min session of upper and lower body exercises three times per week, has been shown to increase the NAD^+ salvage capacity of skeletal muscle, thereby improving protein synthesis and muscle strength following ACL injury (58). Other studies have shown that ACL injury impairs mitochondrial health and reduces muscle size in the quadriceps (59,60). This may be due to local redox collapse affecting the muscle phenotype and mitochondrial content (60).

6. Association between proinflammatory cytokines and redox molecules in muscle atrophy in ACL injury

Tissue breakdown following an ACL injury can trigger the secretion of inflammatory cytokines, leading to muscle atrophy, while the reduced expression of muscle growth factors commonly results in a loss of muscle strength (45,46). Studies have shown that patients who have undergone ACL reconstruction exhibit elevated levels of cytokines and reduced quadricep muscle strength, suggesting that cytokines contribute to muscle atrophy (45,61). This finding may be

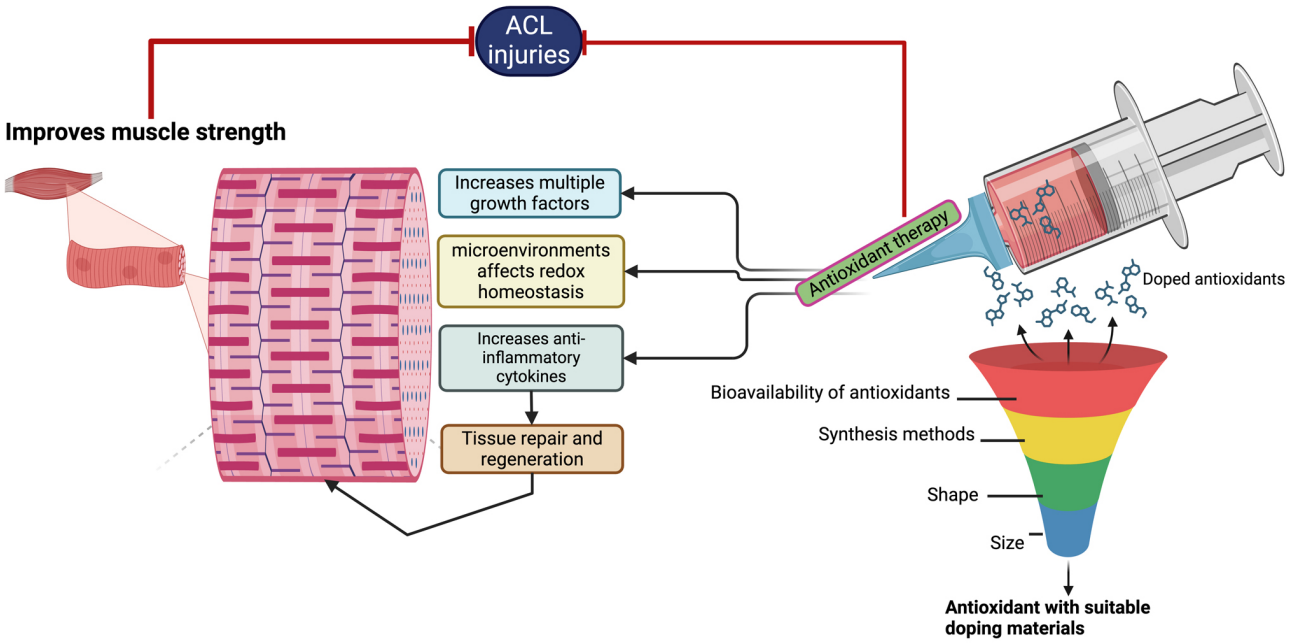

Figure 4. Delivery of antioxidants via appropriate doping materials enhances muscle recovery and prevents atrophy in ACL injuries. ACL, anterior cruciate ligament.

