Sports Med (2013) 43:179–194
DOI 10.1007/s40279-013-0017-1

REVIEW ARTICLE

Potential Mechanisms for a Role of Metabolic Stress in Hypertrophic Adaptations to Resistance Training

Brad J. Schoenfeld

Published online: 22 January 2013

Abstract It is well established that regimented resistance training can promote increases in muscle hypertrophy. The prevailing body of research indicates that mechanical stress is the primary impetus for this adaptive response and studies show that mechanical stress alone can initiate anabolic signalling. Given the dominant role of mechanical stress in muscle growth, the question arises as to whether other factors may enhance the post-exercise hypertrophic response. Several researchers have proposed that exercise-induced metabolic stress may in fact confer such an anabolic effect and some have even suggested that metabolite accumulation may be more important than high force development in optimizing muscle growth. Metabolic stress pursuant to traditional resistance training manifests as a result of exercise that relies on anaerobic glycolysis for adenosine triphosphate production. This, in turn, causes the subsequent accumulation of metabolites, particularly lactate and H^+. Acute muscle hypoxia associated with such training methods may further heighten metabolic buildup. Therefore, the purpose of this paper will be to review the emerging body of research suggesting a role for exercise-induced metabolic stress in maximizing muscle development and present insights as to the potential mechanisms by which these hypertrophic adaptations may occur. These mechanisms include increased fibre recruitment, elevated systemic hormonal production, alterations in local myokines, heightened production of reactive oxygen species and cell swelling. Recommendations are provided for potential areas of future research on the subject.

B. J. Schoenfeld (✉)
Department of Health Sciences, Program of Exercise Science, APEX Building, Room # 265, Lehman College, CUNY, 250 Bedford Park Blvd West, Bronx, NY 10468, USA
e-mail: brad@workout911.com

1 Introduction

It has been well established that regimented resistance training can promote increases in muscle hypertrophy. The prevailing body of research indicates that mechanical stress is the primary impetus for this adaptive response. These findings were described in the seminal work of Goldberg et al. [1], who reported that increased force development is the critical event in initiating compensatory muscular growth. Subsequently, numerous studies have confirmed this finding both *in vitro* (within the glass), *ex vivo* (outside the living), and *in vivo* (within the living) [2–6].

Current theory suggests that forces associated with resistance exercise disturb the integrity of skeletal muscle, causing mechano-chemically-transduced molecular and cellular responses in myofibres and satellite cells [7]. Exercise-induced hypertrophy is facilitated by a complex cascade of anabolic and catabolic signalling pathways, whereby the effects of mechano-stimulation are molecularly transduced to downstream targets that shift muscle protein balance to favour synthesis over degradation. Many anabolic signalling pathways are involved in exercise-induced gains in muscle mass with certain pathways functioning in a permissive role while others directly mediate cellular processes that influence messenger RNA (mRNA) translation and thus hypertrophy [8]. Pathways that have been identified as particularly important to muscle anabolism include mammalian target of rapamycin (mTOR), mitogen-activated protein kinase (MAPK), and various calcium-dependent pathways, amongst others. Although these pathways may overlap at key regulatory steps, there is evidence that they are synergistic rather than redundant [9]. However, the precise mechanisms and interplay between them have yet to be fully elucidated. A complete discussion of the topic is beyond the scope of this

article and interested readers are referred to reviews by Bassel-Duby and Olson [10], Miyazaki and Esser [11] and Glass [12]. Figure 1 presents a simplified flowchart of various signalling cascades and their relevance to anabolic and catabolic processes.

Mechanical stress alone has been shown to directly stimulate mTOR [13], possibly through activation of the extracellular regulated kinase/tuberous sclerosis complex 2 (ERK/TSC2) pathway [6]. It is theorized that these actions are mediated via the synthesis of the lipid second messenger phosphatidic acid (PA) by phospholipase D [13, 14]. There also is evidence that PA can phosphorylate the downstream anabolic translational regulator p70S6 kinase (p70S6k) independent of mTOR [15], presenting another potential avenue whereby mechanical stimuli may directly influence muscle protein synthesis.

Given the dominant role of mechanical stress in muscle growth, the question arises as to whether other factors may enhance the post-exercise hypertrophic response. Several researchers have proposed that exercise-induced metabolic stress may in fact confer such an effect [16–18] and some have even suggested that metabolite accumulation may be more important than high force development in optimizing muscle growth [19]. Other researchers, however, dispute such claims [20]. Therefore, the purpose of this paper will be to review the emerging body of research suggesting a role for exercise-induced metabolic stress in maximizing muscle development, and present insights as to the potential mechanisms by which these hypertrophic adaptations may occur. To carry out this review, English-language literature searches of the PubMed, EBSCO, and Google Scholar databases were conducted for all time periods up to April 2012. Combinations of the following keywords were used as search terms: 'metabolic stress', 'metabolite buildup', 'metabolite accumulation', 'resistance training', 'resistance exercise', 'weight lifting', 'bodybuilding', 'powerlifting', 'anabolic hormone', 'Kaatsu', 'occlusion exercise', 'blood flow restricted exercise' and 'cell swelling'. The reference lists of articles retrieved in the search were then screened for any additional articles that had relevance to the topic. Given the broad scope of this review, a narrative approach was chosen as the best way to convey pertinent information and inclusion criteria was based on applicability to the particular area of discussion.

2 Evidence for a Hypertrophic Effect from Metabolic Stress

Metabolic stress pursuant to exercise manifests as a result of the accumulation of metabolites, particularly lactate, Pi and H^+ [21, 22], and acute muscle hypoxia associated with resistance training may serve to further heighten metabolic buildup and, hence, stimulate hypertrophic adaptations [7, 23]. It is conceivable that hypoxia may have a direct effect on contractile protein accretion and thereby contribute to the hypertrophic stimulus, although this has not been well studied. Other metabolites of possible relevance to anabolism include calcium and various electrolytes.

Support for the potential hypertrophic role of exercise-induced metabolic stress can be noted empirically by examining the moderate-intensity training regimens

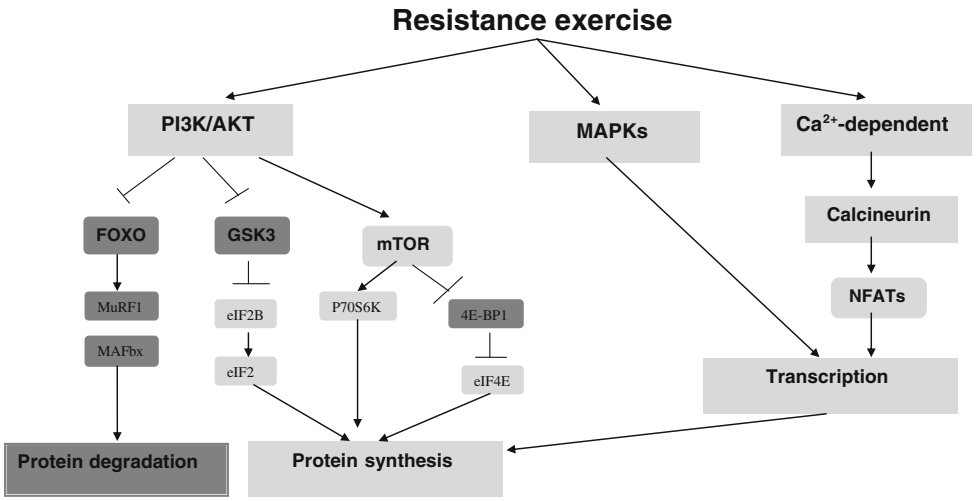

Fig. 1 Simplified schematic of intracellular signalling pathways. Flowchart shows the pathways associated with intracellular signalling for muscle hypertrophy. Light grey boxes represent anabolic processes while the dark grey boxes represent catabolic processes. *4E-BP1* 4E binding protein-1, *AKT* protein kinase B, Ca^{2+} calcium, *eIF2, 2B and 4E* eukaryotic initiation factor 2 and 2B, *FOXO* forkhead box O, *GSK3* glycogen synthase kinase-3, *MAFbx* muscle atrophy F-box, *MAPKs* mitogen-activated protein kinases, *mTOR* mammalian target of rapamycin, *MuRF1* muscle ring finger-1, *NFATs* nuclear factor of activated T-cells, *PI3K* phosphatidylinositol 3-kinase, *P70S6K* P70S6 kinase

adopted by a majority of bodybuilders, which are intended to heighten metabolic buildup at the expense of higher training intensities [24, 25]. Typical hypertrophy-oriented bodybuilding routines involve the performance of multiple sets of 6–12 repetitions per set with relatively short inter-set rest intervals [26]. These routines have been found to induce significantly more metabolic stress than higher-intensity regimens typically employed by powerlifters [27–29]. Yet, despite training with reduced intensities, bodybuilders commonly display extreme levels of muscularity at least as great, if not more so, than that achieved by powerlifters [25, 30]. Indeed, several studies have reported greater increases in muscle growth from moderate-intensity bodybuilding-type training protocols as compared with high-intensity powerlifting-style routines [31–33], although these findings are not consistent across all trials when equating for volume load [34]. It should be noted that both bodybuilders and powerlifters are known to use anabolic steroids and other pharmacological aids, which may confound the ability to make firm conclusions on the topic.

The increased metabolic response associated with moderate-intensity training (~60–80% 1-repetition maximum [1RM]) can be attributed at least in part to the increased energy contribution from fast glycolysis, which results in peripherally as opposed to centrally induced fatigue (i.e. fatigue related to metabolic and/or biochemical changes as opposed to reductions in neural drive) [35]. Muscle lactate levels of 91 mmol/kg (dry weight) have been reported after the performance of 1 set of 12 repetitions to failure (total time under tension mean ± standard deviation [SD] 37 ± 3 s) and these values spiked to 118 mmol/kg after three sets [36]. This is in contrast to high-intensity protocols (~90% + 1RM), where energy provision is primarily derived from the phosphagen system and thus results in minimal metabolic buildup. Moreover, oxygen delivery to muscle is compromised at moderate lifting intensities due to persistent compression of arterial and venous flow over an extended time period, resulting in acute hypoxia [37]. In combination, these factors cause the rapid accumulation of metabolites within muscle as well as lowering intramuscular pH levels [38].

Experimental evidence showing that metabolic stress contributes to the hypertrophic response can be exemplified by Kaatsu training studies, where resistance exercise is combined with blood flow restriction. Kaatsu is carried out at low intensities (generally <40% 1RM) while using a pressure cuff to induce muscle ischaemia. A large body of evidence shows that this type of training stimulates anabolic signalling and protein synthesis [39], and produces marked skeletal muscle hypertrophy [40] despite the fact that intensities below ~60 1RM are often considered too low to generate a significant hypertrophic response [34, 41].

