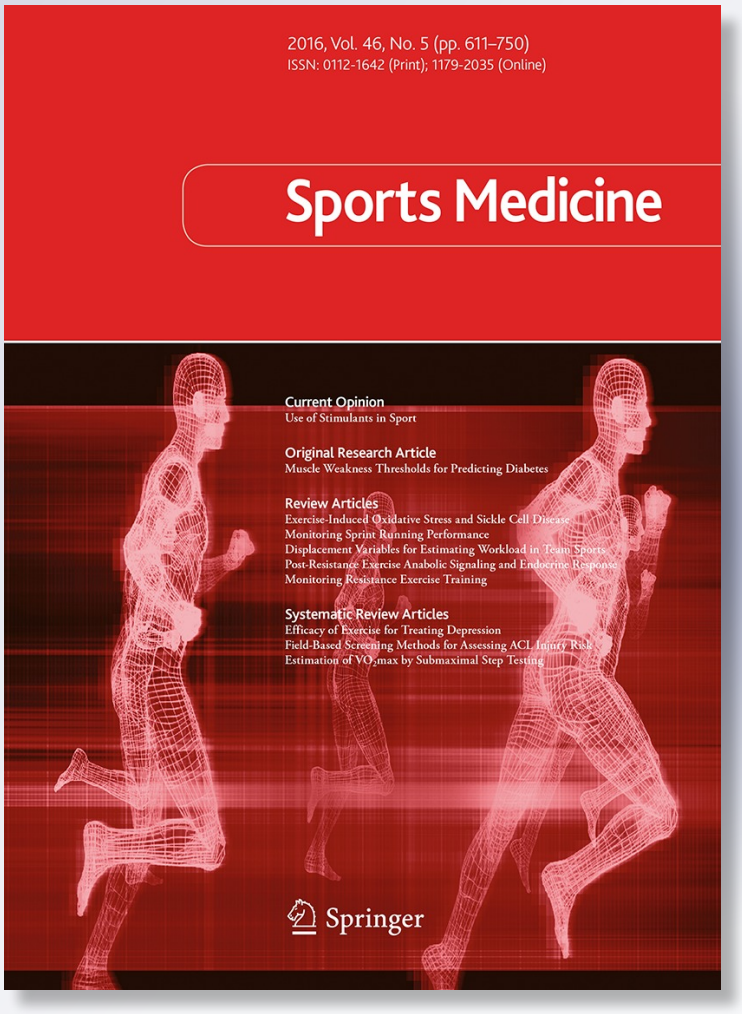
Intramuscular Anabolic Signaling and Endocrine Response Following Resistance Exercise: Implications for Muscle Hypertrophy

Adam M. Gonzalez, Jay R. Hoffman, Jeffrey R. Stout, David H. Fukuda & Darryn S. Willoughby

Sports Medicine

ISSN 0112-1642
Volume 46
Number 5

Sports Med (2016) 46:671-685
DOI 10.1007/s40279-015-0450-4



Springer

Sports Med (2016) 46:671–685
DOI 10.1007/s40279-015-0450-4

REVIEW ARTICLE

Intramuscular Anabolic Signaling and Endocrine Response Following Resistance Exercise: Implications for Muscle Hypertrophy

Adam M. Gonzalez[1] · Jay R. Hoffman[2] · Jeffrey R. Stout[2] · David H. Fukuda[2] · Darryn S. Willoughby[3]

Published online: 14 December 2015

Abstract Maintaining skeletal muscle mass and function is critical for disease prevention, mobility and quality of life, and whole-body metabolism. Resistance exercise is known to be a major regulator for promoting muscle protein synthesis and muscle mass accretion. Manipulation of exercise intensity, volume, and rest elicit specific muscular adaptations that can maximize the magnitude of muscle growth. The stimulus of muscle contraction that occurs during differing intensities of resistance exercise results in varying biochemical responses regulating the rate of protein synthesis, known as mechanotransduction. At the cellular level, skeletal muscle adaptation appears to be the result of the cumulative effects of transient changes in gene expression following acute bouts of exercise. Thus, maximizing the resistance exercise-induced anabolic response produces the greatest potential for hypertrophic adaptation with training. The mechanisms involved in converting mechanical signals into the molecular events that control muscle growth are not completely understood; however, skeletal muscle protein synthesis appears to be regulated by the multi-protein phosphorylation cascade, mTORC1 (mammalian/mechanistic target of rapamycin complex 1). The purpose of this review is to examine the physiological response to resistance exercise, with particular emphasis on the endocrine response and intramuscular anabolic signaling through mTORC1. It appears that resistance exercise protocols that maximize muscle fiber recruitment, time-under-tension, and metabolic stress will contribute to maximizing intramuscular anabolic signaling; however, the resistance exercise parameters for maximizing the anabolic response remain unclear.

Key Points

The endocrine system and intramuscular anabolic signaling are primary regulators of muscle growth.

Resistance exercise elicits an acute endocrine response and up-regulation of intramuscular signaling proteins; however, the resistance exercise parameters for maximizing the anabolic effect remain unclear.

1 Introduction

Maintaining skeletal muscle mass and function is critical for disease prevention [1, 2], mobility and quality of life [3, 4], and whole-body metabolism [5]. Skeletal muscle mass is also desired by many types of athletes to enhance athletic performance, increase body size, and improve aesthetic appearance. The balance between synthesis and breakdown of muscle proteins governs muscle mass accretion. If protein synthesis exceeds protein degradation, an increase in skeletal muscle mass can occur [6]. The rate of protein synthesis appears to be more dynamic than that of protein

✉ Jay R. Hoffman
jay.hoffman@ucf.edu

[1] Department of Health Professions, Hofstra University, Hempstead, NY, USA

[2] Institute of Exercise Physiology and Wellness, Sport and Exercise Science, College of Education and Human Performance, University of Central Florida, P.O. Box 161250, Orlando, FL 32816-1250, USA

[3] Exercise and Biochemical Nutrition Laboratory, Baylor University, Waco, TX, USA

breakdown, suggesting that growth of skeletal muscle is primarily dictated by regulation of muscle protein synthesis [7]. Hypertrophy is reflected by a greater muscle cross-sectional area (CSA), which may be attributable to increases in myofibrillar volume of individual muscle fibers [8–10]. Increases in the number of individual myofibers within a muscle, termed hyperplasia, is also a potential mechanism contributing to muscle growth; however, documented reports are primarily in rodents [11]. Muscle protein synthesis and muscle mass accretion are affected by several factors, including nutritional support, cytokines, hormones, and growth factors, yet resistance exercise is known to be a major regulator for promoting hypertrophy. Resistance exercise can stimulate an increase in muscle protein synthesis for up to 48 h post-exercise [12–15], and repeated bouts of resistance exercise (i.e., training) can significantly increase muscle CSA and muscle fiber hypertrophy [16–19]. However, the parameters of a resistance training program for the regulation of muscle growth remain unclear [20].

A broad range of resistance exercise intensities, volume, and rest intervals have been demonstrated to elicit muscular hypertrophy in humans [16–19]. The stimulus of muscle contraction that occurs during resistance exercise results in various biochemical responses regulating the rate of protein synthesis, known as mechanotransduction [21]. At the cellular level, skeletal muscle adaptation appears to occur from the cumulative effects of transient changes in gene expression following acute bouts of exercise [22]. Thus, maximizing the resistance exercise-induced anabolic response produces the greatest potential for hypertrophic adaptation with training. The purpose of this review is to examine the physiological response to resistance exercise, with particular emphasis on the endocrine system and intramuscular anabolic signaling through the mammalian/mechanistic target of rapamycin complex 1 (mTORC1) pathway.

