What are the potential mechanisms of fatigue-induced skeletal muscle hypertrophy with low-load resistance exercise training?

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List of Abbreviations:

Resistance exercise training – (RET)

1-repetition maximum – (1-RM)

Cross-sectional area – (CSA)

Muscle protein synthesis – (MPS)

mechanistic target of rapamycin – (mTOR)

Mitogen-activated protein kinase – (MAPKs)

Growth hormone – (GH)

Electromyography (EMG)

Blood flow restriction – (BFR)

Calcium – (Ca^{2+})

Myoplasmic free [Ca^{2+}] – ([Ca^{2+}]$_i$)

Mitochondrial Ca^{2+} uniporter – (MCU)

Proliferator-activated receptor gamma coactivator 1 alpha 4 gene – (PGC1α4)

Duchenne muscular dystrophy –(DMD)

Exercise-induced muscle damage –(EIMD)

Insulin-like growth factor 1 – (IGF-1)

Reactive oxygen and nitrogen species – (RONS)

Extracellular signal-regulated kinase ½ – ($ERK_{1/2}$)

Hydrogen peroxide – (H_2O_2)

Nonsteroidal anti-inflammatory drugs – (NSAIDs)

Ras homolog enriched in the brain – (Rheb)

Glyceraldehyde-3-phosphate – (GAPDH)

Tuberous sclerosis complex 2 – (TSC2)

Abstract

High-load resistance exercise (>60% of 1-repetition maximum) is a well-known stimulus to enhance skeletal muscle hypertrophy with chronic training. However, studies have intriguingly shown that low-load resistance exercise training (RET) (≤60% of 1-repetition maximum) can lead to similar increases in skeletal muscle hypertrophy as compared to high-load RET. This has raised questions about the underlying mechanisms for eliciting the hypertrophic response with low-load RET. A key characteristic of low-load RET is performing resistance exercise to, or close to, task failure, thereby inducing muscle fatigue. The primary aim of this evidence-based narrative review is to explore whether muscle fatigue may act as an indirect or direct mechanism contributing to skeletal muscle hypertrophy during low-load RET. It has been proposed that muscle fatigue could indirectly stimulate muscle hypertrophy through increased muscle fibre recruitment, mechanical tension, ultrastructural muscle damage, the secretion of anabolic hormones, and/or alterations in the expression of specific proteins involved in muscle mass regulation (e.g., myostatin). Alternatively, it has been proposed that fatigue could directly stimulate muscle hypertrophy through the accumulation of metabolic by-products (e.g., lactate), and/or inflammation and oxidative stress. This review summarizes the existing literature eluding to the role of muscle fatigue as a stimulus for low-load RET-induced muscle hypertrophy and provides suggested avenues for future research to elucidate how muscle fatigue could mediate skeletal muscle hypertrophy.

Introduction

The current American College of Sports Medicine position statement for resistance exercise recommends that individuals train using at least 70% of their one repetition maximum (1-RM) for 8-12 repetitions per set for 1-3 sets to maximize resistance exercise-induced adaptations such as muscle hypertrophy and strength (1). These guidelines are based on the notion that hypertrophic adaptations are maximized by activating higher threshold motor units at ≥ 70% 1-RM (2), consistent with the load-dependent Henneman size principle of motor unit recruitment (3). These recommendations are based on training with high loads (>60% of 1-RM). However, similar muscle hypertrophic adaptations have been reported in response to high- and low-load (≤60% of 1-RM) resistance exercise training (RET) when muscle contractions are performed to task failure (i.e. to volitional fatigue) (4–7). Low-load RET may be a beneficial exercise modality for encouraging adherence to a RET program (8), as it can stimulate muscle hypertrophy similar to high-load RET (9, 10) while reducing joint reactive forces compared to higher-load training (8). Understanding the mechanisms underpinning muscle hypertrophy in response to both high-load and low-load RET is crucial from a practical perspective, as these interventions elicit comparable hypertrophic outcomes. However, the upstream stimuli and underlying downstream molecular cell signalling mechanisms involved in the hypertrophic response may exhibit similarities and differences between high-load and low-load RET. Muscle hypertrophy is primarily defined by an increase in skeletal muscle cross-sectional area (CSA), predominantly driven by the expansion of contractile elements (11). This hypertrophic process requires the stimulation of muscle protein synthesis (MPS) rates, which must exceed the rate of muscle protein breakdown to facilitate a positive net protein balance and subsequent protein accretion in muscle tissue (12). The regulation of MPS is multifaceted, involving both mechanistic target of rapamycin complex 1 (mTORC1)-dependent and independent mechanisms (e.g., via the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase 1/2 (ERK1/2) pathway). These pathways are thought to be critical for promoting exercise-induced anabolism and the expansion of contractile elements (11, 13–18). Although not discussed in depth in the present review, muscle satellite cells and myonuclear accretion may also contribute to RET-mediated muscle hypertrophy (19–22). Additionally, ribosome biogenesis plays a key role in skeletal muscle hypertrophy, as the rate of protein synthesis within a myocyte is partly determined by translational capacity, which is limited by the number of ribosomes (23). However, this topic is beyond the scope of this review. Readers are referred to several detailed review papers for a comprehensive overview of these hypertrophic mechanisms (21, 22, 24).

During RET with relatively high loads, the majority of muscle fibres are recruited immediately, including high-threshold motor units that innervate type II fibres, which are recognized for their enhanced hypertrophic potential (25, 26). In contrast, low-load RET likely involves a delayed recruitment of high-threshold motor units, with muscle fatigue, with repeated contractions, these higher-threshold motor units are recruited to sustain force output (5, 27). Therefore, training to task failure during low-load RET may enable the activation of these muscle fibres independently of the load (28), while higher loads may facilitate greater motor unit recruitment even before reaching the point of task failure (29). For example, terminating high-load RET prior to failure yields similar increases in muscle mass over eight weeks compared to high-load RET performed to task failure (30, 35).

Nonetheless, both high and low loads can induce fatigue. Muscle hypertrophy can also occur with sets terminated before task failure (5-8 repetitions in reserve), regardless of the training load (31). Still, hypertrophy is generally more pronounced when sets are performed closer to task failure (31). Thus, proximity to task failure appears necessary for maximizing muscle hypertrophy with low-load RET (7, 32–36), whereas training to failure may not be as essential with high-load RET (37–39). Consequently, training to or near task failure, particularly with lower training loads, may be critical for optimizing skeletal muscle hypertrophy. This suggests that RET-induced fatigue might significantly stimulate muscle hypertrophy, highlighting the importance of fatigue in low-load RET.