Metabolite accumulation is significantly elevated in Kaatsu [42], suggesting a relationship between metabolic stress and muscle development. Interestingly, Abe et al. [43] found that walking with pressure cuffs resulted in a significant increase in thigh muscle cross-sectional area (CSA) in college-aged males (4–7%) over a period of just 3 weeks. Such low-intensity aerobic training is generally not associated with increased muscle size in healthy young subjects, indicating that factors other than mechanical stress were responsible for hypertrophic adaptations.

Further evidence for an association between metabolic stress and muscle hypertrophy can be inferred from studies where training is carried out in a hypoxic environment. Kon et al. [44] displayed that performing multiple sets of low-intensity exercise (~50% 1RM) with moderate inter-set rest intervals (~1 min) while breathing 13% oxygen significantly increased metabolite accumulation, as determined by blood lactate levels compared with similar normoxic exercise. Support for the potential hypertrophic ramifications of these findings were provided by Nishimura et al. [45] who found that performing a typical hypertrophy-based protocol (4 sets of 10 repetitions at 70% 1RM) under acute hypoxic conditions resulted in a significantly greater increase in muscle CSA of the elbow flexors and extensors versus comparable training in a normoxic environment.

3 Potential Mechanisms of Action

The mechanisms theorized to mediate hypertrophic adaptations from exercise-induced metabolic stress include increased fibre recruitment, elevated systemic hormonal production, alterations in local myokines, heightened production of reactive oxygen species (ROS) and cell swelling [45–48]. The following section will discuss each of these putative mechanisms and explore their potential role in the hypertrophic response to resistance training. Figure 2 provides an overview of how these factors may combine to augment muscle growth.

4 Fibre Recruitment

The size principle of recruitment dictates that as training intensity increases, larger motor units containing fast-twitch (FT) fibres are progressively recruited to sustain muscle contraction [49]. Given that fibres must be recruited in order to respond and adapt to resistance exercise [50], it would therefore appear necessary to train at very high levels of intensity to maximize muscular development. However, there is compelling evidence that metabolic stress does, in fact, increase the recruitment of

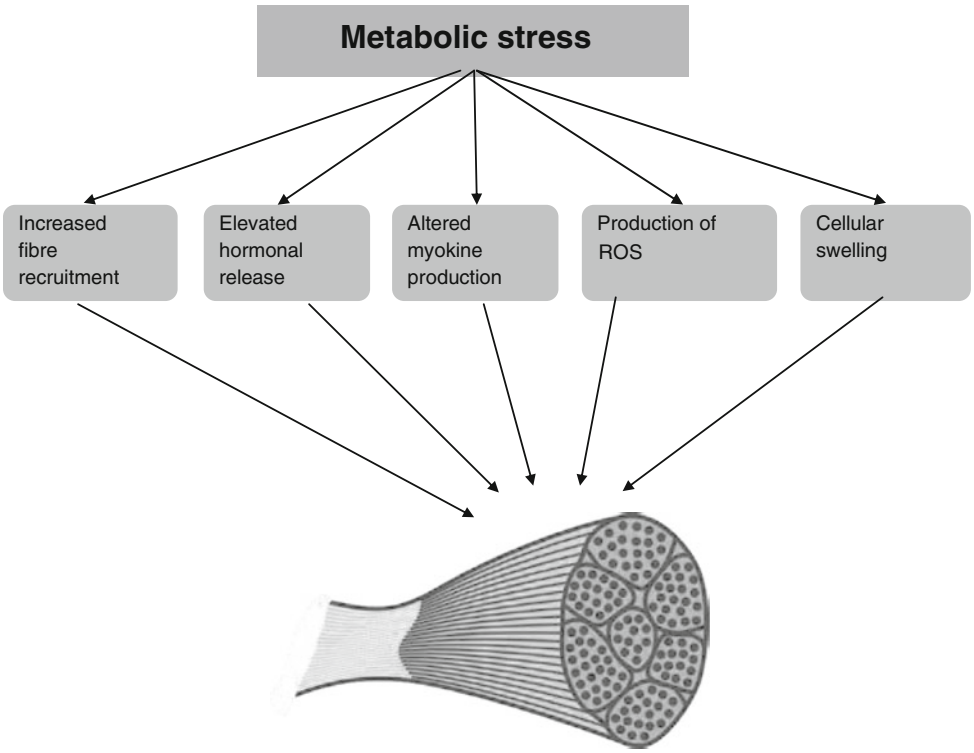

Fig. 2 Proposed mechanisms by which exercise-induced metabolic stress may mediate muscle hypertrophy. *ROS* reactive oxygen species

higher-threshold motor units even under low-loading conditions. Multiple studies have found that recruitment thresholds diminish during sustained submaximal exercise with increasing levels of fatigue [51–53]. In this way, a greater number of FT fibres are called into play as the point of muscular fatigue is reached. Further, studies using electromyography (EMG) [48, 54], glycogen depletion [55], and organic phosphate splitting [22, 38] have all shown enhanced FT fibre recruitment in Kaatsu training, and several researchers have proposed that this is the primary mechanism by which such exercise elicits hypertrophic adaptations [56, 57].

The exact mechanisms whereby metabolic stress enhances FT fibre recruitment have yet to be elucidated. There is speculation that effects are mediated by H^+ accumulation, which inhibits muscle contractility and thereby promotes the recruitment of additional high-threshold motor units [54, 58, 59]. In addition, some researchers have proposed that hypoxia induces the activation of FT fibres in an attempt to maintain necessary levels of force generation [60, 61]. Another possibility is that free radical generation, which is increased in metabolically taxing exercise, elicits increased FT recruitment by hastening the onset of fatigue [59]. Considering the complexity of exercise-induced muscle fatigue, it seems plausible that a combination of these factors, and perhaps others, are ultimately involved in the process.

Although increased fibre recruitment presents a compelling rationale for metabolically induced muscle growth associated with resistance training, it remains questionable as to whether this is the only mechanism responsible for such adaptations. Employing a model that examined organic phosphate splitting via ^{31}P-magnetic resonance spectroscopy, Suga et al. [22] found that FT fibre recruitment occurred in only 31% of subjects who performed occlusion training at 20% 1RM compared with 70% of those who trained at 65% 1RM. Given that this low level of intensity (20% 1RM) has been shown to increase hypertrophy when combined with blood flow restriction to a similar or greater extent as high-intensity resistance training [62, 63], it therefore seems likely that factors other than recruitment also contribute to the hypertrophic effect of exercise-induced metabolic stress. To lend further support to this conclusion, EMG studies have shown that exercise performed at 80% 1RM produced substantially greater muscle activity compared with blood flow restricted exercise at 20% 1RM, indicating reduced recruitment at the lower intensity [64].

5 Systemic Hormonal Production

Another popular theory proposed to explain the hypertrophic mechanisms associated with metabolic stress is that a buildup of metabolites increases growth-oriented hormonal concentrations, thereby enhancing the anabolic milieu and subsequent accretion of muscle proteins [46, 65]. Theoretically, high levels of circulating hormones increase the

likelihood of interaction with receptors [66], which may have particular hypertrophic importance in the post-workout period when muscles are primed for anabolism. Some researchers have speculated that these acute hormonal elevations to training are more critical to tissue growth and remodelling than chronic changes in resting hormonal concentrations [67]. Metabolically-induced spikes in insulin-like growth factor (IGF)-1, testosterone, and growth hormone (GH), in particular, have been implicated as having a positive effect on post-exercise muscle protein synthesis. The following is an overview of each of these hormones and their potential hypertrophic relevance to resistance exercise that promotes substantial changes in the intracellular metabolic environment.

5.1 IGF-1

IGF-1 is a homologous peptide hormone that has both mitogenic and anabolic effects on skeletal muscle [68]. A clear cause-effect relationship has been established between IGF-1 and muscle hypertrophy [68], and some researchers have professed that IGF-1 is the primary physiological regulator of muscle mass [69]. The anabolic effects of IGF-1 appear to be magnified in response to mechanical loading [70] and increases in IGF-1 protein have been shown to be proportional to increases in muscle strength following resistance training [71]. However, research indicates that a functional IGF-1 receptor is not obligatory for compensatory muscle growth [3].

Three distinct IGF-1 isoforms have been identified: the systemic forms IGF-1Ea and IGF-1Eb, and a splice variant, IGF-1Ec. Although each of these isoforms are expressed in muscle tissue [72], only IGF-1Ec appears to be locally activated by mechanical signals and thus it has been termed mechano-growth factor (MGF) [70]. Despite the fact that MGF functions in an autocrine/paracrine fashion and thus is not a true hormone, it nevertheless will be discussed in this section given its close relationship with the other IGF-1 isoforms.

While the liver is the primary site of endocrine IGF-1 production, other non-hepatic tissues including muscle also express the systemic isoforms. In fact, during intense exercise the majority of IGF-1Ea is actually derived from working muscles rather than the liver, and most of the circulating IGF-1 is ultimately taken up by the musculature [73]. The effects of systemically produced IGF-1 on muscle hypertrophy are not clear, and there is some doubt as to whether it plays a significant role in post-exercise muscle protein accretion [74]. It may well be that the primary hypertrophic role for these isoforms is in stimulating the fusion of satellite cells with existing muscle fibres, thereby facilitating the donation of myonuclei and helping to maintain optimal DNA-to-protein ratios in muscle tissue [7, 75].

Since a muscle's nuclear-content-to-fibre-mass ratio remains constant during hypertrophy, the satellite cell-derived addition of new myonuclei is believed to be essential for realizing long-term increases in muscle mass [76]. This is consistent with the concept of myonuclear domain, which proposes that the myonucleus regulates mRNA production for a finite sarcoplasmic volume and any increases in fibre size must be accompanied by a proportional increase in myonuclei [77]. The relevance of myonuclear domain remains controversial and those interested in a detailed discussion of the topic are referred to the point/counterpoint articles by O'Connor and Pavlath [78] and McCarthy and Esser [79].

In contrast, locally expressed MGF is believed to be the isoform principally responsible for compensatory hypertrophy [80]. Because of its rapid expression following mechanical loading, MGF is thought to help 'kick start' the post-exercise hypertrophic response and facilitate local repair of damaged tissue [73]. MGF carries out signalling through multiple anabolic cascades including phosphatidylinositol 3-kinase-protein kinase B-mammalian target of rapamycin (PI3K-Akt-mTOR) [81], MAPK-ERK 1/2 [82], and various calcium-dependent pathways [9], thereby directly mediating synthesis of muscle proteins. A recent *post hoc* cluster analysis by Bamman et al. [83] found that MGF was differentially expressed across clusters, with extreme responders to resistance training showing the most robust increase and non-responders having only a non-significant upward trend. These results strongly imply that acute, transient elevations in MGF gene expression are important cues for hypertrophic adaptations pursuant to mechanical loading. Furthermore, whereas systemically produced IGF-1Ea mediates satellite cell fusion [7, 75], locally expressed MGF is believed to activate satellite cells and mediate their proliferation and differentiation [84, 85]. In this way, there seems to be a synergism between local and systemic isoforms to optimize myonuclear content and thus promote long-term gains in muscle mass. A complete discussion of the roles of the various IGF-1 isoforms is beyond the scope of this paper. Those interested in further exploration of the topic are referred to recent reviews by Velloso and Harridge [74] and Philippou et al. [86].