2 Magnitude of Hypertrophy Following Resistance Exercise Protocols of Different Intensities

Controversy exists regarding a training paradigm that will maximize hypertrophic adaptation. Long-term studies evaluating the effects of varying exercise intensity on the magnitude of muscle hypertrophy have yielded inconclusive findings. Comparisons of high-intensity versus low-intensity resistance training programs for up to 12 weeks in previously untrained subjects have shown no differences in muscle CSA as measured by magnetic resonance imaging (MRI) [23–29], computed tomography (CT) [30, 31], dual-energy x-ray absorptiometry (DEXA) [32], and ultrasonography [32, 33]. However, Holm et al. [34] found low-intensity loads (15.5 % 1 repetition maximum [RM]) to be inferior to high-intensity loads (70 % 1 RM) for evoking increases in quadriceps CSA assessed via MRI. Similarly, low-intensity loads were also shown to be inferior to high-intensity loads for increasing muscle fiber hypertrophy as assessed via histochemistry from muscle biopsies [35, 36]. Other investigations, however, have indicated that lower-intensity loads (40–80 % 1 RM) produce greater gains in muscle fiber CSA than high-intensity loads (90 % 1 RM) [37, 38].

Defining an intensity load recommendation for enhancing muscle hypertrophy is difficult due to the inconsistency of findings. Additionally, the contradictory nature of these findings may be attributed to the different assessment methods (i.e., MRI, CT, ultrasonography vs. muscle histochemistry), experimental designs (i.e., within- vs. between-subject designs), activated musculature (i.e., single- vs. multi-joint movements), rest intervals utilized, and protocol parameters (i.e., equated vs. non-equated volume). A number of researchers equate volume to account for the potentially greater dose response associated with hypertrophic adaptation [39]. Furthermore, these studies are collectively limited as observations of early-phase hypertrophic adaptations among untrained subjects. Greater training experience has been shown to attenuate post-exercise anabolic responses, including muscle protein synthesis rates [40–42] and intracellular anabolic signaling [42–45]. Therefore, these findings cannot be generalized to a well-trained population. Schoenfeld et al. [46] recently assessed the magnitude of hypertrophy following 8 weeks of a hypertrophy-style resistance training program versus a volume-equated strength-style program in resistance-trained men and found no significant differences in muscle thickness of the biceps brachii assessed via ultrasonography. In a subsequent study by the same research team, muscle thickness of the elbow flexors, elbow extensors, and quadriceps femoris assessed via ultrasonography was not significantly different following 8 weeks of low-load (25–35 RM) versus high- load resistance training (8–12 RM) in resistance-trained men [47]. In conjunction with training intensity, factors including muscle fiber recruitment [48], time-under-tension [49], and metabolic stress [50] have all been suggested to influence intramuscular anabolic signaling. Furthermore, muscular adaptation following regimented resistance training is highly variable between individuals [51–54]. Several factors appear to influence muscle remodeling and the magnitude of hypertrophy, including nutritional support, muscle fiber-type distribution, and genetic predisposition [20, 55]. An additional concern when examining divergent resistance exercise protocols in trained individuals is

the novelty of the stimulus, as muscle adaptations may be enhanced when unaccustomed program variables are utilized [56].

The intensity of training necessary to stimulate muscle growth has been suggested to be greater than 60 % of an individual's 1 RM [57, 58], while others have suggested that maximal growth occurs at training intensities between 80 and 95 % of 1 RM [59]. However, recent research has shown that training intensities as low as 30 % of 1 RM can be equally as effective at stimulating muscle protein synthesis and muscle hypertrophy when performed to volitional fatigue in previously untrained men [24, 25, 60]. Moreover, a majority of the scientific evidence supporting a greater anabolic response following a high-volume, moderate-intensity training protocol (i.e., designed to elicit muscle hypertrophy) has emerged from acute investigations indicating a superior endocrine response compared to other training paradigms [61–67]. However, the mechanisms of exercise-mediated muscle hypertrophy have been suggested to be solely an intrinsic process, which is not influenced by transient changes in circulating hormones [54, 68–70]. Thus, the acute activation of intrinsically located signaling proteins and the acute elevation of muscle protein synthesis may be more reflective of the potential to increase muscle mass with resistance training [69]. Whether a high-volume, moderate-intensity training protocol activates intramuscular anabolic signaling to a greater degree than other training paradigms remains to be determined.

3 Role of Mammalian/Mechanistic Target of Rapamycin Complex 1 (mTORC1) in Skeletal Muscle Adaptation to Resistance Exercise

One of the most widely recognized mechanisms for regulating muscle mass involves mechanical tension [71]. Resistance exercise initiates a multifaceted series of events converting the stimulus of muscle contraction into biochemical responses regulating the rate of protein synthesis, known as mechanotransduction [21]. The mechanisms involved in converting mechanical signals into the molecular events that control muscle growth are not completely understood; however, phosphorylation of intramuscular signaling molecules appears to play an important role in skeletal muscle adaptation to resistance exercise [21]. Protein phosphorylation is a reversible post-translational modification causing conformational changes in protein structure accompanied by an increase or decrease in enzymatic activity [72]. Skeletal muscle protein synthesis appears to be regulated by the multi-protein phosphorylation cascade, mTORC1 [73–75]. Upon activation, phosphorylation of upstream (i.e., insulin receptor substrate 1 [IRS1], protein kinase B [Akt], tumor sclerosis complex 2 [TSC2]) and downstream (i.e., mammalian/mechanistic target of rapamycin [mTOR], ribosomal S6 kinase 1 [p70S6k], RPS6 [ribosomal protein S6]) effectors of mTORC1 signal to promote anabolic and inhibit catabolic cellular functions, providing a biochemical mechanism for controlling processes related to cell differentiation and muscle remodeling (Fig. 1) [75]. The protein kinase mTOR serves as a critical protein that confers signaling to p70S6k and several other downstream signaling molecules that regulate protein synthesis and skeletal muscle mass [21, 75].

The mTORC1 complex plays an important regulatory role during the process of skeletal muscle hypertrophy [76]. mTORC1 is involved in many cell processes, including the regulation of cell size, mRNA translation, biogenesis of mitochondria and ribosomes, and autophagy [77]. At the cellular level, mTORC1 functions as a critical regulator of translation initiation, the rate-limiting step in protein synthesis [72, 75]. It appears that the phosphorylation of signaling molecules in response to resistance exercise is a prerequisite for increasing translation initiation and muscle protein synthesis. The inhibition of mTOR via rapamycin treatment has been consistently demonstrated to blunt increases in muscle protein synthesis [78–80] and prevent skeletal muscle hypertrophy, which normally occurs following prolonged resistance training [76, 81]. In humans, rapamycin treatment has been shown to block the acute exercise-induced increase in muscle protein synthesis in addition to blunting several downstream components of the mTORC1 signaling pathway, including p70S6k [73, 80]. Further, the magnitude of p70S6k phosphorylation has been shown to be a proxy marker of myofibrillar protein synthesis rates [82, 83], and also corresponds with resistance training-induced muscle hypertrophy [54, 84–86]. Collectively, these observations suggest that mTOR acts as the primary regulator of intracellular anabolic signaling via phosphorylation of p70S6k and several other downstream signaling molecules that regulate protein synthesis and skeletal muscle mass [73–75, 87]. Although the exact mechanism underlying increased mTORC1 activation following resistance exercise remains relatively elusive, mechanical loading has been suggested to promote mTORC1 activation by increasing the activity of Rheb (Ras homolog enriched in brain) and increasing the abundance of phosphatidic acid (PA) [88].