Muscle fatigue is often defined by an exercise-induced decline in muscle contractile performance (i.e., decreased force or power) (40) and is commonly attributed to metabolic perturbations. Broadly, fatiguing exercise can induce the accumulation of metabolites (e.g., inorganic phosphate, H^+, lactate) and result in energy substrate depletion (e.g., glycogen), impairing the volitional drive to skeletal muscle and/or decrease intrinsic muscle force generation capacity (40–46). However, fatigue during low-load RET may not primarily result from the classic mechanisms of fatigue (e.g., metabolite accumulation or substrate depletion), yet it can still effectively stimulate skeletal muscle hypertrophy. We, therefore, propose that fatigue could act 'directly' and/or 'indirectly' through various mechanisms to stimulate skeletal muscle hypertrophy, which we describe below. Fatigue may function as a 'direct stimulus' for muscle hypertrophy by inducing various physiological changes within the muscle (e.g., increased metabolite accumulation and inflammation), with those stimulating a hypertrophic response. For example, fatigue could directly influence the mechanisms of skeletal muscle growth through the accumulation of specific metabolites (e.g., lactate), localized oxidative stress and inflammation (32, 47). Conversely, we propose that fatigue might be an 'indirect stimulus' through secondary mechanisms, such as enhanced fibre recruitment and mechanical tension applied to these newly recruited fibres. These mechanisms are activated in response to repeated contractions that lead to fatigue-induced reductions in contractile force output. We propose that mechanical tension and muscle damage may act as indirect mechanisms for inducing muscle hypertrophy, particularly in response to fatigue-inducing RET. Initially, mechanical tension activates a subset of muscle fibres. As these fibres become fatigued, additional fibres are recruited to sustain the required force (3). This progressive recruitment and the associated mechanical tension and muscle damage contribute to the overall hypertrophic response (3, 5, 27). Increased recruitment of muscle fibres during fatiguing contractions at low loads (48) could also be enhanced by metabolic stress (i.e., low intracellular energy/accumulation of metabolites), initiating an indirect signalling cascade to activate anabolic processes in muscle (49). Hormones with anabolic properties [e.g., testosterone, growth hormone (GH), insulin-like growth factor 1 (IGF-1)] have also been suggested to impact the hypertrophic response to RET, as fatigue-related factors (e.g. inorganic phosphate, H^+, glycogen depletion) have been previously proposed to indirectly stimulate their production through various mechanisms (e.g. lactate, muscle damage, reactive nitrogen species) (50, 51).

Despite the differences among the proposed upstream mechanisms of low-load induced skeletal muscle hypertrophy (Figure. 1), performing low-load RET to task failure due to muscle fatigue appears necessary to stimulate maximal hypertrophic adaptations (7, 32–35). While RET is the most effective exercise modality to induce skeletal muscle hypertrophy, other types of exercise (e.g., high-intensity interval training) are also associated with increases in whole muscle CSA/volume, as previously reviewed (52). However, it should be noted that not all forms of fatigue-inducing exercise lead to muscle hypertrophy, and some types of prolonged endurance exercise may attenuate the hypertrophic response of skeletal muscle to RET (53–56). Thus, with sufficient load, fatigue-inducing RET likely induces divergent downstream cellular signalling compared to fatigue-inducing endurance exercise. This review will explore the potential of RET-induced fatigue to act as an indirect and/or direct stimulus to elicit skeletal muscle hypertrophy during low-load RET. Avenues for future research to elucidate how fatigue could mediate skeletal muscle hypertrophy will also be discussed.

Potential Indirect Mechanisms of Fatigue Induced Skeletal Muscle Hypertrophy

Low-load fatigue-induced hypertrophy is proposed to be mediated by several indirect mechanisms. Specifically, mechanisms associated with fatigue (e.g. increased metabolite concentration, substrate depletion) (40–43, 45, 46) may have secondary effects, which could increase skeletal muscle hypertrophy. These include increased recruitment of type II muscle fibres during exercise to task failure (34, 48, 49, 57), mechanical tension signalling mechanosensors (11, 58), muscle damage stimulating MPS rates to facilitate tissue repair/remodelling (59), increasing the concentration of circulating anabolic hormones (60–62) and modifying gene expression and content

of proteins implicated in the regulation of muscle mass (i.e., myostatin) (63). The notion that high and low loads can result in similar hypertrophy when performed to task failure is grounded in the theory that, regardless of the load, the entire spectrum of available motor units will eventually be recruited. Full motor unit recruitment occurs in part because, as contractions become fatiguing, the brain must activate higher-threshold motor units to maintain the necessary force (2, 64). Furthermore, it has been proposed that an acute increase in systemic and localized hormone concentrations, such as testosterone and GH, can influence the muscle anabolic response, which may be indirectly stimulated through fatiguing contractions (60, 61). However, this hypothesis is frequently contested (65–67). The proposed effects of exercise load and volume on fibre recruitment, muscle damage, and fatigue are outlined in Figure 2. This section will explore indirect mechanisms potentially linked to fatigue-induced muscle hypertrophy, including 1) fibre recruitment, 2) mechanical tension, 3) exercise-induced muscle damage, 4) hormonal changes, and 5) alterations in the expression of specific proteins involved in muscle mass regulation.

1. Fibre Recruitment

High and low training loads are generally accepted to promote whole muscle hypertrophy by increasing muscle fibre CSA. One of the most widely accepted hypotheses linking fatigue to muscle hypertrophy during low-load RET involves the additional recruitment of type II muscle fibres when exercise is performed to task failure (48, 49, 57, 68). Regardless of load or time under tension, performing resistance exercises to task failure is proposed to activate both type I and type II muscle fibres maximally (28). As a result, MPS rates and muscle hypertrophy are expected to be more pronounced in recruited fibres. Previous research on muscle activation and hypertrophy in the triceps-brachii demonstrated that increases in CSA over 12 weeks of RET were strongly correlated with and induced by the regions most activated during an acute bout of exercise (69, 70). Therefore, muscle activation, and by extension, fibre recruitment, is a key mechanism driving muscle hypertrophy in response to RET.

1.1 Metabolic Stress and Blood Flow Restriction

During exercise, the increased ADP/ATP ratio and the resulting accumulation of various metabolites are termed ‘metabolic stress.’ Metabolic stress has previously been proposed as a potential mechanism to induce muscle hypertrophy in response to RET (discussed in later sections) (71, 72). The higher within-set repetitions and greater time under tension with low-load RET results in greater metabolic stress (73), leading to additional fibre recruitment with the onset of muscle fatigue. Therefore, this increased fibre recruitment may ultimately contribute to increased skeletal muscle hypertrophy. Multiple studies have demonstrated that recruitment thresholds diminish as fatigue accumulates during sustained submaximal exercise (74–76). Consequently, more muscle fibres are recruited as fatigue sets in.