Performance of hypertrophy-type training routines that generate extensive metabolic buildup have been found to result in significantly greater elevations of circulating IGF-1 levels compared with high-intensity protocols that cause minimal metabolite accumulation [28, 29, 87], although these results have not been consistent across all trials [88]. Moreover, some [89–91], but not all [92] studies on Kaatsu have shown increased post-exercise IGF-1 elevations following occlusion exercise, suggesting a metabolically induced influence on the hormone. The reason for these discrepancies is not clear and may be a function of

methodological differences between protocols. Moreover, the aforementioned studies primarily investigated systemic IGF-1 production, making it difficult to assess the potential hypertrophic ramifications if an association does in fact exist.

5.2 Testosterone

Testosterone is a cholesterol-derived hormone synthesized and secreted primarily by the Leydig cells of the testes via the hypothalamic-pituitary-gonadal axis, with small amounts derived from the ovaries and adrenals [93]. The anabolic effects of testosterone on muscle tissue are incontrovertible [94, 95]. For one, testosterone increases muscle protein synthesis and decreases proteolysis [96, 97]. These effects are induced by its binding to the intracellular androgen receptor, which in turn translocates to the nucleus where the complex mediates gene transcription [98]. In addition to these direct anabolic roles, testosterone also has indirect hypertrophic effects that include potentiating the release of other anabolic hormones such as GH [66] and IGF-1/MGF [99], as well as mediating satellite cell activation and proliferation [100].

There is speculation that acute post-exercise elevations in testosterone may directly stimulate anabolism by increasing the protein synthetic rate while inhibiting proteolysis [93]. This is consistent with evidence showing significant correlations between training-induced elevations in testosterone and increases in muscle CSA [101]. Results seem to be more pronounced in strength athletes compared with endurance athletes and sedentary individuals [102], suggesting that the post-exercise testosterone response may play a greater role as one gains resistance training experience [103]. However, a causal relationship between acute testosterone production and hypertrophy has yet to be established, and there is strong evidence that post-exercise testosterone elevations are not required for compensatory muscle growth [104].

Attempts to determine the effects of metabolic stress on testosterone have been largely inconclusive. Although several studies have found that hypertrophy-oriented resistance training programmes cause greater post-exercise testosterone elevations compared with routines that do not substantially increase metabolic stress [93, 105–108], others have failed to find significant differences [28, 38, 109]. Moreover, Kaatsu training has generally failed to demonstrate significant post-exercise elevations in testosterone despite high levels of metabolites [91, 109, 110], calling into question as to whether the hormone plays a role in the metabolic stress-induced hypertrophic response. It should be noted that gender, age, training experience and nutritional status can affect testosterone release [67], and these factors may account for the inconsistent results seen in the research to date. Further investigation into the topic is needed so that a more definitive conclusion can be reached.

5.3 Growth Hormone

GH is a superfamily of polypeptide hormones that act as repartitioning agents to induce fat metabolism toward mobilization of triglycerides, as well as stimulating cellular uptake and incorporation of amino acids into various proteins, including muscle [111]. Despite its name, however, the direct hypertrophic actions of GH on muscle protein accretion appear to be negligible, with effects seemingly limited to synthesis of non-contractile tissue (i.e. collagen) [112]. It is believed that GH primarily carries out muscle anabolism by potentiating release of IGF-1 [75], although some researchers dispute this theory and postulate the hypertrophic effects of GH and IGF-1 are in fact additive [113]. There is evidence that recombinant GH administration markedly enhances mRNA levels of MGF when combined with resistance exercise in the elderly [70] but not in healthy young adults [114]. GH also appears to have a permissive or perhaps even a synergistic effect on testosterone-mediated protein synthesis [98]. However, it is not clear what, if any, effects transient endogenous post-exercise GH spikes have on levels of MGF or testosterone at this time. The actions of the GH superfamily are highly diverse and complex, and a complete discussion is beyond the scope of this paper. Those interested in further reading are referred to recent reviews by Ehrnborg and Rosen [115] and Kraemer et al. [116].

The prevailing body of research supports a strong correlation between exercise-induced metabolic stress and increased hypophyseal GH secretion [23, 46–48, 90, 105, 106]. The absolute magnitude of these hormonal elevations is substantial. Fujita et al. [91] found that Kaatsu increased post-exercise GH levels 10-fold above compared with low-intensity exercise without blood flow restriction while Takarada et al. [48] reported elevations of 290-fold over baseline. Post-exercise elevations are presumably mediated by increased lactate and/or H^+ buildup in the blood [47, 106]. A reduction in pH associated with metabolite accumulation also may potentiate GH release via chemoreflex stimulation mediated by intramuscular metaboreceptors and group III and IV afferents [42, 110].

While increased hormonal concentrations present an intriguing hypothesis as to the growth-related effects of exercise-induced metabolic stress on skeletal muscle, it is not clear whether such acute elevations do in fact mediate an enhanced hypertrophic response. Several researchers have questioned the hormone hypothesis [56, 117], with some speculating that such biological events are intended to mobilize fuel stores following a bout of exercise rather than promote tissue anabolism [118]. The anabolic role of

acute GH production in particular, has been dismissed largely based on studies showing that exogenous administration of recombinant GH does not lead to greater increases in muscle protein accretion [119–121]. While this may be true, it should be noted that exogenous injections do not mimic the *in vivo* response to exercise-induced GH secretions either temporally or in magnitude. The anabolic milieu is primed during the post-workout period, and it is possible that large spikes of GH following resistance exercise, which can approach 300 times that of baseline levels [48], may facilitate remodelling pursuant to myotrauma. Further, recombinant GH is solely made up of the 22-kDa isoform [115] whereas more than 100 molecular isoforms of GH are produced endogenously [122]. A wide spectrum of these isoforms peak at the conclusion of resistance exercise with a greater proportional concentration of non-22-kD isoforms [115]. Supraphysiological doses of recombinant GH actually impede post-exercise stimulation of these alternative isoforms [115], potentially obscuring hypertrophic effects. Whether these factors have a significant effect on muscular adaptations is not clear at this time and requires further study.

West et al. [123] found that transient hormonal spikes had no effect on post-exercise muscle protein synthesis in young males when compared with a protocol where hormonal levels were low. Furthermore, p70S6k phosphorylation was similar between groups, indicating that anabolic signalling was also unaffected by post-exercise hormonal elevations. It is important to note, however, that protein synthesis measured in response to an acute bout of exercise does not always correlate with chronic upregulation of causative myogenic signals [124] and is not necessarily predictive of long-term hypertrophic responses to regimented resistance training [76]. Thus, while these findings are intriguing, their practical implications are limited.

Direct studies evaluating the effect of acute anabolic hormonal production on hypertrophy have been contradictory. Madarame et al. [125] found that performing occlusion training for the lower body musculature after unilateral arm exercise resulted in a significant increase in muscle CSA of the elbow flexors compared with identical arm training routine combined with non-occlusion lower body exercise. Although differences in GH levels did not rise to statistical significance, the authors state that this was likely due to the study being underpowered. Considering that similar protocols have shown large post-exercise hormonal increases [23, 46–48, 90, 106], results therefore seem to suggest that systemic factors may have played a role in the adaptive response. It also is interesting to note that no changes in muscle CSA were observed in the non-trained arm, indicating that acute systemic hormonal increases have no effect on muscle size in the absence of mechanical stress. West et al. [126] employed a within-person design to investigate the role of acute hormonal elevations on muscle hypertrophy using a traditional resistance exercise protocol. Twelve untrained men (aged mean ± SD 21.8 ± 1.2 years) trained their elbow flexors on separate days under two different hormonal environments: a low hormone condition where one arm performed arm curl exercise only and a high hormone condition where the contralateral arm performed the same arm curl exercise followed immediately by a bout of leg resistance exercises designed to elicit large increases in circulating hormones. After 15 weeks, no differences were found between groups in muscle girth as determined by magnetic resonance imaging despite significantly greater elevations in circulating IGF-1, GH, and testosterone in the high-hormone group following exercise.

A recent study by Ronnestad et al. [127] employed a similar within-subject design to West et al. [126], except that leg training was performed before the arm curl in the high-hormone group. In contrast to West et al. [126], those in the high-hormone group displayed a significantly greater increase in muscle CSA of the elbow flexors implying that elevated hormones were responsible for hypertrophic gains. Interestingly, differences were specific to distinct regions of elbow flexors, with increases in CSA seen only at the two middle sections where muscle girth was largest.

Considering the conflicting evidence, it is premature to draw definitive conclusions as to whether or not the post-exercise anabolic hormonal response associated with metabolic stress plays a role in muscle hypertrophy. What seems apparent from the research is that if such a role does in fact exist, the overall magnitude of the effect size would be fairly modest. However, even modest increases in muscle hypertrophy could potentially be meaningful for certain populations, particularly bodybuilders and strength athletes. It is conceivable that acute hormonal elevations may have a greater effect on satellite cell activity rather than post-exercise protein synthetic rate, thereby impacting long-term, as opposed to shorter-term, hypertrophic adaptations. If so, the anabolic effects of these hormonal spikes might be limited by genetic differences in pre-training satellite cell availability and one's subsequent ability to expand the available satellite cell pool [77]. Finally, studies in trained individuals on the subject are lacking, so it remains to be elucidated if those with previous training experience respond differently to acute exercise-induced hormonal output compared with untrained subjects.

6 Local Myokines

Exercise training results in the synthesis of various cytokines and other peptides within skeletal muscle (a.k.a. myokines), and an emerging body of evidence indicates

that these local factors can significantly contribute to hypertrophic adaptations [128–130]. Many of these agents can exert effects in an autocrine/paracrine fashion to bring about unique effects on skeletal muscle adaptation, and resistance exercise appears to enhance their response [131]. There is speculation that metabolic stress may mediate muscle hypertrophy by either upregulating anabolic myokines and/or downregulating catabolic myokines.

Interleukin (IL)-6 is an early-stage myokine purported to influence satellite-cell mediated myonuclear accretion [130], and it has been postulated that exercise-induced metabolic stress may stimulate its production [132]. Despite a seemingly sound theoretical rationale, though, evidence in support of this contention is lacking. Takarada et al. [48] found that restricted blood flow exercise of the knee extensors resulted in gradual increase in IL-6, with levels maintained at an elevated rate 24 h post-exercise versus controls. The overall effect size was small, however, with levels reaching only one-fourth of that reported for higher-intensity eccentric exercise. Fujita et al. [133] reported a 2.4% increase in muscle/bone CSA of the thigh musculature following 6 days of Kaatsu despite the fact that IL-6 levels remained unchanged throughout the training period. Similarly, studies by Abe et al. [134] and Fry et al. [39] failed to detect a change in IL-6 levels following occlusion training. These results cast doubt as to whether IL-6 is in fact a mechanism by which metabolic stress induces hypertrophy.