attributed to the initial redox flux in the injury sites increasing cytokine synthesis and triggering catabolic processes in the muscle (62). For example, the increased production of ROS by NOXs or electron transport chains activates the Nod-like receptor protein 3 inflammasome, thereby leading to the activation of IL-1 and IL-18 (62). Furthermore, TNF-α activation further increases ROS production (63), which initiates proteolytic events in the muscle and results in muscle atrophy in ACL injury (45). However, while the initial bout of exercise appears to trigger pro-inflammatory cytokines and exacerbate redox homeostasis, the adaptive phase of the exercise response has been indicated to induce anti-inflammatory cytokines and antioxidants, ultimately improving muscle health (11). However, it is important to determine whether exogenous supplements, such as vitamins C and E, can help to mitigate the initial disruption of redox homeostasis caused by exercise in ACL injury. One study demonstrated that natural antioxidants, including vitamins C and E, as well as certain polyphenols and terpenoids, effectively support tissue regeneration and recovery in ACL injury (64). These biomolecules may regulate the redox status by reversing inflammation in the tissue environment, thereby creating a more favorable environment prior to surgical implantation during ACL reconstruction (65).

7. Targeted delivery of antioxidants affects the tissue environment in ACL injury

When delivering antioxidants locally, it is imperative to ensure that they are non-toxic to the surrounding tissue. Otherwise, the antioxidants may exacerbate the ACL injury during and after surgery. For example, specific doses of antioxidants have been reported to activate multiple growth factors and attenuate redox-related pathways that are critical for tissue repair and regeneration (Fig. 4) (66).

When administering antioxidants, achieving effective delivery to the targeted tissues is of great importance (67). Biomaterials can help to preserve the efficacy of antioxidants during their delivery to targeted tissues. However, their biochemical properties, such as how they interact with enzymes, and their biocompatibility and biodegradability, may limit the advantages of these molecules (68). The antioxidant dose can influence redox homeostasis within the microenvironment of an ACL injury. Therefore, the delivery of antioxidants using particular biomaterials, such as coatings or scaffolds, can effectively regulate the quantity of antioxidant delivered, improve redox homeostasis around the ACL region, and promote the diffusion of the antioxidant into the surrounding tissue, and increase bioavailability (69). Studies have demonstrated that nanoparticles, particularly gold nanoparticles (AuNPs), are able to deliver antioxidants efficiently (69,70). For example, superoxide dismutase (SOD)-doped AuNPs can break the chain of free radical reactions by inhibiting superoxide generation (69,71). In addition, AuNPs doped with taurine can improve tissue repair in the later phase of the healing process by reducing the expression of IL-4 and IL-10 and upregulating myogenic regulatory factor 5, thereby improving muscle recovery (69,70). Also, a recent study reported that AuNPs alone were able to enhance ACL graft performance in an ovine model. This improvement was suggested to be due to the antioxidant and anti-inflammatory properties of the AuNPs affecting the remodeling process following ACL injury. However, the biological properties of AuNPs are dependent upon their size, shape and method of synthesis (69,71).

Polyethylene terephthalate can be used to product artificial ligaments that are commonly used for ACL reconstruction (68). However, despite polyethylene terephthalate having good mechanical properties, its low biocompatibility reduces its efficiency. The fusion of polyethylene glycol with

appropriate antioxidants has been demonstrated to restore the muscle structure, and ameliorate muscle atrophy via the reduction of oxidative stress (72). Nanoemulsions infused with antioxidants have exhibited the ability to decrease ROS formation and promote muscle repair, which indicates that combining antioxidants with appropriate delivery agents can yield favorable outcomes after ACL reconstruction, with minimal non-specific side effects (73).

8. Effect of redox-modifying drugs and exercise on ACL injury

Redox-based drugs can help to mitigate oxidative stress-induced muscle weakness associated with ACL injury and atrophy. However, their efficacy remains unsatisfactory. For example, antioxidants such as vitamin C and E have not been found to improve muscle dysfunction following ACL surgery, suggesting that they do not promote the synthesis of antioxidant enzymes, such as SOD, catalase and glutathione peroxidase (GSH) (64). Therefore, combining physical exercise with these supplements may be necessary to yield a more positive effect on ACL-related injuries.