mTORC1 activity is regulated by the modulation of tumor suppressor tuberous sclerosis complex 1/2 (TSC 1/2) activity [77]. TSC 1/2 negatively regulates mTORC1 activity by converting Rheb into its inactive guanosine diphosphate (GDP)-bound state [89]. Tumor sclerosis complex 2 (TSC2) acts as the guanosine triphosphatase (GTPase)-activating enzyme that keeps Rheb in the GDP-bound state [90]. TSC2 phosphorylation inactivates the

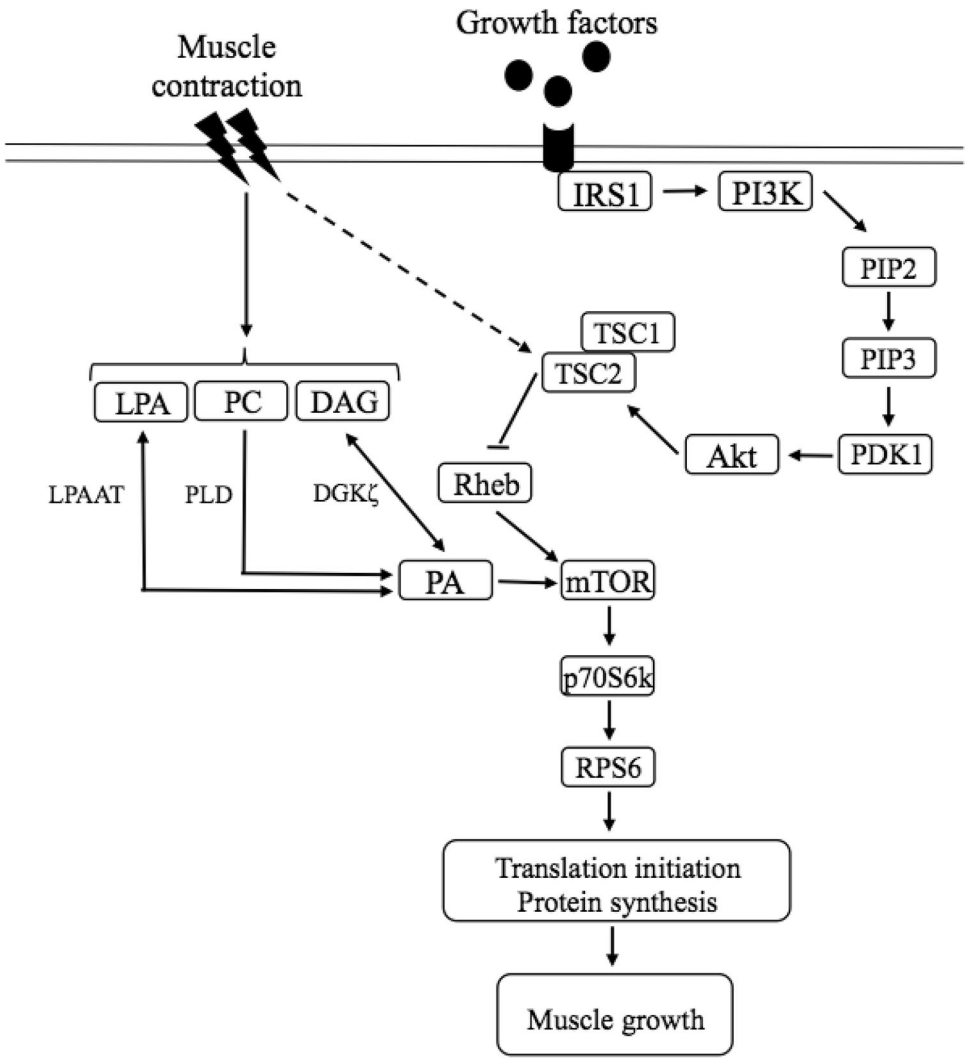


Fig. 1 Simplistic overview of the influence of muscle contraction and growth factors on mTORC1 signaling and the regulation of muscle growth. *Broken arrows* indicate 'remains unclear'. *Akt* protein kinase B, *DAG* diacylglycerol, *DGKζ* diacylglycerol kinase ζ, *IRS1* insulin receptor substrate 1, *LPA* lysophosphatidic acid, *LPAAT* lysophosphatidic acid acyltransferases, *mTOR* mammalian/mechanistic target of rapamycin, *mTORC1* mammalian/mechanistic target of rapamycin complex 1, *p70S6k* ribosomal S6 kinase 1, *PA* phosphatidic acid, *PC* phosphatidyl choline, *PDK1* 3-phosphoinositide-dependent protein kinase-1, *PI3K* phosphatidylinositol-3 kinase, *PIP2* phosphoinositol (4,5)-bisphosphate, *PIP3* phosphoinositol (3,4,5)-trisphosphate, *PLD* phospholipase D, *Rheb* Ras homolog enriched in brain, *RPS6* ribosomal protein S6, *TSC1* tuberous sclerosis complex 1, *TSC2* tuberous sclerosis complex 2

GTPase-activating enzyme activity of TSC2, repressing the hydrolysis of Rheb–GTP (guanosine triphosphate) [91]. When Rheb is in its active GTP-bound state, it translocates to the lysosome, allowing mTORC1 activity to continue [91, 92]. Jacobs et al. [93] showed that TSC2 localizes with Rheb at rest; however, following resistance exercise, TSC2 phosphorylation corresponds with the movement of TSC2 away from Rheb. In summary, resistance exercise-induced activation of mTORC1 requires the TSC2 complex (a negative regulator of Rheb) to be sequestered away from Rheb (Fig. 2). However, it remains unclear what mediates TSC2 phosphorylation following resistance exercise [88]. While insulin and growth factors phosphorylate TSC2 through Akt, resistance exercise-induced activation of mTORC1 appears to be Akt-independent [94]. Several studies have shown that Akt phosphorylation either does not change [43, 45, 49] or decreases [95, 96] following resistance exercise, despite downstream activation of mTORC1.