There is some evidence to suggest that metabolic stress may have a greater impact on compensatory hypertrophy by reducing local catabolic factors as opposed to increasing growth-oriented factors. Given that muscle growth represents the dynamic balance between protein synthesis and breakdown, a decrease in protein degradation ultimately leads to an increase in protein accretion. Research on potential mediators has largely focused on myostatin, a member of the transforming growth factor-3 super family that acts as a negative regulator of muscle growth [135]. Kawada and Ishii [136] found that myostatin levels significantly decreased in the plantaris muscle of Wistar rats following restricted blood flow exercise in comparison to a sham operation group. In contrast, a human trial by Drummond et al. [92] reported no differences in myostatin gene expression between Kaatsu training and low-intensity exercise without blood flow restriction 3 h post-exercise. Interestingly, Manini et al. [137] found that although Kaatsu did not reduce myostatin, it significantly downregulated various proteolytic transcripts (forkhead box O3A [FOXO3A], Atrogin-1 and muscle ring finger-1 [MuRF-1]) 8 h post-exercise compared with a control group that performed non-occluded low-intensity training. Recently, Laurentino et al. [63] investigated the effects of Kaatsu on chronic myostatin levels in physically active males. After 8 weeks of training, Kaatsu produced a significant 45% chronic reduction in myostatin gene expression while low-intensity exercise without blood flow restriction showed only non-significant decreases.

Given the disparate data, it is difficult to draw firm conclusions as to whether metabolic stress influences hypertrophy by altering myokine production. It is important to note that many additional myokines have been identified in the literature (including IL-1, IL-7, IL-8, IL-10, IL-13, IL-15, fibroblast growth factor, leukaemia inhibitory factor, and tumour necrosis factor, amongst others), and the effects of metabolic stress on these myokines have yet to be investigated. Moreover, no studies could be located that directly compare post-exercise myokine differences between traditional hypertrophy-oriented routines versus high-intensity strength-oriented regimens. This topic should be a prime area of focus for future research.

7 Reactive Oxygen Species

ROS presents an intriguing potential mechanism by which metabolic stress may mediate muscle hypertrophy. The term ROS collectively includes both oxygen radicals (i.e. superoxide, hydroxyl, peroxyl and hydroperoxyl radicals) and non-radical oxidizing agents (i.e. hydrogen peroxide and hypochlorous acid) [138]. A complete discussion about the sources of contraction-induced ROS production is beyond the scope of this paper, but distinctions are made between ROS produced chronically during resting conditions and those generated transiently during exercise. Under normal physiological conditions, ROS are primarily generated by the mitochondrial electron transport chain and oxidation of polyunsaturated fats, and their production is significantly influenced by environmental stress and aging [138]. During exercise, contracting muscles are a prominent source of acute ROS production, with the extent of elevations dependent on the type and intensity of training [139]. For further information on the subject, the interested reader is referred to recent reviews by Powers et al. [140] and Jackson [141].

Although chronically elevated levels of ROS have been implicated as having negative effects on various muscle tissues and may even trigger the onset of sarcopenia [142, 143], acutely they can function as key cellular signalling molecules in the response to exercise [144–147], potentially mediating post-workout anabolic adaptations. ROS production has been shown to promote growth in both smooth muscle and cardiac muscle [148], and it is theorized to have similar hypertrophic effects on skeletal muscle as well [54]. Transgenic mice with suppressed levels of selenoproteins, a class of proteins that function as

potent antioxidants, display increased exercise-induced muscle growth, suggesting a ROS-mediated hypertrophic effect through redox sensitive signalling pathways [149].

Although the mechanisms of action have not been fully elucidated, research has shown that ROS can influence muscle hypertrophy via enhanced MAPK signalling. Kefaloyianni et al. [150] displayed that treatment of C2 myoblasts with a ROS variant increases MAPK activation, with the response of the various MAPK subfamilies (ERK 1/2, c-Jun N-terminal kinase [JNK], and p38-MAPK) differing over time. In cardiac myocytes, ROS can regulate phospholipase D and thus potentially mediate protein synthesis via activation of PA [151]. Whether ROS influences this pathway in skeletal muscle has not been determined. There is also evidence that antioxidant treatment markedly blunts IGF-I-induced phosphorylation of the IGF-I receptor in C2C12 myocytes treated with ROS, suggesting that ROS has a critical function in the biological action of IGF-I [152].

Research supporting the hypertrophic role of ROS in routines producing metabolic stress remains speculative and is largely derived from implied data. Mitochondria in FT fibres have unique properties that promote higher levels of ROS activity compared with slow twitch fibres [140]. Given that hypertrophy-type training associated with metabolic stress would conceivably involve the mitochondria to a greater degree than high-intensity training, it seems reasonable to conclude that such exercise would generate more ROS. Moreover, hypoxia and subsequent reperfusion heightens ROS production [153, 154]. Since the greater time under tension associated with a hypertrophy-type routine would necessarily be associated with an increased ischaemic response compared with high-intensity training, it stands to reason that higher levels of ROS would be produced. Whether these differences in ROS production are sufficient to promote a hypertrophic response is unknown at this time and requires further study.

The direct effect of exercise-induced metabolic stress on ROS has not been well studied. Goldfarb et al. [155] displayed that plasma protein carbonyl levels and blood glutathione ratio, both markers of oxidative stress, were significantly greater in a hypertrophy-type routine (3 sets at ~70% 1RM) compared with a low-intensity routine with blood flow restriction (3 sets at ~30% 1RM), suggesting that muscle damage plays the dominant role in generating ROS. Support for this hypothesis was demonstrated by Takarada et al [48], who found no change in post-exercise lipid peroxide levels following performance of the seated leg extension combined with vascular occlusion whereby muscle damage was minimal.

An interesting but relatively unexplored facet of research in this area involves nitric oxide (NO), a ROS variant. NO production has been linked to compensatory muscle hypertrophy [156, 157], and there is evidence that it mediates an increase in satellite-cell activation and proliferation [158], possibly via synthesis of hepatocyte growth factor [159]. Kawada and Ishii [136] demonstrated that venous occlusion of the hindlimbs in Wister rats resulted in an increased expression of NO synthase-1 (NOS-1), an enzyme that catalyzes the production of NO from L-arginine. However, although levels of NO showed a trend toward an increase at 2 weeks post-surgery ($p = 0.10$), results did not rise to statistical significance purportedly due to a large intersubject variation. Supporting research in humans is lacking at this time.

ROS may also indirectly influence hypertrophy by mediating transcription of highly conserved stress proteins called heat shock proteins (HSPs). Under normal physiological conditions, HSPs act as a chaperone protein, facilitating the folding of new peptide chains and translocation of proteins [160]. When the body is subjected to stress, however, HSPs are thought to serve a protective role that includes limiting oxidative damage caused by ROS [161], and some researchers have theorized that they may play a role in compensatory muscle hypertrophy as well [136, 162]. A number of HSPs have been identified, each of which are named according to their molecular mass in kiloDaltons (i.e. HSP27, HSP60, HSP70, and HSP72, etc). It should be noted that, in addition to ROS-mediated transcription, HSPs are also induced by hypoxia, acidosis, and ischaemia-reperfusion [163] – all byproducts of resistance exercise associated with high levels of metabolic stress.

Kawada and Ishii [136] found that HSP72 was significantly elevated in the plantaris muscle of rats following 2 weeks of vascular occlusion. These findings were associated with a significant increase in muscle hypertrophy, leading researchers to speculate that HSP72 might contribute post-exercise muscular development. Conversely, Fry et al. [39] found no differences in total protein content of HSP70 following restricted blood flow exercise at 20% 1RM in elderly males. Further, a recent study by Paulsen et al. [164] showed that training volume (one set vs. three sets) had no influence on cytosolic or cytoskeletal levels of HSP27 and HSP70 in either the vastus lateralis or trapezius muscles following 11 weeks of progressive hypertrophy-type training (7–10 RM). Given that higher volumes of exercise would necessarily result in greater metabolite accumulation, this argues against the presence of a dose-response between metabolic stress and HSPs. Perhaps, most importantly, HSP transcription resultant to resistance exercise is likely more due to structural and functional myodamage rather than increased ROS production [165]. The combination of these findings raises doubt as to whether HSPs are in fact a significant hypertrophic mechanism associated with exercise-induced metabolic

stress, at least with respect to traditional resistance exercise.

8 Cell Swelling

One of the more novel mechanisms that might be involved in the hypertrophic response to metabolic stress involves an increase in intracellular hydration. This phenomenon, known as cell swelling, is believed to serve as a physiological regulator of cell function [166, 167]. Numerous studies have shown that hydration-mediated cell swelling results in an increase in protein synthesis and a decrease in proteolysis in a variety of different cell types, which include hepatocytes, osteocytes, breast cells and muscle fibres [168]. With respect to muscle, it has been theorized that the stimulus associated with cell swelling may trigger proliferation of satellite cells and facilitate their fusion to hypertrophying myofibres [169], thereby enhancing potential long-term hypertrophic adaptations.

The underlying mechanisms for cell swelling-induced anabolism have yet to be fully determined. It has been proposed that increased pressure against the cytoskeleton and/or cell membrane is perceived as a threat to cellular integrity, which causes the cell to initiate a signalling response that ultimately leads to reinforcement of its ultrastructure [24, 170]. There is evidence that signalling is carried out via integrin-associated volume osmosensors within cells [171]. The sensors, in turn, activate anabolic protein-kinase transduction pathways, possibly mediated by autocrine effects of growth factors [172, 173]. Research indicates that anabolic functions are carried out in an mTOR-independent fashion [174] and there is suggestion that MAPK modules may be the primary mediator of swelling-induced anabolism [175, 176].

To date, there is a paucity of research directly investigating whether cellular hydration pursuant to exercise-induced metabolite accumulation enhances muscle growth. However, a compelling case can be made whereby this occurs. Resistance exercise has been shown to induce alterations of intra- and extracellular water balance [177], the extent of which is dependent upon the type of exercise and intensity of training. Cell swelling is maximized by exercise that relies heavily on glycolysis, with the resultant lactate accumulation acting as a primary contributor to osmotic changes in skeletal muscle [178, 179]. The intramuscular buildup of lactate has been shown to trigger volume regulatory mechanisms, and these effects may be magnified by the acidic environment associated with exercise-induced metabolite accumulation [168]. Although speculative, the amount of swelling would seem to be heightened by reactive hyperaemia subsequent to compression of blood vessels during such training. FT fibres are particularly sensitive to osmotic changes, presumably related to a high concentration water transport channels called aquaporin-4 (AQP4). AQP4 has been shown to be strongly expressed in the sarcolemma of mammalian FT glycolytic and FT oxidative-glycolytic fibres, facilitating the influx of fluid into the cell [179]. Given that FT fibres are most responsive to hypertrophy [180], it is plausible that cellular hydration influences the hypertrophic response during resistance training that includes a strong glycolytic component by producing a favorable effect on net protein balance and thus enhancing muscle protein accretion. Consequently, the 'muscle pump' that bodybuilders often strive to achieve may in fact help to promote a growth response after all and hypertrophy-oriented training routines may therefore benefit by maximizing this phenomenon.