One method to investigate the role of metabolic stress is through blood flow restriction (BFR). When BFR is combined with RET, MPS is acutely stimulated (77, 78) , and muscle hypertrophy is promoted (62, 79–81), which has been proposed to be due to metabolite accumulation (33) and muscle cell swelling (discussed in subsequent sections) (82, 83) enhancing fatigue and, therefore, muscle fibre recruitment. However, MPS is not stimulated when BFR is applied without RET (84), and BFR alone is inadequate to mitigate muscle loss during bed rest (85). The recruitment and hypertrophy of type II fibres in response to BFR-RET may be attributed to changes in the intramuscular environment (86). Metabolic stress and the accumulation of metabolites such as hydrogen ions (H^+), lactate, and inorganic phosphate (discussed in subsequent sections) can accelerate the onset of fatigue during exercise (40, 46, 87), leading to a reduced time under tension and fewer repetitions to task failure (5, 87, 88), consequently limiting training volume. Another hypothesis for BFR-RET-induced hypertrophy is that acute elevations in systemic anabolic hormones (discussed in later sections) may contribute to the stimulation of MPS (60, 89). Overall, studies utilizing BFR-RET suggest that increased recruitment of type II fibres, driven by increased metabolic stress, likely plays a key role in promoting muscle hypertrophy as exercise-induced fatigue progresses.

1.2 Fibre-Specific Recruitment and Hypertrophy

Type II fibres exhibit a greater hypertrophic capacity compared to type I fibres (25, 26, 90). This heightened hypertrophic potential is often attributed to the fact that fibre-type-specific hypertrophy is predominantly observed following high-load RET (91). High loads preferentially activate higher-threshold motor units (2), a phenomenon corroborated by the greater surface electromyography (EMG) amplitudes observed during high-load

versus low-load RET (92, 93). To effectively recruit these higher-threshold motor units, low-load RET must be performed to task failure, thereby increasing time under tension (2, 94) and ensuring full recruitment of type II muscle fibres (28). These factors are essential for achieving skeletal muscle hypertrophy (95).

When low-load RET is not performed to task failure, high-load RET proves to be a superior hypertrophic stimulus (35), resulting in greater growth of both type I and type II muscle fibres (2, 96) and more significant increases in strength than low-load RET (2, 10, 97). These greater strength adaptations may be attributed to enhanced neural mechanisms, such as improved motor unit activation and reduced antagonistic activation, independent of fibre-specific hypertrophy (10, 98, 99). High-load RET has been shown to produce more substantial neural adaptations, including increases in maximal voluntary isometric contraction force, voluntary activation, and EMG amplitude, compared to low-load RET (100, 101).

When low-load RET is performed to task failure, previous findings generally suggest greater hypertrophy in type I muscle fibres compared to high-load RET (2, 96, 97). However, not all research supports this distinction (102). A systematic review concluded that low-load BFR-RET may result in similar or even greater hypertrophy of type I fibres compared to type II fibres, potentially due to increased metabolic stress or inflammation (94). The authors, however, did not propose a specific mechanism for this observation, describing it as "preliminary evidence" and emphasizing the need for further research (94). Other studies suggest that similar hypertrophy can be achieved with low and high loads in muscles such as the soleus (type I dominant) and the gastrocnemius (mixed fibre type) muscles (103). It is also common to observe a decrease in the percentage of type IIX fibres following RET (97, 104, 105). Therefore, while fibre-specific hypertrophy remains a contentious topic, the hypothesis that low-load RET performed to task failure may result in greater type I muscle fibre hypertrophy than high-load RET is intriguing and warrants further investigation.

1.3. Increased Intracellular Calcium

Intracellular calcium (Ca^{2+}) is a key mediator that can convert mechanical load into an intracellular signalling pathway (106). Additionally, fibre recruitment activates excitation-contraction coupling processes to enable force generation, with increased myoplasmic free [Ca^{2+}] ([Ca^{2+}]$_i$) being a major regulator of crossbridge force generation. One hypothesis suggests that increased [Ca^{2+}]$_i$, resulting from the recruitment of muscle fibres and elevated motor unit discharge rates during fatiguing exercise, activates calmodulin, which in turn activates calcineurin and increases MPS rates (107), thereby stimulating muscle fibre hypertrophy (107). In mice, the muscle-specific deletion of sarcolipin, a sarcoplasmic reticulum calcium ATPase (SERCA) pump inhibitor, reduces calcineurin activation and induces muscle atrophy by accelerating Ca^{2+} removal from the myoplasm (108). Another hypothesis proposes that increased [Ca^{2+}]$_i$ induces Ca^{2+} entry into the inner mitochondrial membrane via a dedicated Ca^{2+} channel, the mitochondrial Ca^{2+} uniporter (MCU) (109). This Ca^{2+} entry activates the insulin growth factor-1/Akt pathway and the transcription of the proliferator-activated receptor gamma coactivator 1 alpha 4 gene (PGC1α4) (109), a potent regulator of muscle hypertrophy (110). However, it remains unknown whether these Ca^{2+}-mediated mechanisms can fully explain hypertrophy in human skeletal muscle and whether they underlie an indirect pathway by which the activation of muscle fibres during increased fibre recruitment associated with fatiguing low-load RET stimulates muscle hypertrophy.

2. Mechanical Tension

Mechanical tension is typically recognized as the most robust regulator of MPS rates, demonstrating increased skeletal muscle hypertrophy and muscle mass when performing high-load RET (11, 111). It is well established that muscle mass and strength are rapidly lost when mechanical tension is removed from muscles, as seen during periods of immobilization, bed rest, or exposure to microgravity (112, 113). The mechanisms of mechanical load-induced skeletal muscle growth have been extensively reviewed (11). The proposed mechanisms through which mechanical tension induces muscle hypertrophy are primarily through mechanotransduction, but have also been suggested to include increased anabolic hormone production, muscle damage, ROS production, and increased recruitment of fast-twitch muscle fibres (11, 47). However, it remains uncertain whether mechanical tension is the mechanism underlying muscle hypertrophy with low-load RET, as this training imposes less mechanical tension on the whole muscle. Furthermore, muscle fatigue also decreases the contractile force of already recruited muscle fibres, decreasing the mechanical tension imposed on those fibres.

The hypertrophic response to mechanical load involves mechanotransduction, a process where mechanosensors convert musculoskeletal stress from mechanical loading into chemical signals that activate intracellular anabolic and catabolic pathways, ultimately leading to the enlargement of myofiber (2, 114). A key mediator of this load-induced mechanotransduction is focal adhesion kinase (FAK). This non-receptor kinase transduces skeletal muscle stress into signals transmitted across the cytoplasmic membrane, activating cell growth pathways (115–117). Focal adhesions are associated with the Hippo pathway effectors Yes-associated protein 1 (Yap1) and its paralogue gene Wwtr1 (Taz). Yap and Taz are mechanosensitive transcriptional cofactors (118) that respond to various exercise-associated stimuli, including RET (119). These factors regulate muscle differentiation and satellite cell function (120). Yap activation leads to skeletal muscle hypertrophy (121, 122) and is known to be associated with mTORC1 activation through downstream signalling processes (123–125).