An additional mTORC1 activator associated with resistance exercise-induced muscle hypertrophy involves the lipid second messenger known as PA [97]. Exogenous administration of PA, or an over-expression of enzymes that produce PA, results in an increase in mTORC1 activation [98–100]. Similarly, limiting PA production attenuates mTORC1 activity [97]. It has been suggested that PA mediates mTORC1 activation by competing with the FKBP12 (FK506 binding protein 12)–rapamycin complex for binding to the FKBP12–rapamycin-binding (FRB) domain of mTOR [101, 102]. PA may also promote mTORC1 activation as a primary effector of Rheb [103]. GTP-bound Rheb has been shown to activate phospholipase D (PLD), an enzyme that generates PA from phosphatidylcholine [103]. PA can be synthesized by various classes of enzymes, such as PLD, diacylglycerol kinase ζ (DGKζ), and lysophosphatidic acid acyltransferases (LPAAT) [74, 98, 104, 105]. Joy et al. [106] found that stimulating myoblast cells with PA in vitro increased

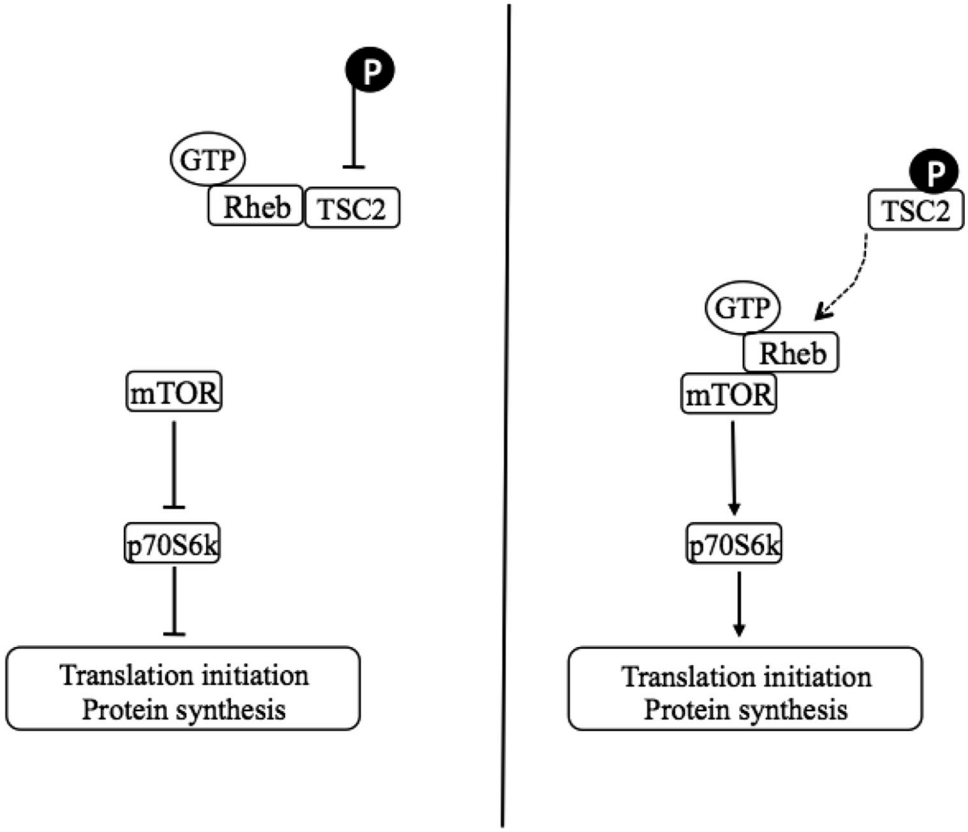


Fig. 2 Simplistic overview mTORC1 activation (*curved arrow*) via phosphorylation of TSC2. *GTP* guanosine triphosphate, *mTOR* mammalian/mechanistic target of rapamycin, *mTORC1* mammalian/mechanistic target of rapamycin complex 1, *P* phosphorylation, *p70S6k* ribosomal S6 kinase 1, *Rheb* Ras homolog enriched in brain, *TSC2* tuberous sclerosis complex 2

mTORC1 signaling, and trained subjects supplementing with PA significantly improved skeletal muscle hypertrophy following 8 weeks of resistance training. Thus, evidence suggests that PA is a direct regulator of resistance exercise-induced mTORC1 signaling promoting muscle hypertrophy.

4 Growth Factor Activation of mTORC1

Within the mTORC1 signaling pathway, growth factors including insulin and insulin-like growth factor (IGF)-1 bind to their respective receptors, which promote the inhibition of Rheb in an Akt-dependent pathway, resulting in an increase in mTORC1 activity [91]. When insulin/IGF-1 bind to their receptors at the muscle membrane, the receptor autophosphorylates, creating a docking site for IRS1 [107]. IRS1 moves to the plasma membrane, which subsequently recruits phosphatidylinositol-3 kinase (PI3K) [107]. PI3K phosphorylates the membrane phospholipid phosphoinositol (4,5)-bisphosphate (PIP2), resulting in phosphoinositol (3,4,5)-trisphosphate (PIP3) [108]. PIP3 causes the co-localization of Akt and 3-phosphoinositide-dependent protein kinase-1 (PDK-1) to the membrane, resulting in Akt phosphorylation [109]. Subsequently, TSC2 is phosphorylated by Akt, resulting in relocalization away from Rheb [91, 110]. Akt also inhibits PRAS40 (proline-rich Akt substrate of 40 kDa), a negative regulator of mTORC1 signaling [111]. In summary, similar to resistance exercise-induced mTORC1 activation, insulin and growth factors appear to activate mTORC1 via phosphorylation of TSC2. However, insulin and growth factors appear to activate mTORC1 through Akt, while resistance exercise induces an Akt-independent activation of mTORC1.

5 Association Between Circulating Hormones, mTORC1 Signaling, and Muscle Growth

The endocrine system plays an integral role in the regulation of muscle mass. Hormones including testosterone, growth hormone (GH), insulin, IGF-1 and cortisol influence muscle growth and development throughout life, and states of hormonal excess or deficiency alter the balance between skeletal muscle anabolism and catabolism [112, 113]. While the fundamental roles of hormones are imperative for developmental growth and maintenance of skeletal muscle throughout a lifetime, the impact of physiological fluctuations (i.e., non-pharmacological-based changes) in anabolic hormones has been debated [114]. Resting hormonal concentrations appear to be unaltered

following resistance training programs of up to 24 weeks [115, 116]; therefore, there has been considerable speculation about the role of the post-exercise endocrine response in mediating increases in muscle size [117]. Systemic elevations of circulating hormones presumably increase the likelihood of interaction with receptors located within the muscle tissue and have been speculated to contribute to muscle growth consequent to resistance training [117]. However, in humans, elevations of the anabolic hormones do not appear to be necessary for muscle hypertrophy [118], intramuscular signaling [70, 119], or muscle protein synthesis [70], leading to the supposition that the mechanisms of muscle hypertrophy are intrinsically specific to the activated skeletal tissue [69]. Exogenous supra-physiological doses of testosterone have shown to significantly increase muscle protein synthesis and lean body mass [120, 121], especially when combined with resistance training [122, 123]. Additionally, administration of exogenous testosterone supplementation to restore normal physiological values in androgen-deficient older men is associated with significant increases in muscle mass [124–129]. However, others have suggested that physiological fluctuations of hormones are not required for resistance exercise-induced skeletal muscle hypertrophy [88]. These hormones, including testosterone, GH, insulin, IGF-1, and cortisol, have been suggested to be far more important for developmental growth rather than exercise-induced muscle growth [88].

Transient hormonal elevations appear to play a permissive, rather than stimulatory, role in the regulation of muscle protein synthesis [130]. Over-expression of Rheb in skeletal muscle stimulates a PI3K/Akt-independent activation of mTORC1 that is sufficient to induce muscle hypertrophy [131]. Although it has been suggested that growth factor activation of the PI3K/Akt axis is also sufficient for skeletal muscle growth, these mechanisms do not appear to be necessary for maximizing mTORC1 activation or the hypertrophic response that occurs in response to resistance exercise [21, 88]. Resistance exercise and growth factors share the same final step in mTORC1 activation (via phosphorylation of TSC2) (Fig. 2) [88]. Since the end result of both resistance exercise and growth factors is the movement of TSC2 away from Rheb via different upstream kinases, resistance exercise and growth factor exposure may not offer a synergistic effect.