Although the cell swelling hypothesis is intriguing, a recent study by Gundermann et al. [181] provides evidence to the contrary. The study compared low-intensity resistance training whereby hyperaemia was simulated by a pharmacological vasodilator to low-intensity blood flow-restricted exercise. Results showed that occlusion exercise produced a 49% increase in mixed muscle fractional synthetic rate as well as significant elevations in phosphorylation of mTOR, S6K1, and ERK1/2, while those who performed exercise supplemented by pharmacological vasodilation reported no changes in any of these variables. The study was limited by the fact that researchers were unable to accurately reproduce the immediate (first $\sim$10 min) post-exercise hyperaemic response, making it difficult to determine whether the initial signal from increased hydration plays a role in post-exercise protein synthesis. Further, protein breakdown was not measured, and an attenuation of proteolysis is believed to be a primary means by which cellular hydration mediates muscle hypertrophy.

It is possible that metabolic stress may lead to long-term hypertrophic gains as a result of increased glycogen stores mediated by chronic cell swelling. Chronic, consistent resistance training utilizing a repetition range that relies on anaerobic glycolysis for energy has been shown to significantly upregulate glycogen storage capacity [182]. Research also shows that bodybuilders display a 50% greater intramuscular glycogen content compared with non-athletes, indicating an adaptive response from hypertrophy-type training [21]. Given that glycogen attracts three grams of water for every gram of glycogen [183], an increase in glycogen stores may mediate a favourable muscle protein balance over time via heightened cellular hydration, thereby enhancing long-term hypertrophic gains. This theory remains untested and requires further study.

9 Conclusions

In summary, while mechanical stress is unquestionably a primary driving stimulus in post-exercise muscle growth, there is compelling evidence that metabolic stress also may contribute to hypertrophic adaptations. What is not clear is whether metabolic stress is additive to mechanically-derived signalling or perhaps redundant provided a given level of intensity is achieved. A problem with current research is that mechanical and metabolic stress occur in tandem, making it difficult to tease out the effects of one from other. This can potentially result in misinterpreting metabolic factors as causal in nature when muscle actions are in fact playing the dominant hypertrophic role or *vice versa*.

Furthermore, the mechanisms by which metabolic stress influences compensatory hypertrophy have yet to be fully explored. Although increased muscle recruitment appears to be highly involved, it is doubtful that recruitment alone is responsible for the full magnitude of growth-related gains. Rather, the combined integration of multiple local and systemic factors likely contribute to muscle development in a direct and/or permissive manner [184]. In addition to the mechanisms discussed in this review, it is possible that other yet-to-be determined factors may also be involved and additional research is needed to explore the topic in depth.

Current theory suggests that a given threshold of mechanical stress is necessary to promote muscular growth, which is purported to be in the range of approximately 60–65% 1RM [41]. Support for this recommendation can be inferred from the study by Campos et al. [34], who found that volume-adjusted high intensity (3–5 RM) and moderate intensity (9–11 RM) routines promoted significant increases in muscle CSA of the thigh while a low intensity (20–28 RM) routine did not. Recent studies, however, seem to contradict these findings. Tanimoto et al. [185] demonstrated that training at 50% 1RM with slow movement and tonic force generation (3 s for eccentric and concentric actions with no relaxation phase) showed comparable increases in muscle size compared with training at 80% 1RM with a traditional cadence (1 s for concentric and eccentric actions). Results were attributed to increased metabolic stress associated with the lower-intensity protocol. More recently, Mitchell et al. [186] showed that 10 weeks of resistance exercise of the leg extensors performed at an intensity of 30% 1RM produced a similar hypertrophic response as training at 80% 1RM, although results were confounded by a substantially greater volume in the low-intensity group. In contrast, Holm et al. [187] reported that a moderate-intensity protocol (70% 1RM) produced a 3-fold greater increase in muscle hypertrophy compared with a volume-equated low intensity (15.5% 1RM) over a 12-week training period. Discrepancies between these studies are likely related to methodology and require further study. It should be noted that hypertrophy associated with lower-intensity training is highly dependent on training to failure. This is likely related to the fact that fatiguing sets are necessary at lower-intensity to induce substantial metabolic stress and thereby heighten the associated mechanisms responsible for muscle growth.

Future research should seek to elucidate the precise mechanisms by which metabolic stress mediates compensatory muscle growth, including whether or not hypoxia itself plays a direct role in the process. In addition, attempts should be made to clarify optimal hypertrophic loading intensities along the strength-endurance continuum, and determine the precise role that metabolic stress plays in this process. Specific focus should be centered on whether a dose-response relationship exists between metabolic stress and muscle hypertrophy and, if so, whether an upper threshold exists beyond which such benefits plateau and/or results are impaired. Given the large influence of age, gender and genetics on muscular adaptations, it is likely that any such threshold would vary based on interindividual differences. For example, an elderly marathon runner with a high proportion of type I fibres in the thigh muscles would seemingly have a different threshold response from a young sprinter who has predominantly type II fibres. These issues warrant further study.

A potential confounding issue is that exercise-induced metabolic stress generally occurs in concert with muscle damage during hypertrophy-oriented resistance exercise. Given that myodamage is believed to play a role in post-exercise muscle growth [188], this may alter results and thus needs to be addressed in study design. Also, studies to date have been largely confined to the use of untrained subjects, therefore limiting the ability to generalize results to trained populations. Researchers should therefore seek to carry out future studies on lifters with at least a year or more of dedicated resistance training experience. An enhanced understanding of these factors will ultimately improve our ability to design programs that maximize hypertrophic adaptations based on the needs, abilities and genetics of the individual.

Acknowledgements This review was not funded by any outside organization. Brad Schoenfeld is the sole author of this work. There are no conflicts of interest present that are directly relevant to the content of this review.

References

1. Goldberg AL, Etlinger JD, Goldspink DF, et al. Mechanism of work-induced hypertrophy of skeletal muscle. Med Sci Sports. 1975 Fall;7(3):185–98.
2. Witkowski S, Lovering RM, Spangenburg EE. High-frequency electrically stimulated skeletal muscle contractions increase

p70s6k phosphorylation independent of known IGF-I sensitive signaling pathways. FEBS Lett. 2010;584(13):2891–5.
3. Spangenburg EE, Le Roith D, Ward CW, et al. A functional insulin-like growth factor receptor is not necessary for load-induced skeletal muscle hypertrophy. J Physiol. 2008;586(1): 283–91.
4. Hornberger TA, Stuppard R, Conley KE, et al. Mechanical stimuli regulate rapamycin-sensitive signalling by a phosphoinositide 3-kinase-, protein kinase B- and growth factor-independent mechanism. Biochem J. 2004;380(Pt 3):795–804.
5. Vandenburgh H, Kaufman S. In vitro model for stretch-induced hypertrophy of skeletal muscle. Science. 1979;203(4377):265–8.
6. Miyazaki M, McCarthy JJ, Fedele MJ, et al. Early activation of mTORC1 signalling in response to mechanical overload is independent of phosphoinositide 3-kinase/Akt signalling. J Physiol. 2011;589(Pt 7):1831–46.
7. Toigo M, Boutellier U. New fundamental resistance exercise determinants of molecular and cellular muscle adaptations. Eur J Appl Physiol. 2006;97(6):643–63.
8. Mayhew DL, Hornberger TA, Lincoln HC, et al. Eukaryotic initiation factor 2B epsilon induces cap-dependent translation and skeletal muscle hypertrophy. J Physiol. 2011;589(Pt 12): 3023–37.
9. Tidball JG. Mechanical signal transduction in skeletal muscle growth and adaptation. J Appl Physiol. 2005;98(5):1900–8.
10. Bassel-Duby R, Olson EN. Signaling pathways in skeletal muscle remodeling. Annu Rev Biochem. 2006;75:19–37.
11. Miyazaki M, Esser KA. Cellular mechanisms regulating protein synthesis and skeletal muscle hypertrophy in animals. J Appl Physiol. 2009;106(4):1367–73.
12. Glass DJ. Skeletal muscle hypertrophy and atrophy signaling pathways. Int J Biochem Cell Biol. 2005;37(10):1974–84.
13. Hornberger TA, Chu WK, Mak YW, et al. The role of phospholipase D and phosphatidic acid in the mechanical activation of mTOR signaling in skeletal muscle. Proc Natl Acad Sci USA. 2006;103(12):4741–6.
14. O'Neil TK, Duffy LR, Frey JW, et al. The role of phosphoinositide 3-kinase and phosphatidic acid in the regulation of mammalian target of rapamycin following eccentric contractions. J Physiol. 2009;587(Pt 14):3691–701.
15. Lehman N, Ledford B, Di Fulvio M, et al. Phospholipase D2-derived phosphatidic acid binds to and activates ribosomal p70 S6 kinase independently of mTOR. FASEB J. 2007;21(4): 1075–87.
16. Rooney KJ, Herbert RD, Balnave RJ. Fatigue contributes to the strength training stimulus. Med Sci Sports Exerc. 1994;26(9): 1160–4.
17. Schott J, McCully K, Rutherford OM. The role of metabolites in strength training. II. Short versus long isometric contractions. Eur J Appl Physiol Occup Physiol. 1995;71(4):337–41.
18. Smith RC, Rutherford OM. The role of metabolites in strength training. I. A comparison of eccentric and concentric contractions. Eur J Appl Physiol Occup Physiol. 1995;71(4):332–6.
19. Shinohara M, Kouzaki M, Yoshihisa T, et al. Efficacy of tourniquet ischemia for strength training with low resistance. Eur J Appl Physiol Occup Physiol. 1998;77(1–2):189–91.
20. Folland JP, Irish CS, Roberts JC, et al. Fatigue is not a necessary stimulus for strength gains during resistance training. Br J Sports Med. 2002;36(5):370–3.
21. Tesch PA, Colliander EB, Kaiser P. Muscle metabolism during intense, heavy-resistance exercise. Eur J Appl Physiol Occup Physiol. 1986;55(4):362–6.
22. Suga T, Okita K, Morita N, et al. Intramuscular metabolism during low-intensity resistance exercise with blood flow restriction. J Appl Physiol. 2009;106(4):1119–24.
23. Pierce JR, Clark BC, Ploutz-Snyder LL, et al. Growth hormone and muscle function responses to skeletal muscle ischemia. J Appl Physiol. 2006;101(6):1588–95.
24. Schoenfeld BJ. The mechanisms of muscle hypertrophy and their application to resistance training. J Strength Cond Res. 2010;24(10):2857–72.
25. Fry AC. The role of resistance exercise intensity on muscle fibre adaptations. Sports Med. 2004;34(10):663–79.
26. Lambert CP, Flynn MG. Fatigue during high-intensity intermittent exercise: application to bodybuilding. Sports Med. 2002;32(8):511–22.
27. Kraemer WJ, Fleck SJ, Dziados JE, et al. Changes in hormonal concentrations after different heavy-resistance exercise protocols in women. J Appl Physiol. 1993;75(2):594–604.
28. Kraemer WJ, Marchitelli L, Gordon SE, et al. Hormonal and growth factor responses to heavy resistance exercise protocols. J Appl Physiol. 1990;69(4):1442–50.
29. Kraemer WJ, Gordon SE, Fleck SJ, et al. Endogenous anabolic hormonal and growth factor responses to heavy resistance exercise in males and females. Int J Sports Med. 1991;12(2): 228–35.
30. Katch VL, Katch FI, Moffatt R, et al. Muscular development and lean body weight in body builders and weight lifters. Med Sci Sports Exerc. 1980;12(5):340–4.
31. Schmidtbleicher D, Buehrle M. Neuronal adaptation and increase of cross-sectional area studying different strength training methods. In: Jonsson GB, editor. Biomechanics X-B volume 6-B. Champaign: Human Kinetics; 1987. p. 615–20.
32. Choi J, Takahashi H, Itai Y. The difference between effects of 'power-up type' and 'bulk-up type' strength training exercises: with special reference to muscle cross-sectional area. Jpn J Phys Fitness Sports Med. 1998;47(1):119–29.
33. Masuda K, Choi JY, Shimojo H, et al. Maintenance of myoglobin concentration in human skeletal muscle after heavy resistance training. Eur J Appl Physiol Occup Physiol. 1999; 79(4):347–52.
34. Campos GER, Luecke TJ, Wendeln HK, et al. Muscular adaptations in response to three different resistance-training regimens: specificity of repetition maximum training zones. Eur J Appl Physiol. 2002;88(1–2):50–60.
35. Robbins DW, Goodale TL, Docherty D, et al. The effects of load and training pattern on acute neuromuscular responses in the upper body. J Strength Cond Res. 2010;24(11):2996–3007.
36. MacDougall JD, Ray S, Sale DG, et al. Muscle substrate utilization and lactate production. Can J Appl Physiol. 1999;24(3): 209–15.
37. Tamaki T, Uchiyama S, Tamura T, et al. Changes in muscle oxygenation during weight-lifting exercise. Eur J Appl Physiol Occup Physiol. 1994;68(6):465–9.
38. Suga T, Okita K, Morita N, Yokota T, et al. Dose effect on intramuscular metabolic stress during low-intensity resistance exercise with blood flow restriction. J Appl Physiol. 2010; 108(6):1563–7.
39. Fry CS, Glynn EL, Drummond MJ, et al. Blood flow restriction exercise stimulates mTORC1 signaling and muscle protein synthesis in older men. J Appl Physiol. 2010;108(5):1199–209.
40. Loenneke JP, Wilson JM, Marin PJ, et al. Low intensity blood flow restriction training: a meta-analysis. Eur J Appl Physiol. 2012;112(5):1849–59.
41. Kraemer WJ, Adams K, Cafarelli E, et al. American College of Sports Medicine position stand: progression models in resistance training for healthy adults. Med Sci Sports Exerc. 2002;34(2): 364–80.
42. Loenneke JP, Wilson GJ, Wilson JM. A mechanistic approach to blood flow occlusion. Int J Sports Med. 2010;31(1):1–4.