Dystrophin plays a crucial protein in modulating mechanical tension (126), stabilizing the muscle membrane during contraction, and helping to prevent contraction-induced muscle damage (127). Additionally, dystrophin serves as a mediator of cell signalling processes (128). These mechanisms underscore the critical role of mechanical tension in skeletal muscle growth, as its absence leads to significant atrophy. To our knowledge, no studies have specifically investigated the activation of FAK or Yap following high- and low-load RET. However, it is reasonable to hypothesize that mechanotransduction occurs in both scenarios when RET is performed to task failure, potentially serving as a signal for hypertrophy.

Although high-load exercise is generally associated with increased muscle hypertrophy and strength (2, 129), mechanical tension may not be the primary mechanism for muscle hypertrophy in low-load RET due to the relatively low tension involved (47). Therefore, rather than mechanical tension alone being the primary driver of skeletal muscle hypertrophy with low loads, we propose that performing RET to failure allows for an extended time under tension, facilitating additional muscle fibre recruitment to sustain the force output. This recruitment places mechanical tension on the newly activated fibres, even though the overall mechanical tension on the entire muscle remains lower. The mechanical load on these newly activated fibres could stimulate hypertrophy through mechanotransduction, even with low loads. Consequently, while mechanical tension is an important factor in skeletal muscle hypertrophy, we propose that mechanical tension and fibre recruitment are closely interconnected and are necessary to induce hypertrophy with low-load RET.

3. Exercise-Induced Muscle Damage

Exercise-induced declines in contractile force, i.e., fatigue, can also be partially explained by mechanical factors related to exercise-induced muscle damage (EIMD) (130). EIMD can affect specific macromolecules within the tissue or lead to significant tears in the sarcolemma, basal lamina, and supportive connective tissue, injuring the contractile elements and the cytoskeleton (131). Research has demonstrated that EIMD promotes MPS (132), triggers an acute inflammatory response, increases cell swelling, ROS, and satellite cell activity (131), and stimulates anabolic hormone signalling, potentially enhancing hypertrophy, as previously reviewed (133). Indirect markers of EIMD, such as elevated blood creatine kinase concentration, suggest that performing RET to task failure may lead to greater muscle damage compared to non-failure conditions (134). Therefore, EIMD resulting from fatigue-induced low-load RET could theoretically contribute indirectly to increased muscle hypertrophy.

Indirect markers of muscle damage, including elevated blood creatine kinase and myoglobin concentrations, reductions in maximal voluntary contraction torque, and increased perceptions of muscle soreness, suggest that high-load RET induces greater muscle damage than low-load RET (61, 135–137). However, Haun et al. (2017) found that 48 hours after an exercise bout with high or low loads, some indirect markers of muscle damage, such as perceptions of muscle soreness and myoglobin concentrations, were similar between groups (138). Other studies have found that low-load BFR-RET induces muscle damage, as evidenced by elevated creatine kinase concentration, increased perception of muscle soreness, and decreased force production during maximum voluntary contractions (139–141), ultimately showing low-load BFR-RET performed to task failure can lead to comparable muscle damage to high-load RET (142). The topic of BFR-RET-induced EIMD has been discussed in greater detail elsewhere (143). Although low-load BFR-RET can elicit muscle damage, hypertrophy, and satellite cell proliferation (142, 144), most studies suggest that high-load RET and low-load RET with BFR induce greater muscle damage than low-load RET alone across various populations (140, 145).

Despite EIMD being associated with increased MPS rates under various RET modalities (132), the increased MPS observed in the early stages of resistance exercise appears primarily directed toward tissue

repair/remodelling subsequent to muscle damage rather than contributing to skeletal muscle hypertrophy (146). Therefore, while EIMD following a novel bout of RET increases MPS, this increase is unlikely to significantly contribute to increases in muscle mass, especially in exercise-naïve individuals. That is to say, the acute metabolic alterations in myofibrillar protein metabolism in the presence of accompanying EIMD are not representative of chronic skeletal muscle hypertrophic adaptations induced by RET (147). Furthermore, if EIMD does increase MPS, the extent of EIMD is not likely a major contributor to hypertrophy induced by low-load RET.

4. Hormones

Resistance exercise has been shown to elicit acute changes in the circulating concentration of various anabolic hormones (e.g., testosterone, GH, IGF-1) (89). Many of these hormones, particularly testosterone, play a role in regulating the molecular pathways involved in RET-induced skeletal muscle hypertrophy (148). Specifically, it has been suggested that the acute post-exercise increase in anabolic hormone concentrations contributes to exercise-induced muscle hypertrophy (60–62). The acute increase in circulating anabolic hormone concentrations has been attributed to increases in metabolite concentrations and metabolic stress resulting from fatiguing exercise rather than solely the mechanical stimulus during RET (60, 61), as well as EIMD (133). However, evidence indicates that RET involving high muscle tension still elevates the concentrations of circulating anabolic hormones (50, 149), suggesting that some mechanical tension may be necessary for effective anabolic signalling. Furthermore, the effects on hormonal responses can vary depending on whether RET is performed closer to, or further from task failure (134). Performing RET with high volume and effort and activating a substantial amount of total muscle mass results in elevated circulating concentrations of testosterone, GH (150, 151), and IGF-1 (61). These findings suggest that RET enhances anabolic hormone concentrations and that training to failure may be crucial for maximizing these hormonal responses.

Despite the anabolic properties of testosterone and GH on certain tissues, the acute exercise-induced release of these hormones is unlikely to impact skeletal muscle hypertrophy substantially (151–153). Increases in endogenous anabolic hormone (i.e., testosterone, GH, and IGF-1) concentrations following RET do not increase MPS rates or consistently enhance muscle hypertrophy (65–67, 153–155). Furthermore, Morton et al. (2016) showed no significant differences in anabolic hormone levels between two groups of young men undertaking either high-load or low-load RET (102). Specifically, after 12 weeks of training, both groups demonstrated comparable increases in lean body mass and type I and type II fibre CSA, with no significant differences observed between the training groups (102). Additionally, androgen receptor content appears to be more closely associated with RET-induced skeletal muscle hypertrophy than systemic hormone concentrations (154). Overall, we propose that while fatigue-inducing exercise can influence endogenous hormone concentrations, these changes are unlikely to play a major role in driving skeletal muscle hypertrophy in healthy individuals with a normal hormonal milieu.