6 Influence of Acute Endocrine and Intramuscular Signaling Response on Muscle Growth

Substantial evidence indicates that resistance exercise protocols of high volume (3–6 sets; 8–12 repetitions), moderate intensity (60–85 % 1 RM), and short rest intervals (30–90 s), which activate a large muscle mass, elicit the greatest acute elevations in testosterone and GH [61–67, 132–139]. Studies investigating the acute hormonal response following different heavy-resistance exercise protocols are presented in Table 1. Several studies have also investigated the association between acute exercise-induced hormone responses and changes in muscle size following a structured resistance training program (Table 2). McCall et al. [115] found a significant correlation ($r = 0.70$–0.71; $p < 0.05$) between acute exercise-induced GH elevations and the degree of both type I and type II muscle fiber hypertrophy following 15 weeks of resistance training in 11 recreationally trained men. Ahtiainen et al. [116] reported a significant correlation ($r = 0.76$; $p < 0.05$) between changes in the acute testosterone response and the degree of muscle hypertrophy following 21 weeks of resistance training in 16 men (eight strength athletes and eight non-athletes). However, both of these studies had a relatively small number of subjects, thereby limiting the ability to draw meaningful conclusions. In a more recent study examining a larger cohort of 56 untrained men, West and Phillips [140] reported that the acute systemic hormonal response of GH and cortisol were weakly correlated ($r = 0.28$–0.36; $p < 0.05$) with resistance training-induced changes in muscle fiber CSA explaining 8 and 12 % of the variance, respectively. Although cortisol, a catabolic hormone, was weakly correlated with changes in lean body mass ($r = 0.29$; $p < 0.05$), no significant correlations were observed between GH, testosterone, and IGF-1 and changes in lean body mass [140]. Additionally, the variability within the gains of muscle hypertrophy seen in 'high responders' and 'low responders' could not be explained by the acute hormone response [140]. However, these investigations are based on limited blood sampling timepoints following an acute bout of resistance training. Furthermore, Wilkinson et al. [118] observed significant gains in hypertrophy in the absence of systemic changes in GH, testosterone, and IGF-1 [118]. Thus, the effect of changes in the acute anabolic hormonal response to resistance exercise on muscle growth is still not well-understood.

Mitchell et al. [54] examined post-exercise changes in anabolic hormone concentrations (testosterone, GH, and IGF-1) and intramuscular signaling and their association with muscle fiber hypertrophy following 16 weeks of training. Post-exercise increases in these circulating hormones following the initial bout of resistance exercise did not appear to be related to training-induced hypertrophy, whereas acute increases in p70S6k phosphorylation and androgen receptor (AR) protein content following the initial bout of resistance exercise were highly associated ($r = 0.54$–0.60; $p < 0.05$) with resistance training-induced hypertrophy [54]. The magnitude of p70S6k

Table 1 Studies investigating the acute hormonal response following different resistance exercise protocols

Study	Participants	Crossover design?	Design	Protocols	Hormones measured	Results
Beaven et al. [134]	15 trained men	Yes	Full body	1. 4 × 10; 70 % 1 RM (2 min rest) 2. 3 × 5; 85 % 1 RM (3 min rest) 3. 5 × 15; 55 % 1 RM (1 min rest) 4. 3 × 5; 40 % 1 RM (3 min rest)	Testosterone Cortisol (salivary)	Protocols 1, 2, and 4 elicited significant decreases in cortisol following exercise. No significant differences in testosterone between protocols
Crewther et al. [61]	11 recreationally trained men	Yes	Lower body	1. 8 × 6; 45 % 1 RM (3 min rest) 2. 10 × 10; 75 % 1 RM (2 min rest) 3. 6 × 4; 88 % 1 RM (4 min rest)	Testosterone Cortisol (salivary)	Only protocol 2 elicited significant increases in testosterone and cortisol concentration following exercise
Hakkinen and Pakarinen [62]	10 trained men	Yes	Lower body	1. 10 × 10; 70 % 1 RM (3 min rest) 2. 20 × 1; 100 % 1 RM (3 min rest)	Testosterone Cortisol GH	Protocol 1 elicited significant increases in testosterone, cortisol, and GH following exercise. Protocol 2 elicited significant increase in GH following exercise
Kraemer et al. [67]	9 recreationally trained men	Yes	Full body	1. 3 × 10; 10 RM (1 min rest) 2. 5 × 5; 5 RM (3 min rest)	Testosterone Cortisol GH	Protocol 1 elicited significantly greater GH following exercise. Both protocols significantly increased testosterone; however, not at the same magnitude and duration (no difference in AUC). Both protocols showed only random acute increases in cortisol
Linnamo et al. [63]	8 recreationally active men	Yes	Full body	1. 5 × 10; 10 RM (2 min rest) 2. 5 × 10; 70 % 10 RM (2 min rest)	Testosterone GH	Only protocol 1 elicited significant increases in GH and testosterone following exercise
McCaulley et al. [64]	10 trained men	Yes	Lower body	1. 4 × 10; 75 % 1 RM (1.5 min rest) 2. 11 × 3; 90 % 1 RM (5 min rest)	Testosterone Cortisol	Only protocol 1 elicited significant increases in testosterone and cortisol following exercise
Raastad et al. [139]	7 trained men	Yes	Lower body	1. 3 × 3; 3 RM (6 min rest) (squat and front squat) and 3 × 6; 6 RM (4 min rest) (leg extension) 2. 3 × 3; 70 % 3 RM (6 min rest) (squat and front squat) and 3 × 6; 76 % 6 RM (4 min rest) (leg extension)	Testosterone Cortisol GH IGF-1 Insulin	Protocol 1 elicited significantly greater testosterone AUC than protocol 2. Protocol 1 elicited significantly greater cortisol AUC than protocol 2. No significant difference in GH, IGF-1, or insulin between protocols
Smilios et al. [65]	11 trained men	Yes	Full body	1. [b] × 5; 88 % 1 RM (3 min rest) 2. [b] × 10; 75 % 1 RM (2 min rest) 3. [b] × 15; 60 % 1 RM (1 min rest)	Testosterone Cortisol GH	Protocols 2 and 3 elicited significantly greater GH and cortisol following exercise. No significant differences were observed for testosterone for any protocol
Uchida et al. [66]	27 trained men	No	Upper body	1. 4 × ~20; 50 % 1 RM (2 min rest) 2. 5 × ~11; 75 % 1 RM (2 min rest) 3. 10 × ~4; 90 % 1 RM (2 min rest) 4. 8[a] × ~4; 110 % 1 RM (2 min rest)	Testosterone Cortisol	Protocol 2 elicited significantly greater cortisol following exercise. No differences in testosterone following each protocol

AUC area under the concentration–time curve, *GH* growth hormone, *IGF* insulin-like growth factor-1, *RM* repetition maximum

[a] Eccentric only

[b] Each was performed using 2, 4, and 6 sets

Table 2 Research investigating the association between acute exercise-induced hormone responses and changes in muscle size following a structured resistance training program

Study	Participants	Study length (weeks)	Results
McCall et al. [115]	11 recreationally trained men	12	Significant correlation between acute GH elevation and the degree of type I ($r = 0.70$) and type II ($r = 0.71$) muscle fiber hypertrophy
Ahtiainen et al. [116]	8 physically active men; 8 strength athletes	21	Significant correlation between acute testosterone elevation and change in muscle CSA ($r = 0.76$)
West and Phillips [140]	56 recreationally active men	12	Significant correlation between acute GH elevation and the degree of type I fiber hypertrophy ($r = 0.36$). Significant correlation between acute cortisol elevation and the degree of type II fiber hypertrophy ($r = 0.35$) and changes in lean body mass ($r = 0.29$)
Mitchell et al. [54]	23 recreationally active men	16	No correlation between acute testosterone, GH, or IGF-1 elevation and muscle hypertrophy

CSA cross-sectional area, *GH* growth hormone, *IGF-1* insulin-like growth factor-1

phosphorylation has shown to be associated with myofibrillar protein synthesis rates ($r = 0.31$–0.34; $p < 0.05$) [82, 83], and its acute phosphorylation following resistance exercise has been reported to correlate with muscle hypertrophy following training in both rodents ($r = 0.998$; $p < 0.05$) [84] and untrained men ($r = 0.53$–0.89; $p < 0.05$) [85, 86]. However, not all studies have found such a relationship [24]. Still, correlations between transient changes in muscular and systemic markers of anabolism following acute bouts of exercise and training-induced muscle hypertrophy are not evidence of a causative role for cellular adaptations in the trained muscle [141].