43. Abe T, Kearns CF, Sato Y. Muscle size and strength are increased following walk training with restricted venous blood flow from the leg muscle, Kaatsu-walk training. J Appl Physiol. 2006;100(5):1460–6.
44. Kon M, Ikeda T, Homma T, et al. Effects of low-intensity resistance exercise under acute systemic hypoxia on hormonal responses. J Strength Cond Res. 2012;26(3):611–7.
45. Nishimura A, Sugita M, Kato K, et al. Hypoxia increases muscle hypertrophy induced by resistance training. Int J Sports Physiol Perform. 2010;5(4):497–508.
46. Goto K, Ishii N, Kizuka T, et al. The impact of metabolic stress on hormonal responses and muscular adaptations. Med Sci Sports Exerc. 2005;37(6):955–63.
47. Gordon SE, Kraemer WJ, Vos NH, et al. Effect of acid-base balance on the growth hormone response to acute high-intensity cycle exercise. J Appl Physiol. 1994;76(2):821–9.
48. Takarada Y, Nakamura Y, Aruga S, et al. Rapid increase in plasma growth hormone after low-intensity resistance exercise with vascular occlusion. J Appl Physiol. 2000;88(1):61–5.
49. Henneman E, Somjen G, Carpenter DO. Functional significance of cell size in spinal motoneurons. J Neurophysiol. 1965;28: 560–80.
50. Kraemer WJ, Ratamess NA. Fundamentals of resistance training: progression and exercise prescription. Med Sci Sports Exerc. 2004;36(4):674–88.
51. Houtman CJ, Stegeman DF, Van Dijk JP, et al. Changes in muscle fiber conduction velocity indicate recruitment of distinct motor unit populations. J Appl Physiol. 2003;95(3):1045–54.
52. Sahlin K, Soderlund K, Tonkonogi M, et al. Phosphocreatine content in single fibers of human muscle after sustained submaximal exercise. Am J Physiol. 1997;273(1 Pt 1):C172–8.
53. Vollestad NK, Vaage O, Hermansen L. Muscle glycogen depletion patterns in type I and subgroups of type II fibres during prolonged severe exercise in man. Acta Physiol Scand. 1984;122(4):433–41.
54. Takarada Y, Takazawa H, Sato Y, et al. Effects of resistance exercise combined with moderate vascular occlusion on muscular function in humans. J Appl Physiol. 2000;88(6):2097–106.
55. Ingemann-Hansen T, Halkjaer-Kristensen J, Halskov O. Skeletal muscle phosphagen and lactate concentrations in ischaemic dynamic exercise. Eur J Appl Physiol Occup Physiol. 1981;46(3): 261–70.
56. Loenneke JP, Fahs CA, Wilson JM, et al. Blood flow restriction: the metabolite/volume threshold theory. Med Hypotheses. 2011; 77(5):748–52.
57. Meyer RA. Does blood flow restriction enhance hypertrophic signaling in skeletal muscle? J Appl Physiol. 2006;100(5): 1443–4.
58. Miller KJ, Garland SJ, Ivanova T, et al. Motor-unit behavior in humans during fatiguing arm movements. J Neurophysiol. 1996;75(4):1629–36.
59. Debold EP. Recent insights into the molecular basis of muscular fatigue. Med Sci Sports Exerc. 2012;44(8):1440–52.
60. Moritani T, Sherman WM, Shibata M, et al. Oxygen availability and motor unit activity in humans. Eur J Appl Physiol Occup Physiol. 1992;64(6):552–6.
61. Sundberg CJ. Exercise and training during graded leg ischaemia in healthy man with special reference to effects on skeletal muscle. Acta Physiol Scand Suppl. 1994;615:1–50.
62. Yasuda T, Abe T, Sato Y, et al. Muscle fiber cross-sectional area is increased after two weeks of twice daily KAATSU-resistance training. Int J KAATSU Train Res. 2005;1(2):65–70.
63. Laurentino GC, Ugrinowitsch C, Roschel H, et al. Strength training with blood flow restriction diminishes myostatin gene expression. Med Sci Sports Exerc. 2012;44(3):406–12.
64. Manini TM, Clark BC. Blood flow restricted exercise and skeletal muscle health. Exerc Sport Sci Rev. 2009;37(2):78–85.
65. Hansen S, Kvorning T, Kjaer M, et al. The effect of short-term strength training on human skeletal muscle: the importance of physiologically elevated hormone levels. Scand J Med Sci Sports. 2001;11(6):347–54.
66. Crewther B, Keogh J, Cronin J, et al. Possible stimuli for strength and power adaptation: acute hormonal responses. Sports Med. 2006;36(3):215–38.
67. Kraemer WJ, Ratamess NA. Hormonal responses and adaptations to resistance exercise and training. Sports Med. 2005;35(4): 339–61.
68. Haddad F, Adams GR. Inhibition of MAP/ERK kinase prevents IGF-I-induced hypertrophy in rat muscles. J Appl Physiol. 2004;96(1):203–10.
69. Stewart CE, Pell JM. Point:Counterpoint: IGF is/is not the major physiological regulator of muscle mass. Point: IGF is the major physiological regulator of muscle mass. J Appl Physiol. 2010;108(6):1820,1; discussion 1823-4; author reply 1832.
70. Hameed M, Lange KH, Andersen JL, et al. The effect of recombinant human growth hormone and resistance training on IGF-I mRNA expression in the muscles of elderly men. J Physiol. 2004;555(Pt 1):231–40.
71. Kostek MC, Delmonico MJ, Reichel JB, et al. Muscle strength response to strength training is influenced by insulin-like growth factor 1 genotype in older adults. J Appl Physiol. 2005;98(6): 2147–54.
72. Philippou A, Papageorgiou E, Bogdanis G, et al. Expression of IGF-1 isoforms after exercise-induced muscle damage in humans: characterization of the MGF E peptide actions in vitro. In Vivo. 2009;23(4):567–75.
73. Goldspink G. Mechanical signals, IGF-I gene splicing, and muscle adaptation. Physiology (Bethesda). 2005;20:232–8.
74. Velloso CP, Harridge SD. Insulin-like growth factor-I E peptides: implications for aging skeletal muscle. Scand J Med Sci Sports. 2010;20(1):20–7.
75. Velloso CP. Regulation of muscle mass by growth hormone and IGF-I. Br J Pharmacol. 2008;154(3):557–68.
76. Timmons JA. Variability in training-induced skeletal muscle adaptation. J Appl Physiol. 2011;110(3):846–53.
77. Petrella JK, Kim J, Mayhew DL, et al. Potent myofiber hypertrophy during resistance training in humans is associated with satellite cell-mediated myonuclear addition: a cluster analysis. J Appl Physiol. 2008;104(6):1736–42.
78. O'Connor RS, Pavlath GK. Point:counterpoint: satellite cell addition is/is not obligatory for skeletal muscle hypertrophy. J Appl Physiol. 2007;103(3):1099–100.
79. McCarthy JJ, Esser KA. Counterpoint: satellite cell addition is not obligatory for skeletal muscle hypertrophy. J Appl Physiol. 2007;103:1100–2.
80. Owino V, Yang SY, Goldspink G. Age-related loss of skeletal muscle function and the inability to express the autocrine form of insulin-like growth factor-1 (MGF) in response to mechanical overload. FEBS Lett. 2001;505(2):259–63.
81. Sandri M. Signaling in muscle atrophy and hypertrophy. Physiology (Bethesda). 2008;23:160–70.
82. Barton ER. Viral expression of insulin-like growth factor-I isoforms promotes different responses in skeletal muscle. J Appl Physiol. 2006;100(6):1778–84.
83. Bamman MM, Petrella JK, Kim JS, et al. Cluster analysis tests the importance of myogenic gene expression during myofiber hypertrophy in humans. J Appl Physiol. 2007;102(6):2232–9.
84. Hill M, Wernig A, Goldspink G. Muscle satellite (stem) cell activation during local tissue injury and repair. J Anat. 2003;203(1):89–99.