5. Specific Proteins

While numerous metabolic enzymes are activated and upregulated following exercise, fatigue has been linked to specific metabolic enzymes and proteins hypothesized to stimulate hypertrophy. A notable example that responds directly to acutely and chronically fatiguing exercise is the inhibition of myostatin. Myostatin is a negative regulator of muscle mass in many mammals, including humans (156, 157), and its gene expression decreases following resistance exercise (158, 159) both acutely (following a single bout) and chronically (following a training regimen) (63, 160). Fatigue-inducing exercise could inhibit myostatin, thereby contributing to muscle hypertrophy through increased activation of mTORC1, the stimulation of MPS rates, and/or the reduction in proteolysis (161, 162). Myostatin is regulated in various ways; one key factor related to RET involves mature myostatin being stored in a latent complex where it cannot bind to a receptor (163). The activation of this latent myostatin, and thus its inhibition, is proposed to occur through factors such as low pH, ROS, and proteases (164), making this an indirect mechanism of low-load induced hypertrophy. However, to our knowledge, these latent myostatin activation mechanisms have not been evaluated in skeletal muscle post-low-load RET.

Few studies have directly compared myostatin expression following high and low-load RET. One study reported that myostatin gene expression and its related targets were similar in both high- and low-load RET conditions (165). Another study demonstrated a more pronounced decrease in myostatin gene expression following low-load BFR-RET compared to low-load RET without BFR (166). While the pathophysiology of myostatin has been reviewed previously (157, 163), the mechanism behind the reduction of myostatin in the post-exercise period

remains unclear. Therefore, low-load BFR-RET may decrease myostatin expression more than high or low-load RET alone, potentially contributing to greater muscle hypertrophy. However, more research is needed to confirm this in humans and to explore further the effects following high and low-load RET.

Potential Direct Mechanisms of Fatigue-Induced Hypertrophy

Fatigue induced by low-load RET may act as a direct mechanism for skeletal muscle hypertrophy through changes to the myocellular environment (e.g., increased metabolite concentration, inflammation, substrate depletion) (40–43, 45, 46). An increase in the concentration of local metabolites (e.g., H^+, lactate, inorganic phosphate) is common during RET, which may activate signalling pathways known to stimulate MPS rates and thereby induce skeletal muscle hypertrophy with chronic RET (48). Systemic or localized changes in inflammation are also proposed mechanisms that could augment the muscle hypertrophic response (72, 82, 83). In this section, we will explore the current evidence on 1) metabolites, and 2) cell swelling and inflammation, and how fatigue may directly stimulate RET-induced muscle hypertrophy via these mechanisms.

1. Metabolites

While mechanical tension has been suggested as the key to stimulating muscle hypertrophy (48), during high-repetition sets, various metabolites such as lactate and reactive oxygen and nitrogen species (RONS) can accumulate in the blood or muscle (167). The accumulation and dysregulation of many metabolites is termed 'metabolic stress' (as discussed previously). The build-up of metabolic by-products (e.g. lactate, hydrogen ions, inorganic phosphate, and others) from anaerobic metabolism during resistance exercise (168, 169) has been proposed to enhance the anabolic response (26, 48), and these metabolites have been previously suggested as potential mechanisms underlying metabolite-induced muscle hypertrophy (71, 72).

1.1 Lactate

Exercise increases blood and plasma lactate concentrations, with low-load RET performed to failure increasing blood (170) and plasma lactate concentrations (171) more than high-load RET. This may be due to the increased reliance on anaerobic glycolysis to sustain more prolonged exercise at low loads to task failure. Lactate does not cause peripheral muscle fatigue (40, 45), but III/IV muscle afferents sense intramuscular lactate to cause central fatigue (172), which would consequently affect muscle fibre recruitment. Importantly, lactate acts on many body tissues (e.g., brain, heart, and muscle) and integrates several signalling pathways hypothesized to elicit a hypertrophic response (173). Previous studies have shown that oral lactate administration in mice increased skeletal muscle mass and fibre CSA (174, 175). This lactate-dependent hypertrophy is proposed to occur through increased MyoD expression (176), activation of extracellular signal-regulated kinase 1/2 ($ERK_{1/2}$) (177), and decreased p38 MAPK (178) signalling.

Despite the greater lactate accumulation with low-load compared to high-load RET (170, 171), and the possible mechanisms and positive effects of lactate observed in rodents and myotubes, few studies have examined the effects of lactate on muscle hypertrophy in humans. A recent randomized control trial in human participants showed that direct exogenous lactate infusion at rest or with exercise did not support the hypothesis that lactate can alter skeletal muscle anabolic signals via mTOR or ERK signalling (179). While lactate accumulation may elicit many physiological effects in the body (68, 173), it is unlikely that increased lactate concentrations from low-load RET alone would provide a sufficient signal for muscle hypertrophy in humans. For a more comprehensive review of lactate's role in hypertrophy, the reader is referred to (68).

1.2 RONS/Oxidative Stress

Strenuous exercise increases the generation of RONS within skeletal muscle, which can contribute to muscle fatigue by modifying proteins critical for force production (180). However, RONS also serve as essential signalling molecules, regulating various cellular signalling pathways (181), some of which have been implicated in RET-induced muscle hypertrophy (182, 183), a subject extensively reviewed in previous literature (184). For example, nitric oxide has been shown to interact with superoxide to form peroxynitrite, which can activate mTOR signalling (106, 185). Hydrogen peroxide (H_2O_2) has been shown to enhance IGF-1 signalling (186) and trigger a

signalling cascade leading to mTOR activation *in vivo* and *in vitro* (106, 187). Whether low-load RET induces higher oxidative stress than high-load RET remains unclear.

Locally, RONS production is greater with an acute bout of low-load BFR than low-load or high-load RET (188). The increase in RONS with BFR may be partly due to local hypoxia, which plays an important role in nitric oxide production (188); however, this study did not involve exercise to failure. Reviews and meta-analyses have reported that in humans, the inhibition of RONS with the addition of antioxidants has no effect on RET-induced muscle hypertrophy (182, 189). However, some research in humans have shown attenuation of the hypertrophic response with vitamins C and E supplementation (190–192), potential reductions in hypertrophy with N-acetyl cysteine supplementation (186), and complete blunting in neuronal nitric oxide synthase knockout mice (106).

In older individuals (≥ 65 years of age), exercise coupled with 500mg/day of resveratrol increases muscle strength and fibre area more than exercise alone (193), and dietary antioxidant (vitamin C, E, or β-carotene) consumption is related to improved muscle strength and increased physical performance (194). The effects of antioxidant supplementation may, therefore, be age- and dose-dependent. These studies (193, 194) suggest that older individuals with elevated baseline oxidative stress may also display a diminished hypertrophic response to RET without supplemental interventions.