The hormone-receptor complex regulates gene expression and transcription factors that may promote an increase in net muscle protein balance [129, 142]. Thus, the number and sensitivity of receptors in the activated skeletal muscle, along with systemic elevations of the circulating hormone, may mediate the anabolic effects of hormones including testosterone. An up-regulation of either AR protein content and/or AR mRNA expression has been observed following resistance exercise [54, 143–148], and acute increases in AR protein content appear to correspond with subsequent increases in myofibrillar protein [143] and exercise-induced hypertrophy [54]. However, others report no changes, or decreases, in AR expression following resistance exercise [149, 150]. Moreover, AR expression appears to have a bi-phasic response with an initial down-regulation following a bout of resistance exercise followed by an up-regulation several hours after exercise [151]. Additionally, it has been demonstrated that AR expression can vary between different muscles and muscle fiber types [147]. Further, Inoue et al. [152] showed that down-regulation of AR expression (via an AR antagonist) suppressed the hypertrophic response in exercised rats. Alternatively, chemically induced testosterone suppression (via goserelin) did not blunt AR expression or hypertrophy in young men, despite a 10- to 20-fold lower resting concentration and a blocked exercise-induced testosterone response [153]. Enhanced hormone-receptor interaction following resistance exercise may up-regulate the expression of various muscle-specific genes promoting hypertrophy. However, further research has demonstrated that an IGF-1 receptor may not be necessary for resistance exercise-induced mTORC1 signaling and muscle growth [154]. Using a transgenic mouse model, Spangenburg and colleagues [154] reported that both Akt and p70S6k activation can be induced independently of a functioning IGF-1 receptor. The extent to which anabolic hormones mediate their effects directly through the hormone-receptor complex warrants further investigation.

The relationship between transient increases in hormonal concentrations and intramuscular anabolic signaling and muscle growth has also been an area of interest of several investigations (Table 3). Acute intramuscular anabolic signaling and exercise-induced hypertrophy have been examined under different hormonal environments in untrained individuals [68, 70, 119, 155]. Experimental trials eliciting a high hormonal response have not been shown to enhance markers of mTORC1 signaling in the vastus lateralis [119] or biceps brachii [70] compared with trials that did not elicit an increase in hormonal concentrations. Furthermore, the experimental trial eliciting a transient increase in the circulating concentration of anabolic hormones did not enhance muscle protein synthesis in the biceps brachii [70]. In a subsequent study, untrained men performed a 15-week elbow flexor resistance training program, with one arm being grouped into a low hormonal environment and the other into a high hormonal environment for the duration of the study. Results showed no difference between conditions in training-induced muscle hypertrophy of the biceps brachii [68]. However, other investigators provide conflicting evidence. Rønnestad and

Table 3 Research investigating the relationship between transient increases in hormonal concentrations and intramuscular anabolic signaling and muscle growth

Study	Participants	Study length	Results
Acute			
Spiering et al. [119]	7 physically active men	2 trials	No additive effect from elevated circulating hormones on intramuscular anabolic signaling
West et al. [70]	8 recreationally active men	2 trials	No additive effect from elevated circulating hormones on intramuscular anabolic signaling or muscle protein synthesis
Prolonged			
West et al. [68]	12 untrained men	15 weeks	No additive effect from elevated circulating hormones on whole-muscle, type I, or type II CSA
Rønnestad et al. [155]	11 untrained men	11 weeks	Significant increase in muscle CSA as a result of elevated circulating hormones

CSA cross-sectional area

colleagues [155] utilized a similar 11-week research design and demonstrated that the increased concentrations of serum testosterone and GH occurring prior to performing elbow flexor exercises yielded greater increases in CSA of the elbow flexors than elbow flexor exercises performed in a low hormonal environment. The authors hypothesized that their findings may be related to the exercise order. This contrasts with others who suggest that changes in the post-exercise circulating concentrations of testosterone, GH, and IGF-1, and the subsequent interaction within skeletal muscle, is not influenced by the order of the resistance exercises [156]. Evidence to date appears to suggest that exposing activated skeletal muscle to a transient elevation in circulating hormones does not enhance intramuscular signaling.

7 Effect of Resistance Exercise Variables on Activation of mTORC1

Resistance exercise evokes a robust activation of mTORC1 signaling in untrained and recreationally active men in both fed [157–161] and fasted states [73, 85, 162–164]. Resistance exercise-induced mTORC1 activation has also been observed in experienced, resistance-trained men [45, 165, 166], yet the training design (i.e., manipulation of acute training variables: intensity, volume, and rest) for maximizing the anabolic response remains unclear.

Multiple-set resistance exercise elicits greater intramuscular anabolic signaling than single-set exercise, indicating that exercise volume can influence the muscle protein signaling response to exercise [83, 167]. Low- versus high-intensity unilateral leg extensions performed to volitional fatigue have yielded inconclusive results [24, 60]. Burd et al. [60] reported that low-intensity resistance exercise (30 % 1 RM) was more effective than higher-intensity loads (90 % 1 RM) for inducing mTORC1 signaling 4 h post-exercise in recreationally active men. In contrast, Mitchell et al. [24] found high-intensity loads (80 % 1 RM) to be more effective than lower-intensity loads (30 % 1 RM) for inducing mTORC1 signaling 1 h post-exercise in untrained men. Regardless, following 10 weeks of training, no differences between the two different training protocols were observed in the magnitude of muscle hypertrophy [24]. The mTORC1 signaling response has also shown to be greater following a high volume (5 × 10 RM) than a lower volume but higher-intensity (15 × 1 RM) bilateral leg press exercise [168]. The lack of any clear relationship between training program design and the intramuscular anabolic signaling response suggests that additional factors such as muscle fiber recruitment [48], time-under-tension [49], and metabolic stress [50] may have contributing roles in stimulating the anabolic signaling molecules.

Exercise-induced metabolic stress may also play a role in acute activation of mTORC1 signaling. Metabolic stress results from exercise that primarily relies on anaerobic glycolysis as its major energy provider. Lactate directly affects muscle cells in vitro by increasing satellite cell activity as well as mTOR and p70S6k phosphorylation [169]. Elevations in blood lactate have also been demonstrated to be weakly associated ($r = 0.38$; $p < 0.05$) with intramuscular anabolic signaling following resistance exercise in trained men [50]. Lactate production may contribute to increased mTORC1 signaling [170]; however, the mechanisms by which metabolic stress influences anabolic signaling are not fully elucidated and warrant further investigation.