85. Yang SY, Goldspink G. Different roles of the IGF-I ec peptide (MGF) and mature IGF-I in myoblast proliferation and differentiation. FEBS Lett. 2002;522(1–3):156–60.
86. Philippou A, Maridaki M, Halapas A, et al. The role of the insulin-like growth factor 1 (IGF-1) in skeletal muscle physiology. In Vivo. 2007;21(1):45–54.
87. Rubin MR, Kraemer WJ, Maresh CM, et al. High-affinity growth hormone binding protein and acute heavy resistance exercise. Med Sci Sports Exerc. 2005;37(3):395–403.
88. Kraemer WJ, Aguilera BA, Terada M, et al. Responses of IGF-I to endogenous increases in growth hormone after heavy-resistance exercise. J Appl Physiol. 1995;79(4):1310–5.
89. Abe T, Yasuda T, Midorikawa T, et al. Skeletal muscle size and circulating IGF-1 are increased after two weeks of twice daily KAATSU resistance training. Int J Kaatsu Train Res. 2005;1:6–12.
90. Takano H, Morita T, Iida H, et al. Hemodynamic and hormonal responses to a short-term low-intensity resistance exercise with the reduction of muscle blood flow. Eur J Appl Physiol. 2005;95(1):65–73.
91. Fujita S, Abe T, Drummond MJ, et al. Blood flow restriction during low-intensity resistance exercise increases S6K1 phosphorylation and muscle protein synthesis. J Appl Physiol. 2007;103(3):903–10.
92. Drummond MJ, Fujita S, Abe T, et al. Human muscle gene expression following resistance exercise and blood flow restriction. Med Sci Sports Exerc. 2008;40(4):691–8.
93. Buresh R, Berg K, French J. The effect of resistive exercise rest interval on hormonal response, strength, and hypertrophy with training. J Strength Cond Res. 2009;23(1):62–71.
94. Kadi F. Cellular and molecular mechanisms responsible for the action of testosterone on human skeletal muscle: a basis for illegal performance enhancement. Br J Pharmacol. 2008;154(3):522–8.
95. Bhasin S, Woodhouse L, Storer TW. Proof of the effect of testosterone on skeletal muscle. J Endocrinol. 2001;170(1):27–38.
96. Zhao W, Pan J, Zhao Z, et al. Testosterone protects against dexamethasone-induced muscle atrophy, protein degradation and MAFbx upregulation. J Steroid Biochem Mol Biol. 2008;110(1–2):125–9.
97. Urban RJ, Bodenburg YH, Gilkison C, et al. Testosterone administration to elderly men increases skeletal muscle strength and protein synthesis. Am J Physiol. 1995;269(5 Pt 1):E820–6.
98. Vingren JL, Kraemer WJ, Ratamess NA, et al. Testosterone physiology in resistance exercise and training: the up-stream regulatory elements. Sports Med. 2010;40(12):1037–53.
99. Sculthorpe N, Solomon AM, Sinanan AC, et al. Androgens affect myogenesis in vitro and increase local IGF-1 expression. Med Sci Sports Exerc. 2012;44(4):610–5.
100. Sinha-Hikim I, Cornford M, Gaytan H, et al. Effects of testosterone supplementation on skeletal muscle fiber hypertrophy and satellite cells in community-dwelling older men. J Clin Endocrinol Metab. 2006;91(8):3024–33.
101. Ahtiainen JP, Pakarinen A, Alen M, et al. Muscle hypertrophy, hormonal adaptations and strength development during strength training in strength-trained and untrained men. Eur J Appl Physiol. 2003;89(6):555–63.
102. Tremblay MS, Copeland JL, Van Helder W. Effect of training status and exercise mode on endogenous steroid hormones in men. J Appl Physiol. 2004;96(2):531–9.
103. Kraemer WJ, Fry AC, Warren BJ, et al. Acute hormonal responses in elite junior weightlifters. Int J Sports Med. 1992;13(2):103–9.
104. Loenneke JP, Wilson JM, Pujol TJ, et al. Acute and chronic testosterone response to blood flow restricted exercise. Horm Metab Res. 2011;43(10):669–73.
105. Gotshalk LA, Loebel CC, Nindl BC, et al. Hormonal responses of multiset versus single-set heavy-resistance exercise protocols. Can J Appl Physiol. 1997;22(3):244–55.
106. Hakkinen K, Pakarinen A. Acute hormonal responses to two different fatiguing heavy-resistance protocols in male athletes. J Appl Physiol. 1993;74(2):882–7.
107. Smilios I, Pilianidis T, Karamouzis M, et al. Hormonal responses after various resistance exercise protocols. Med Sci Sports Exerc. 2003;35(4):644–54.
108. McCaulley GO, McBride JM, Cormie P, et al. Acute hormonal and neuromuscular responses to hypertrophy, strength and power type resistance exercise. Eur J Appl Physiol. 2009;105(5):695–704.
109. Reeves GV, Kraemer RR, Hollander DB, et al. Comparison of hormone responses following light resistance exercise with partial vascular occlusion and moderately difficult resistance exercise without occlusion. J Appl Physiol. 2006;101(6):1616–22.
110. Viru M, Jansson E, Viru A, et al. Effect of restricted blood flow on exercise-induced hormone changes in healthy men. Eur J Appl Physiol Occup Physiol. 1998;77(6):517–22.
111. Vierck J, O'Reilly B, Hossner K, et al. Satellite cell regulation following myotrauma caused by resistance exercise. Cell Biol Int. 2000;24(5):263–72.
112. Doessing S, Heinemeier KM, Holm L, et al. Growth hormone stimulates the collagen synthesis in human tendon and skeletal muscle without affecting myofibrillar protein synthesis. J Physiol. 2010;588(Pt 2):341–51.
113. Sotiropoulos A, Ohanna M, Kedzia C, et al. Growth hormone promotes skeletal muscle cell fusion independent of insulin-like growth factor 1 up-regulation. Proc Natl Acad Sci USA. 2006;103(19):7315–20.
114. Aperghis M, Velloso CP, Hameed M, et al. Serum IGF-I levels and IGF-I gene splicing in muscle of healthy young males receiving rhGH. Growth Horm IGF Res. 2009;19(1):61–7.
115. Ehrnborg C, Rosen T. Physiological and pharmacological basis for the ergogenic effects of growth hormone in elite sports. Asian J Androl. 2008;10(3):373–83.
116. Kraemer WJ, Dunn-Lewis C, Comstock BA, et al. Growth hormone, exercise, and athletic performance: a continued evolution of complexity. Curr Sports Med Rep. 2010;9(4):242–52.
117. Phillips SM. Physiologic and molecular bases of muscle hypertrophy and atrophy: impact of resistance exercise on human skeletal muscle (protein and exercise dose effects). Appl Physiol Nutr Metab. 2009;34(3):403–10.
118. West DW, Phillips SM. Anabolic processes in human skeletal muscle: restoring the identities of growth hormone and testosterone. Phys Sportsmed. 2010;38(3):97–104.
119. Lange KH, Andersen JL, Beyer N, et al. GH administration changes myosin heavy chain isoforms in skeletal muscle but does not augment muscle strength or hypertrophy, either alone or combined with resistance exercise training in healthy elderly men. J Clin Endocrinol Metab. 2002;87(2):513–23.
120. Yarasheski KE, Campbell JA, Smith K, et al. Effect of growth hormone and resistance exercise on muscle growth in young men. Am J Physiol. 1992;262(3 Pt 1):E261–7.
121. Yarasheski KE, Zachwieja JJ, Campbell JA, et al. Effect of growth hormone and resistance exercise on muscle growth and strength in older men. Am J Physiol. 1995;268(2 Pt 1):E268–76.
122. Nindl BC, Hymer WC, Deaver DR, et al. Growth hormone pulsatility profile characteristics following acute heavy resistance exercise. J Appl Physiol. 2001;91(1):163–72.
123. West DW, Kujbida GW, Moore DR, et al. Resistance exercise-induced increases in putative anabolic hormones do not enhance muscle protein synthesis or intracellular signalling in young men. J Physiol. 2009;587(Pt 21):5239–47.