These findings imply that excessive and insufficient oxidative stress post-exercise may impair RET-induced muscle hypertrophy. In summary, although oxidative stress may contribute to the hypertrophic response, the exact involvement of these pathways in low-load RET-induced muscle hypertrophy requires further investigation.

2. Cell Swelling and Inflammation

During intense exercise, skeletal muscle fibre volumes change rapidly, leading to significant swelling primarily associated with muscle fatigue (195). These periods of intracellular swelling have been proposed as mediators of the anabolic response to RET and BFR-RET (72, 82, 83). Acute cell swelling during RET may result from changes in membrane potential during exercise and the associated redistribution of K^+ and Cl^-, which has been reviewed previously (195). This cell swelling increases muscle thickness during an acute bout of both high and low-load RET (196). Additionally, the hypoxic environment and the accumulation of metabolites and blood from RET and BFR-RET (as discussed previously) create ideal conditions for further increasing cellular swelling, and may also shift intra- and extracellular water balance (82). It is proposed that this cell swelling activates a volume sensor, which may initiate signalling cascades such as the mTORC1 and MAPK pathways, ultimately leading to muscle hypertrophy (82). It should be noted that cell swelling has been previously linked to inflammation, particularly during ischemia-reperfusion (197), commonly observed with BFR.

Inflammatory cells, particularly neutrophils and macrophages, are commonly elevated in the exercised muscle tissue following RET in humans (198, 199) and following isometric contractions or passive stretching in animal models (200, 201). Notably, repeated bouts of these exercises have been linked to subsequent skeletal muscle hypertrophy. Both neutrophils and macrophages produce free radicals and play a significant role in influencing oxidative stress. Evidence supporting the role of inflammation in fatigue-induced muscle hypertrophy includes findings related to the effects of non-steroidal anti-inflammatory drugs (NSAIDs), which have been shown to modulate inflammatory responses and impact muscle adaptation.

Similar to the relationship between oxidative stress and antioxidants (as discussed previously), hypertrophy following RET can be enhanced or impaired by NSAID use, with age- and dose-dependent effects (202). RET with high doses of NSAIDs (>1200mg/day) increases skeletal muscle hypertrophy in older adults more than RET alone (203). Therefore, older adults with higher inflammatory status at baseline might exhibit a compromised hypertrophic response without additional interventions, as RET acutely increases inflammation. Conversely, younger individuals with low baseline inflammatory status who use high doses of NSAIDs (>1200mg/day) could experience a modest blunting in RET-induced muscle hypertrophy (204). A study on older rats (20 months old) supplemented with an NSAID (ibuprofen) also found increased muscle protein synthesis and decreased proteolysis compared to a control group (205).

These findings suggest that excessive and insufficient inflammatory signals may hinder hypertrophy following RET. For a more in-depth review of the influence of NSAIDs on muscle hypertrophy, we direct the reader to (202). It should be noted that elevated oxidative stress (discussed previously) can trigger inflammatory responses

(224), and high levels of inflammation can induce oxidative stress, creating a feedforward loop (206). Although inflammation likely contributes in some way to the hypertrophic response, the precise role of this process in low-load RET-induced muscle hypertrophy requires further investigation.

Conclusion

Fatigue has been identified as a stimulus for eliciting skeletal muscle hypertrophy during chronic low-load RET. Our literature review suggests the most compelling hypotheses linking fatigue to muscle hypertrophy in the context of low-load RET center on increased fibre recruitment. Training to task failure increases fibre recruitment, partially through metabolic stress, which imposes mechanical tension on the newly recruited fibres. This process appears to be a major contributor to hypertrophy. While intramuscular fatigue may serve as a critical stimulus for skeletal muscle hypertrophy with low-load RET via various indirect and direct mechanisms, these pathways are not mutually exclusive. The human body is characterized by redundant signalling pathways that enable multiple signals and stimuli to concurrently trigger muscle hypertrophy during fatigue-inducing low-load RET (Figure 1). Consequently, numerous similar mechanisms can induce skeletal muscle hypertrophy across both high- and low-load conditions. Ultimately, whether through direct or indirect mechanisms, volitional exhaustion (i.e., fatigue) emerges as a crucial factor in optimizing the hypertrophic response during low-load RET.

Future Directions

While we have provided an overview of the potential mechanisms by which fatigue during low-load RET may stimulate skeletal muscle hypertrophy, we acknowledge that this topic has not yet been sufficiently explored. Consequently, several research areas require further investigation to elucidate the specific mechanisms that may be similar or different between high- and low-load RET.

Low-load RET may lead to fibre-specific hypertrophy, particularly in type I fibres, due to progressive fibre recruitment and delayed mechanical tension. However, more research is needed to understand the differences in fibre-specific hypertrophy among low- and high-load BFR-RET. Beyond the classic hypertrophy observed in the contractile elements (e.g., myofibers), other non-contractile sarcoplasmic proteins may accumulate within skeletal muscle fibres. Sarcoplasmic hypertrophy has been discussed previously as an adaptation to RET that may or may not be possible (11, 207). While some suggest that high-volume training may promote sarcoplasmic hypertrophy to a greater extent than high-load training (207), relatively few studies have examined sarcoplasmic hypertrophy in this context.

While potential mechanisms lead us to believe that intracellular Ca^{2+} transients during muscle contractions are a possible mechanism, the influence of intracellular Ca^{2+} contributing to skeletal muscle hypertrophy with low loads has not been examined in humans. Therefore, we suggest this topic needs further exploration in humans, especially when comparing high- and low-load RET. Similarly, while myostatin expression can be augmented in response to RET and skeletal muscle hypertrophy, no studies have compared changes in myostatin signalling after high- or low-load resistance exercise.

An optimal range of inflammation and oxidative stress may be necessary to maximize the hypertrophic response to RET, as hypertrophy appears to be attenuated when inflammation or oxidative stress levels are either excessively high or low. This blunting of the hypertrophic response may be influenced by age-related factors or pharmacological and nutritional interventions (e.g., NSAIDs or antioxidants). However, the specific molecules and pathways through which inflammation and RONS may induce hypertrophy remain unclear. Future studies should focus on examining the effects of specific inflammatory cells or markers, as well as RONS, on muscle hypertrophy. Understanding these dynamics is essential, as they likely contribute to hypertrophy induced by low-load RET.

Author contributions

Conceptualizations: Luke D. Flewwelling, Victor Cao, Tyler A. Churchward-Venne, Arthur J. Cheng.; Literature search: Luke D. Flewwelling, Victor Cao, Sarkis Hannaian; Writing – original draft preparations: Luke D. Flewwelling, Victor Cao; Writing – review & editing: Luke D. Flewwelling, Sarkis Hannaian, Victor Cao, Thomas Chaillou, Tyler A. Churchward-Venne, Arthur J. Cheng.; Supervision: Arthur J. Cheng.; Funding acquisition: Arthur J. Cheng.