Acute activation of mTORC1 signaling may also be influenced by mode of contraction. Eccentric-only resistance exercise has been suggested to provide a stronger anabolic stimulus than concentric-only resistance exercise [171–174], and eccentric contractions have been demonstrated to produce a more rapid rise in myofibrillar muscle

protein synthesis than concentric only contractions [171, 172]. In addition, maximal eccentric contractions have also been demonstrated to significantly activate p70S6k and RPS6 up to 2 h into recovery, while maximal concentric and submaximal eccentric contractions failed to induce changes in Akt, mTOR, p70S6k, or RPS6 phosphorylation status [173]. Additional support was recently provided by Rahbek et al. [174], who demonstrated that maximal eccentric contractions triggered a greater acute anabolic signaling response than concentric contractions. However, despite the greater anabolic signaling response, no differences were noted in myofibrillar protein synthesis rates or in exercise-induced hypertrophy following 12 weeks of high-volume resistance training [174]. Increases in muscle size following 9 weeks of unilateral resistance training have also been shown to be unrelated to muscle contraction type when matched for both exercise intensity and total external work [175]. Thus, eccentric contractions, which emphasize greater tension and stretching of the muscle, may yield a greater acute anabolic response, yet whether it translates into greater muscle hypertrophy with training remains questionable.

It is important to note that the anabolic response following resistance exercise appears to be highly variable between individuals [43, 52, 53, 176]. A number of factors influence the muscle remodeling process following resistance exercise, including nutritional intake and genetic predisposition [88, 177]. Nevertheless, several studies have suggested that training status can also impact resistance exercise-induced intramuscular anabolic signaling. Coffey et al. [43] reported that prior training history blunts the anabolic signaling responses involved in the adaptation to resistance exercise. Chronic resistance training in rats also attenuates p70S6k phosphorylation following an acute exercise bout [178]. Similarly, in humans, the duration of protein synthesis following a bout of resistance exercise was reduced following 8 weeks of resistance training [42]. Additionally, our laboratory recently demonstrated that highly trained, stronger individuals have an attenuated acute anabolic response following a high-volume resistance exercise protocol [45]. Thus, a potential lower adaptive ability among highly trained individuals may, in part, account for the diminished hypertrophic adaptation among experienced, resistance-trained individuals [179, 180].

8 Conclusion

Despite the plethora of information regarding the impact of resistance exercise on muscle hypertrophy, the mechanisms involved in converting mechanical signals into the molecular events that control muscle growth are not completely understood. However, skeletal muscle adaptation appears to be the result of the cumulative effects of transient changes in gene expression following acute bouts of exercise [22]. Specifically, skeletal muscle protein synthesis appears to be regulated by the multi-protein phosphorylation cascade mTORC1; thus, maximizing resistance exercise-induced mTORC1 signaling should yield the greatest potential for hypertrophic adaptation with training [54, 84–86]. A majority of the research to date shows that mTORC1 signaling is not influenced by transient elevations in circulating hormones [54, 68–70]; hence, the design of a resistance training program based on a hormonal response may be futile. However, resistance exercise-induced mTORC1 activation appears to be a multifaceted process, which is influenced by a number of factors. The resistance exercise parameters for maximizing the anabolic response remain unclear, and it is unknown whether different resistance exercise paradigms used by strength and power athletes differentially stimulate intramuscular anabolic signaling. Resistance exercise protocols that maximize muscle fiber recruitment, time-under-tension, and metabolic stress appear to contribute to intramuscular anabolic signaling; however, there does not appear to be a minimal threshold or optimal training scheme per se for maximizing muscle hypertrophy.

Compliance with Ethical Standards

Funding No sources of funding were used to assist in the preparation of this article.

Conflict of interest Adam Gonzalez, Jay Hoffman, Jeffrey Stout, David Fukuda, and Darryn Willoughby declare that they have no conflicts of interest relevant to the content of this review.

References

1. Braith RW, Stewart KJ. Resistance exercise training its role in the prevention of cardiovascular disease. Circulation. 2006;113(22):2642–50.
2. Yanagita M, Shiotsu Y. Role of resistance training for preventing frailty and metabolic syndromes in aged adults. J Phys Fit Sports Med. 2014;3(1):35–42.
3. Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. J Am Geriatr Soc. 2002;50(5):889–96.
4. Peterson MD, Gordon PM. Resistance exercise for the aging adult: clinical implications and prescription guidelines. Am J Med. 2011;124(3):194–8.
5. Baskin KK, Winders BR, Olson EN. Muscle as a "mediator" of systemic metabolism. Cell Metab. 2015;21(2):237–48.
6. Goodman CA, Mayhew DL, Hornberger TA. Recent progress toward understanding the molecular mechanisms that regulate skeletal muscle mass. Cell Signal. 2011;23(12):1896–906.
7. Greenhaff PL, Karagounis L, Peirce N, et al. Disassociation between the effects of amino acids and insulin on signaling, ubiquitin ligases, and protein turnover in human muscle. Am J Physiol Endocrinol Metab. 2008;295(3):E595–604.