124. Coffey VG, Shield A, Canny BJ, et al. Interaction of contractile activity and training history on mRNA abundance in skeletal muscle from trained athletes. Am J Physiol Endocrinol Metab. 2006;290(5):E849–55.
125. Madarame H, Neya M, Ochi E, et al. Cross-transfer effects of resistance training with blood flow restriction. Med Sci Sports Exerc. 2008;40(2):258–63.
126. West DW, Burd NA, Tang JE, et al. Elevations in ostensibly anabolic hormones with resistance exercise enhance neither training-induced muscle hypertrophy nor strength of the elbow flexors. J Appl Physiol. 2010;108(1):60–7.
127. Ronnestad BR, Nygaard H, Raastad T. Physiological elevation of endogenous hormones results in superior strength training adaptation. Eur J Appl Physiol. 2011;111(9):2249–59.
128. Nielsen AR, Pedersen BK. The biological roles of exercise-induced cytokines: IL-6, IL-8, and IL-15. Appl Physiol Nutr Metab. 2007;32(5):833–9.
129. Quinn LS. Interleukin-15: a muscle-derived cytokine regulating fat-to-lean body composition. J Anim Sci. 2008;86(14 Suppl.): E75–83.
130. Serrano AL, Baeza-Raja B, Perdiguero E, et al. Interleukin-6 is an essential regulator of satellite cell-mediated skeletal muscle hypertrophy. Cell Metab. 2008;7(1):33–44.
131. Pedersen BK, Edward F. Adolph distinguished lecture: muscle as an endocrine organ: IL-6 and other myokines. J Appl Physiol. 2009;107(4):1006–14.
132. Febbraio MA, Pedersen BK. Contraction-induced myokine production and release: is skeletal muscle an endocrine organ? Exerc Sport Sci Rev. 2005;33(3):114–9.
133. Fujita T, Brechue WF, Kurita K, et al. Increased muscle volume and strength following six days of low-intensity resistance training with restricted muscle blood flow. Int J Kaatsu Train Res. 2008;4:1–8.
134. Abe T, Beekley MD, Hinata S, et al. Day-to-day change in muscle strength and MRI-measured skeletal muscle size during 7 days KAATSU resistance training: a case study. Int J Kaatsu Train Res. 2005;1:71–6.
135. Roth SM, Walsh S. Myostatin: a therapeutic target for skeletal muscle wasting. Curr Opin Clin Nutr Metab Care. 2004;7(3): 259–63.
136. Kawada S, Ishii N. Skeletal muscle hypertrophy after chronic restriction of venous blood flow in rats. Med Sci Sports Exerc. 2005;37(7):1144–50.
137. Manini TM, Vincent KR, Leeuwenburgh CL, et al. Myogenic and proteolytic mRNA expression following blood flow restricted exercise. Acta Physiol (Oxf). 2011;201(2):255–63.
138. Farooqui T. Iron-induced oxidative stress modulates olfactory learning and memory in honeybees. Behav Neurosci. 2008; 122(2):433–47.
139. Alessio HM, Hagerman AE, Fulkerson BK, et al. Generation of reactive oxygen species after exhaustive aerobic and isometric exercise. Med Sci Sports Exerc. 2000;32(9):1576–81.
140. Powers SK, Talbert EE, Adhihetty PJ. Reactive oxygen and nitrogen species as intracellular signals in skeletal muscle. J Physiol. 2011;589(Pt 9):2129–38.
141. Jackson MJ. Reactive oxygen species and redox-regulation of skeletal muscle adaptations to exercise. Philos Trans R Soc Lond B Biol Sci. 2005;360(1464):2285–91.
142. Simpson PJ, Lucchesi BR. Free radicals and myocardial ischemia and reperfusion injury. J Lab Clin Med. 1987;110(1):13–30.
143. Fulle S, Protasi F, Di Tano G, et al. The contribution of reactive oxygen species to sarcopenia and muscle ageing. Exp Gerontol. 2004;39(1):17–24.
144. Jackson MJ. Free radicals generated by contracting muscle: by-products of metabolism or key regulators of muscle function? Free Radic Biol Med. 2008;44(2):132–41.
145. Gomez-Cabrera MC, Domenech E, Vina J. Moderate exercise is an antioxidant: upregulation of antioxidant genes by training. Free Radic Biol Med. 2008;44(2):126–31.
146. Ji LL, Gomez-Cabrera MC, Vina J. Exercise and hormesis: activation of cellular antioxidant signaling pathway. Ann N Y Acad Sci. 2006;1067:425–35.
147. Thannickal VJ, Fanburg BL. Reactive oxygen species in cell signaling. Am J Physiol Lung Cell Mol Physiol. 2000;279(6): L1005–28.
148. Suzuki YJ, Ford GD. Redox regulation of signal transduction in cardiac and smooth muscle. J Mol Cell Cardiol. 1999;31(2): 345–53.
149. Hornberger TA, McLoughlin TJ, Leszczynski JK, et al. Selenoprotein-deficient transgenic mice exhibit enhanced exercise-induced muscle growth. J Nutr. 2003;133(10):3091–7.
150. Kefaloyianni E, Gaitanaki C, Beis I. ERK1/2 and p38-MAPK signalling pathways, through MSK1, are involved in NF-kappaB transactivation during oxidative stress in skeletal myoblasts. Cell Signal. 2006;18(12):2238–51.
151. Tappia PS, Dent MR, Dhalla NS. Oxidative stress and redox regulation of phospholipase D in myocardial disease. Free Radic Biol Med. 2006;41(3):349–61.
152. Handayaningsih A, Iguchi G, Fukuoka H, et al. Reactive oxygen species play an essential role in IGF-I signaling and IGF-I-induced myocyte hypertrophy in C2C12 myocytes. Endocrinology. 2011;152(3):912–21.
153. Korthuis RJ, Granger DN, Townsley MI, et al. The role of oxygen-derived free radicals in ischemia-induced increases in canine skeletal muscle vascular permeability. Circ Res. 1985;57(4): 599–609.
154. Clanton TL. Hypoxia-induced reactive oxygen species formation in skeletal muscle. J Appl Physiol. 2007;102(6):2379–88.
155. Goldfarb AH, Garten RS, Chee PD, et al. Resistance exercise effects on blood glutathione status and plasma protein carbonyls: influence of partial vascular occlusion. Eur J Appl Physiol. 2008;104(5):813–9.
156. Smith LW, Smith JD, Criswell DS. Involvement of nitric oxide synthase in skeletal muscle adaptation to chronic overload. J Appl Physiol. 2002;92(5):2005–11.
157. Sellman JE, DeRuisseau KC, Betters JL, et al. In vivo inhibition of nitric oxide synthase impairs upregulation of contractile protein mRNA in overloaded plantaris muscle. J Appl Physiol. 2006;100(1):258–65.
158. Anderson JE. A role for nitric oxide in muscle repair: nitric oxide-mediated activation of muscle satellite cells. Mol Biol Cell. 2000;11(5):1859–74.
159. Tatsumi R, Hattori A, Ikeuchi Y, et al. Release of hepatocyte growth factor from mechanically stretched skeletal muscle satellite cells and role of pH and nitric oxide. Mol Biol Cell. 2002;13(8):2909–18.
160. Kiang JG, Tsokos GC. Heat shock protein 70 kDa: molecular biology, biochemistry, and physiology. Pharmacol Ther. 1998; 80(2):183–201.
161. Simar D, Malatesta D, Badiou S, et al. Physical activity modulates heat shock protein-72 expression and limits oxidative damage accumulation in a healthy elderly population aged 60 90 years. J Gerontol A Biol Sci Med Sci. 2007;62(12):1413–9.
162. Locke M. Heat shock protein accumulation and heat shock transcription factor activation in rat skeletal muscle during compensatory hypertrophy. Acta Physiol (Oxf). 2008; 192(3):403–11.
163. Kregel KC. Heat shock proteins: modifying factors in physiological stress responses and acquired thermotolerance. J Appl Physiol. 2002;92(5):2177–86.
164. Paulsen G, Hanssen KE, Ronnestad BR, et al. Strength training elevates HSP27, HSP70 and alphaB-crystallin levels in musculi

vastus lateralis and trapezius. Eur J Appl Physiol. 2012; 112(5):1773–82.
165. Morton JP, Kayani AC, McArdle A, et al. The exercise-induced stress response of skeletal muscle, with specific emphasis on humans. Sports Med. 2009;39(8):643–62.
166. Haussinger D, Lang F, Gerok W. Regulation of cell function by the cellular hydration state. Am J Physiol. 1994;267(3 Pt 1):E343–55.
167. Haussinger D. The role of cellular hydration in the regulation of cell function. Biochem J. 1996;313(Pt 3):697–710.
168. Lang F, Busch GL, Ritter M, et al. Functional significance of cell volume regulatory mechanisms. Physiol Rev. 1998;78(1): 247–306.
169. Dangott B, Schultz E, Mozdziak PE. Dietary creatine monohydrate supplementation increases satellite cell mitotic activity during compensatory hypertrophy. Int J Sports Med. 2000;21(1): 13–6.
170. Lang F. Mechanisms and significance of cell volume regulation. J Am Coll Nutr. 2007;26(5 Suppl.):613S–23S.
171. Low SY, Rennie MJ, Taylor PM. Signaling elements involved in amino acid transport responses to altered muscle cell volume. FASEB J. 1997;11(13):1111–7.
172. Clarke MS, Feeback DL. Mechanical load induces sarcoplasmic wounding and FGF release in differentiated human skeletal muscle cultures. FASEB J. 1996;10(4):502–9.
173. Lambert IH, Hoffmann EK, Pedersen SF. Cell volume regulation: physiology and pathophysiology. Acta Physiol (Oxf). 2008;194(4):255–82.
174. Schliess F, Richter L, vom Dahl S, et al. Cell hydration and mTOR-dependent signalling. Acta Physiol (Oxf). 2006;187(1–2): 223–9.
175. Finkenzeller G, Newsome W, Lang F, et al. Increase of c-jun mRNA upon hypo-osmotic cell swelling of rat hepatoma cells. FEBS Lett. 1994;340(3):163–6.
176. Schliess F, Schreiber R, Haussinger D. Activation of extracellular signal-regulated kinases erk-1 and erk-2 by cell swelling in H4IIE hepatoma cells. Biochem J. 1995;309(Pt 1):13–7.
177. Sjogaard G. Water and electrolyte fluxes during exercise and their relation to muscle fatigue. Acta Physiol Scand Suppl. 1986;556:129–36.
178. Sjogaard G, Adams RP, Saltin B. Water and ion shifts in skeletal muscle of humans with intense dynamic knee extension. Am J Physiol. 1985;248(2 Pt 2):R190–6.
179. Frigeri A, Nicchia GP, Verbavatz JM, et al. Expression of aquaporin-4 in fast-twitch fibers of mammalian skeletal muscle. J Clin Invest. 1998;102(4):695–703.
180. Kosek DJ, Kim JS, Petrella JK, et al. Efficacy of 3 days/wk resistance training on myofiber hypertrophy and myogenic mechanisms in young vs. older adults. J Appl Physiol. 2006;101(2):531–44.
181. Gundermann DM, Fry CS, Dickinson JM, et al. Reactive hyperemia is not responsible for stimulating muscle protein synthesis following blood flow restriction exercise. J Appl Physiol. 2012.
182. MacDougall JD, Ward GR, Sale DG, et al. Biochemical adaptation of human skeletal muscle to heavy resistance training and immobilization. J Appl Physiol. 1977;43(4):700–3.
183. Chan ST, Johnson AW, Moore MH, et al. Early weight gain and glycogen-obligated water during nutritional rehabilitation. Hum Nutr Clin Nutr. 1982;36(3):223–32.
184. Widegren U, Ryder JW, Zierath JR. Mitogen-activated protein kinase signal transduction in skeletal muscle: effects of exercise and muscle contraction. Acta Physiol Scand. 2001;172(3): 227–38.
185. Tanimoto M, Sanada K, Yamamoto K, et al. Effects of whole-body low-intensity resistance training with slow movement and tonic force generation on muscular size and strength in young men. J Strength Cond Res. 2008;22(6):1926–38.
186. Mitchell CJ, Churchward-Venne TA, West DD, et al. Resistance exercise load does not determine training-mediated hypertrophic gains in young men. J Appl Physiol. 2012.
187. Holm L, Reitelseder S, Pedersen TG, et al. Changes in muscle size and MHC composition in response to resistance exercise with heavy and light loading intensity. J Appl Physiol. 2008; 105(5):1454–61.
188. Schoenfeld BJ. Does exercise-induced muscle damage play a role in skeletal muscle hypertrophy? J Strength Cond Res. 2012;26(5):1441–53.