521

522 **Figure legends**

523 **Figure 1.** Proposed mechanisms contributing to low-load fatigue-induced hypertrophy. Direct mechanisms are
524 defined here as mechanisms that can stimulate hypertrophy and are related to fatigue-induced changes in the muscle
525 (e.g. increased metabolites, inflammation, substrate depletion). Indirect mechanisms are defined here as mechanisms
526 that can secondarily induce hypertrophy, not directly via changes resulting from fatigue-inducing RET. Green boxes
527 represent mechanisms that fatigue will likely induce hypertrophy through low-load resistance exercise training.
528 Light green dashed boxes represent potential mechanisms in which fatigue may influence hypertrophy through low-
529 load resistance exercise training. Question marks represent mechanisms which are not fully understood. Red boxes
530 represent mechanisms unlikely to result in hypertrophy from low loads. Lines with arrows represent proposed
531 mechanisms and pathways that drive the previous mechanism. Dashed lines with arrows represent a mechanism
532 exerting influence on another, indicating that the process at the arrow's origin can modulate or affect the process at
533 the arrow's destination. Dashed lines show an interaction between two mechanisms.

534

535 **Figure 2.** Proposed effects of load on muscle recruitment, damage, and fatigue in single muscle fibres between the
536 first and last repetition of acute resistance exercise.