Targeting redox-sensitive proteins with redox-modifying drugs may upregulate antioxidant response elements (ARE) to enhance the production of antioxidants, thereby decreasing ROS levels around or within the ACL region. For example, dimethyl fumarate (DMF) and sulforaphane are redox-based drugs that target the sulfhydryl groups of Cys residues, such as Cys151, Cys273 and Cys288 in KEAP1. These drugs commonly interact with the Cys151 residue to disrupt the KEAP1-cullin 3 interaction, leading to the accumulation of Nrf-2 in the nucleus along with ARE gene activation. Combining these drugs with physical exercise may further improve clinical outcomes and motoneuron inputs, as exercise may modify their efficacy by boosting mitochondrial function, reducing muscle fatigue and improving histopathology through the promotion of Nrf-2 accumulation (74,75). In addition, sulforaphane and curcumin have been shown to ameliorate muscular dystrophy in mdx mice via the activation of Nrf-2 (76,77), whereas running exercise alone, without the activation Nrf-2 transcriptional activity, exhibits no profound effect on muscle pathology (78). These findings highlight the importance of combining these redox-based drugs with exercise to optimize the activation of Nrf-2 and improve muscle recovery.

Other drugs, including ebselen and cadmium chloride, have been indicated to interact with Cys273, Cys288, and C613 residues of KEAP1, causing conformational distortion of the DC domain and dissociation of the KEAP1-Nrf-2 interaction, thereby resulting in the nuclear accumulation of Nrf-2 (79). In addition, combining exercise with ebselen increases muscle glucose uptake at rest by mimicking GSH activity, suggesting that H_2O_2 plays a key role in glucose uptake during exercise combined with ebselen administration (80,81).

NOX is an important contributor to the formation of ROS. Therefore, inhibiting NOX may potentially mitigate the consequences of oxidative stress. Redox drugs, such as GKT1 36901, GKT137831 and VAS2870, have been shown to inhibit the activity of NOX1, NOX4, NOX5 and dual oxidases. For example, GKT1 36901 inhibits NOX1/4, resulting in decreased vasodilation in the collateral-dependent arterioles after exercise training (82). In addition, GLX481304 selectively inhibits the activity of NOX2 and NOX4, thereby decreasing ROS production in cardiomyocytes and improving the contractile properties of the heart (83). Therefore, combining these NOX inhibitors with exercise could be an effective strategy for the management of exercise-induced ROS production.

Xanthine oxidase (XO), a key source of ROS production, contributes to skeletal muscle and cardiovascular injury during high-intensity physical exercise. A study demonstrated that XO inhibitors, such as allopurinol, reduce muscle atrophy via inhibition of the p38 MAPK/MAFbx pathway (84). Similarly, febuxostat blocks XO activity, which has been shown to improve left ventricular function and strengthen the myocardial system during intense treadmill exercise (85). Furthermore, nitric oxide (NO) inhibitors, such as N^G-mono-methyl-l-arginine, reduce NO levels to improve metabolic effects and protein synthesis, and regulate blood flow during continuous and dynamic exercise, thereby mitigating muscle atrophy associated with ACL injury (86,87).

9. Conclusion

Exercise is considered as a key approach for the prevention of ACL injuries. However, the recommendation of exercise for ACL injuries requires careful consideration, since exercise intensity and duration are associated with the dysregulation of redox signaling homeostasis. This can affect muscle protein synthesis, metabolic health, the repair mechanism around the ACL region and recovery rate. The present review highlights the potential of exercise to ameliorate ACL injuries by inducing redox signaling, thereby preventing muscle atrophy. Notably, redox molecules induced by exercise can trigger crosstalk among several molecular pathways in ACL injury to prevent muscle atrophy. In addition, the exercise-induced regulation of redox status in muscle fibers affects fiber type transitions, helping to prevent atrophy following ACL injury. However, the rate and duration of redox-related molecule expression during exercise may guide the use of redox-based therapies in combination with exercise to enhance recovery and prevent atrophy in ACL injury.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

AT was responsible for conceptualization. YW, CG, HZ, ZL and AT prepared and wrote the original draft of the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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