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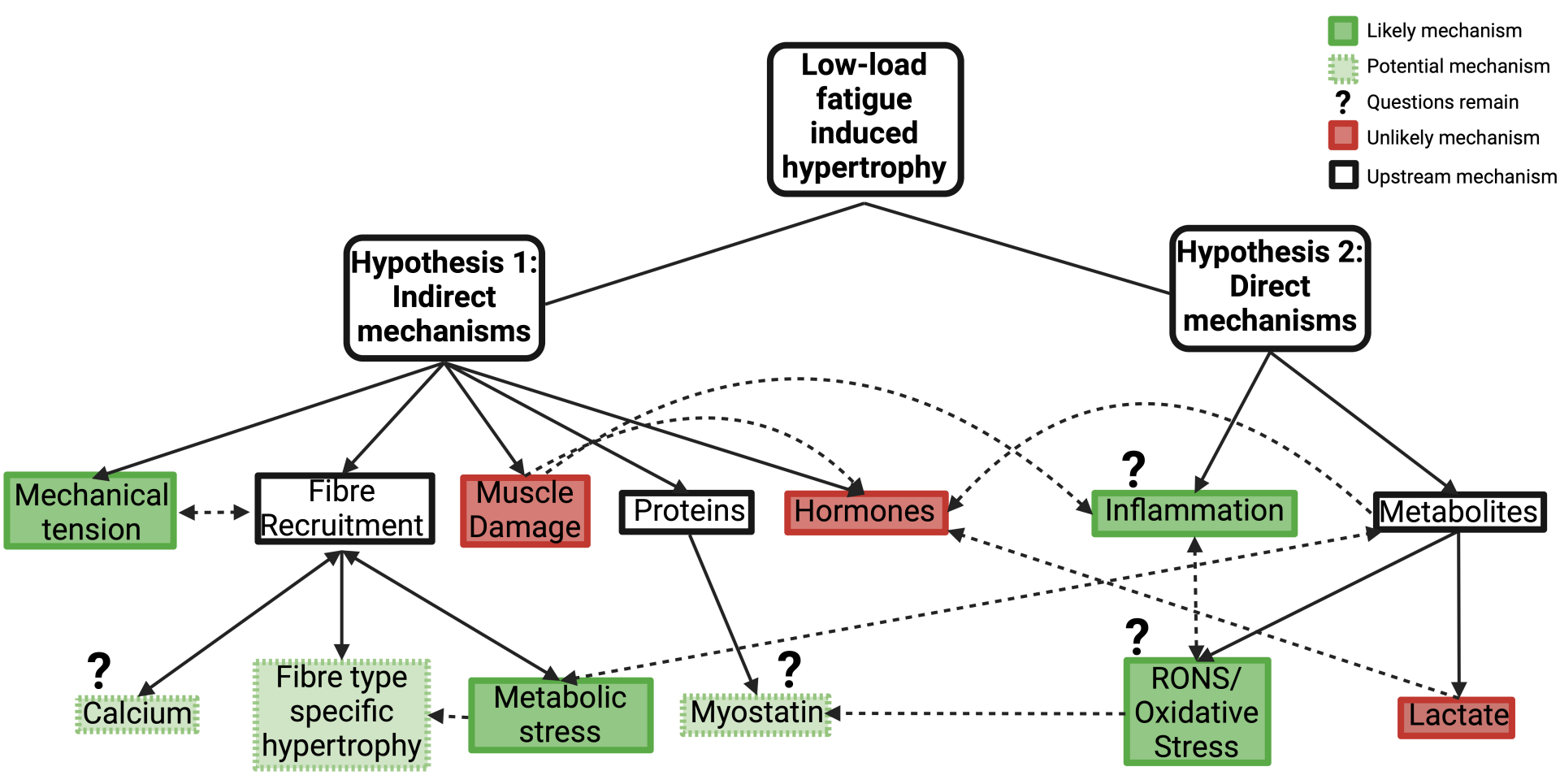
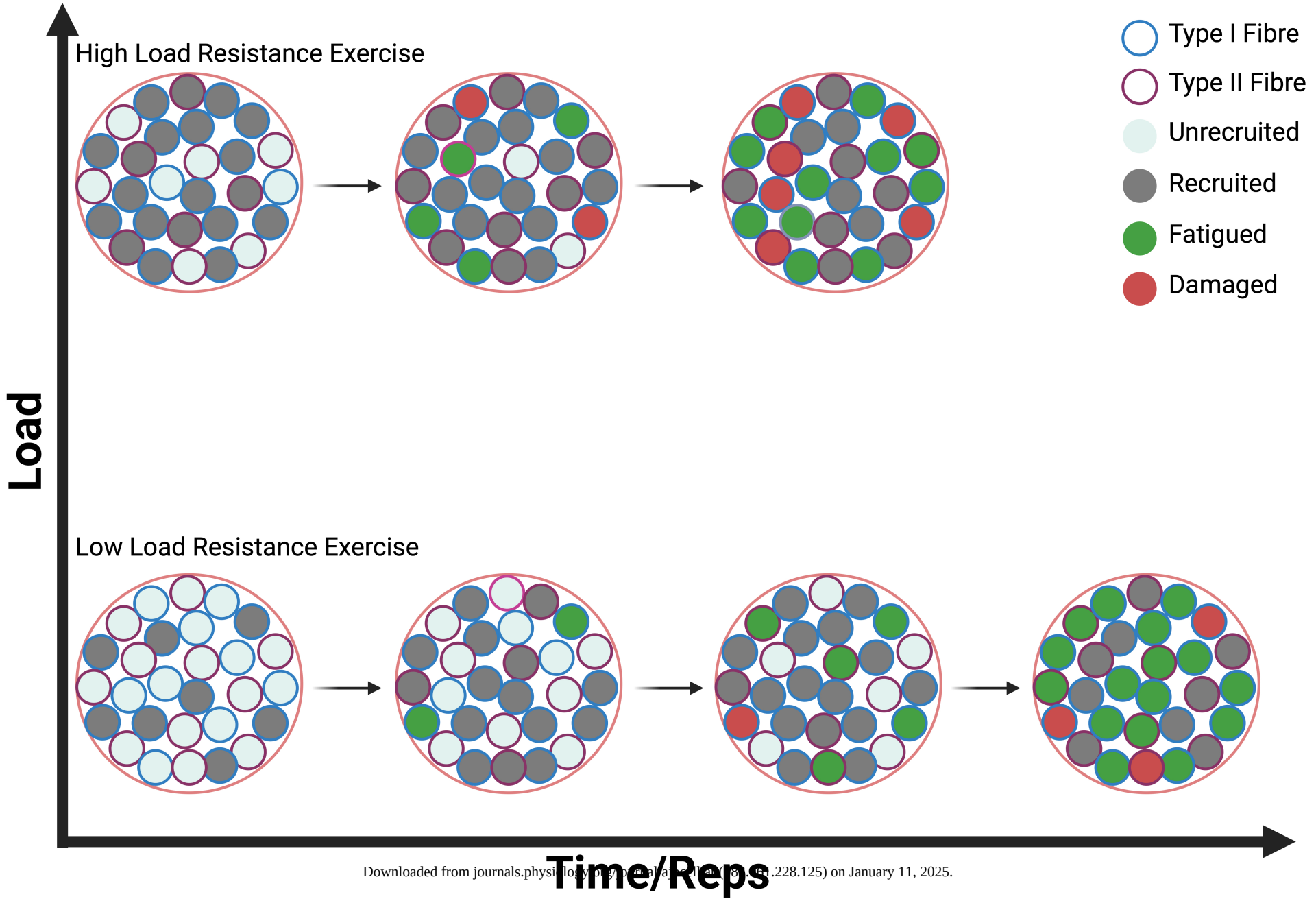
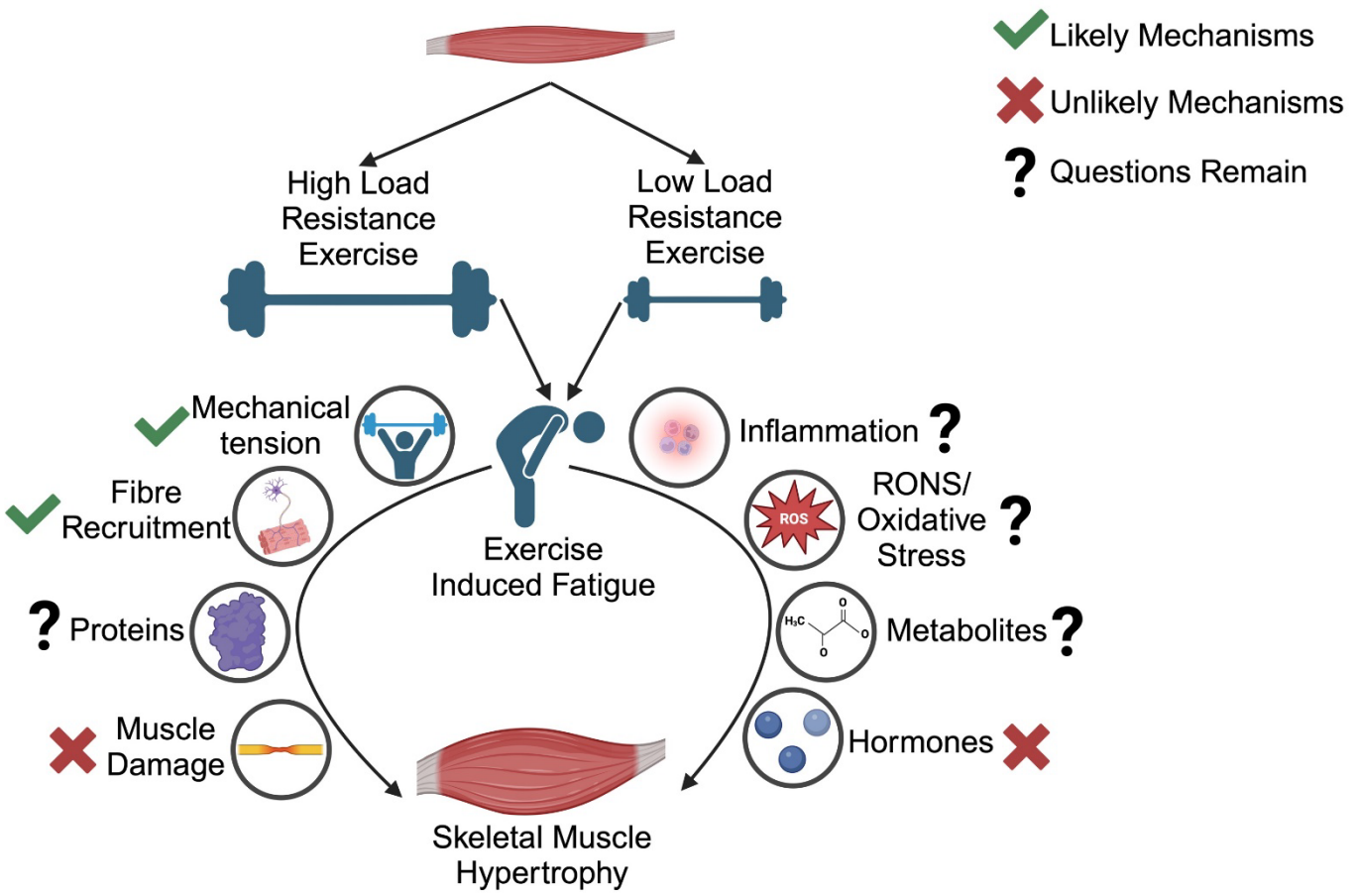




Mechanisms of Fatigue-Induced Skeletal Muscle Hypertrophy with Low-Load Resistance Training



Low-load resistance exercise has been proposed to increase skeletal muscle hypertrophy through multiple mechanisms; however, we propose that exercise-induced fatigue plays a key role in the hypertrophic response via mechanisms that increase muscle fibre recruitment during volitional exhaustion, as well as via increased mechanical tension on the newly recruited fibres.