8. Lüthi J, Howald H, Claassen H, et al. Structural changes in skeletal muscle tissue with heavy-resistance exercise. Int J Sports Med. 1986;7(3):123–7.
9. Paul AC, Rosenthal N. Different modes of hypertrophy in skeletal muscle fibers. J Cell Biol. 2002;156(4):751–60.
10. Toigo M, Boutellier U. New fundamental resistance exercise determinants of molecular and cellular muscle adaptations. Eur J Appl Physiol. 2006;97(6):643–63.
11. Kelley G. Mechanical overload and skeletal muscle fiber hyperplasia: a meta-analysis. J Appl Physiol. 1996;81(4):1584–8.
12. Phillips SM, Tipton KD, Aarsland A, et al. Mixed muscle protein synthesis and breakdown after resistance exercise in humans. Am J Physiol Endocrinol Metab. 1997;36(1):E99.
13. Yarasheski KE, Zachwieja JJ, Bier DM. Acute effects of resistance exercise on muscle protein synthesis rate in young and elderly men and women. Am J Physiol. 1993;265:E210-E.
14. MacDougall JD, Gibala MJ, Tarnopolsky MA, et al. The time course for elevated muscle protein synthesis following heavy resistance exercise. Can J Appl Physiol. 1995;20(4):480–6.
15. Chesley A, MacDougall J, Tarnopolsky M, et al. Changes in human muscle protein synthesis after resistance exercise. J Appl Physiol. 1992;73:1383–8.
16. Aagaard P, Andersen JL, Dyhre-Poulsen P, et al. A mechanism for increased contractile strength of human pennate muscle in response to strength training: changes in muscle architecture. J Physiol. 2001;534(2):613–23.
17. Bell G, Syrotuik D, Martin T, et al. Effect of concurrent strength and endurance training on skeletal muscle properties and hormone concentrations in humans. Eur J Appl Physiol. 2000;81(5):418–27.
18. Seynnes OR, de Boer M, Narici MV. Early skeletal muscle hypertrophy and architectural changes in response to high-intensity resistance training. J Appl Physiol. 2007;102(1):368–73.
19. McCall G, Byrnes W, Dickinson A, et al. Muscle fiber hypertrophy, hyperplasia, and capillary density in college men after resistance training. J Appl Physiol. 1996;81(5):2004–12.
20. Adams GR, Bamman MM. Characterization and regulation of mechanical loading-induced compensatory muscle hypertrophy. Compr Physiol. 2012;2(4):2829–70.
21. Hornberger TA. Mechanotransduction and the regulation of mTORC1 signaling in skeletal muscle. Int J Biochem Cell Biol. 2011;43(9):1267–76.
22. Coffey VG, Hawley JA. The molecular bases of training adaptation. Sports Med. 2007;37(9):737–63.
23. Tanimoto M, Ishii N. Effects of low-intensity resistance exercise with slow movement and tonic force generation on muscular function in young men. J Appl Physiol. 2006;100(4):1150–7.
24. Mitchell CJ, Churchward-Venne TA, West DW, et al. Resistance exercise load does not determine training-mediated hypertrophic gains in young men. J Appl Physiol. 2012;113(1):71–7.
25. Ogasawara R, Loenneke JP, Thiebaud RS, et al. Low-load bench press training to fatigue results in muscle hypertrophy similar to high-load bench press training. Int J Clin Med. 2013;4(2):114.
26. Kraemer WJ, Nindl BC, Ratamess NA, et al. Changes in muscle hypertrophy in women with periodized resistance training. Med Sci Sports Exerc. 2004;36(4):697–708.
27. Popov D, Swirkun D, Netreba A, et al. Hormonal adaptation determines the increase in muscle mass and strength during low-intensity strength training without relaxation. Hum Physiol. 2006;32(5):609–14.
28. Hisaeda H, Miyagawa K, Kuno S, et al. Influence of two different modes of resistance training in female subjects. Ergonomics. 1996;39(6):842.
29. Chestnut JL, Docherty D. The effects of 4 and 10 repetition maximum weight-training protocols on neuromuscular adaptations in untrained men. J Strength Cond Res. 1999;13(4):353–9.
30. Léger B, Cartoni R, Praz M, et al. Akt signalling through GSK-3β, mTOR and Foxo1 is involved in human skeletal muscle hypertrophy and atrophy. J Physiol. 2006;576(3):923–33.
31. Lamon S, Wallace MA, Léger B, et al. Regulation of stars and its downstream targets suggest a novel pathway involved in human skeletal muscle hypertrophy and atrophy. J Physiol. 2009;587(8):1795–803.
32. Alegre LM, Aguado X, Rojas-Martín D, et al. Load-controlled moderate and high-intensity resistance training programs provoke similar strength gains in young women. Muscle Nerve. 2015;51(1):92–101.
33. 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.
34. 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.
35. Campos GE, 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.
36. Schuenke MD, Herman JR, Gliders RM, et al. Early-phase muscular adaptations in response to slow-speed versus traditional resistance-training regimens. Eur J Appl Physiol. 2012;112(10):3585–95.
37. 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.
38. Choi J, Takahashi H, Itai Y, et al. The difference between effects of "power-up type" and "bulk-up type" strength training exercises-with special reference to muscle cross-sectional area, muscular strength, anaerobic power and anaerobic endurance. Jpn J Phys Fit Sports Med. 1998;47(1):119–29.
39. Krieger JW. Single vs. multiple sets of resistance exercise for muscle hypertrophy: a meta-analysis. J Strength Cond Res. 2010;24(4):1150–9.
40. Kim PL, Staron RS, Phillips SM. Fasted-state skeletal muscle protein synthesis after resistance exercise is altered with training. J Physiol. 2005;568(1):283–90.
41. Phillips SM, Tipton K, Ferrando AA, et al. Resistance training reduces the acute exercise-induced increase in muscle protein turnover. Am J Physiol Endocrinol Metab. 1999;276(1):E118–24.
42. Tang JE, Perco JG, Moore DR, et al. Resistance training alters the response of fed state mixed muscle protein synthesis in young men. Am J Phys Reg Integr Compar Physiol. 2008;294(1):R172–8.
43. Coffey V, Zhong Z, Shield A, et al. Early signaling responses to divergent exercise stimuli in skeletal muscle from well-trained humans. FASEB J. 2006;20(1):190–2.
44. Nader GA, von Walden F, Liu C, et al. Resistance exercise training modulates acute gene expression during human skeletal muscle hypertrophy. J Appl Physiol. 2014;116(6):693–702.
45. Gonzalez AM, Hoffman JR, Townsend JR, et al. Association between myosin heavy chain protein isoforms and intramuscular anabolic signaling following resistance exercise in trained men. Physiol Rep. 2015;3(1):e12268.
46. Schoenfeld BJ, Ratamess NA, Peterson MD, et al. Effects of different volume-equated resistance training loading strategies

on muscular adaptations in well-trained men. J Strength Cond Res. 2014;28(10):2909–18.
47. Schoenfeld BJ, Peterson MD, Ogborn D, et al. Effects of low- versus high-load resistance training on muscle strength and hypertrophy in well-trained men. J Strength Cond Res. 2015;29(10):2954–63.
48. Gehlert S, Suhr F, Gutsche K, et al. High force development augments skeletal muscle signalling in resistance exercise modes equalized for time under tension. Pflügers Arch. 2014;467(6):1343–56.
49. Burd NA, Andrews RJ, West DW, et al. Muscle time under tension during resistance exercise stimulates differential muscle protein sub-fractional synthetic responses in men. J Physiol. 2012;590(2):351–62.
50. Popov DV, Lysenko EA, Bachinin AV, et al. Influence of resistance exercise intensity and metabolic stress on anabolic signaling and expression of myogenic genes in skeletal muscle. Muscle Nerve. 2015;51(3):434–42.
51. Timmons JA. Variability in training-induced skeletal muscle adaptation. J Appl Physiol. 2011;110(3):846–53.
52. Bamman MM, Petrella JK, Kim J, et al. Cluster analysis tests the importance of myogenic gene expression during myofiber hypertrophy in humans. J Appl Physiol. 2007;102(6):2232–9.
53. Hubal MJ, Gordish-Dressman H, Thompson PD, et al. Variability in muscle size and strength gain after unilateral resistance training. Med Sci Sports Exerc. 2005;37(6):964–72.
54. Mitchell CJ, Churchward-Venne TA, Bellamy L, et al. Muscular and systemic correlates of resistance training-induced muscle hypertrophy. PLoS One. 2013;8(10):e78636.
55. Koopman R, Zorenc AH, Gransier RJ, et al. Increase in S6K1 phosphorylation in human skeletal muscle following resistance exercise occurs mainly in type II muscle fibers. Am J Physiol Endocrinol Metab. 2006;290(6):E1245–52.
56. Schoenfeld BJ, Ratamess NA, Peterson MD, et al. Influence of resistance training frequency on muscular adaptations in well-trained men. J Strength Cond Res. 2015;29(7):1821–9.
57. McDonagh M, Davies C. Adaptive response of mammalian skeletal muscle to exercise with high loads. Eur J Appl Physiol Occup Physiol. 1984;52(2):139–55.
58. Wernbom M, Augustsson J, Thomeé R. The influence of frequency, intensity, volume and mode of strength training on whole muscle cross-sectional area in humans. Sports Med. 2007;37(3):225–64.
59. Fry AC. The role of resistance exercise intensity on muscle fibre adaptations. Sports Med. 2004;34(10):663–79.
60. Burd NA, West DW, Staples AW, et al. Low-load high volume resistance exercise stimulates muscle protein synthesis more than high-load low volume resistance exercise in young men. PLoS One. 2010;5(8):e12033.
61. Crewther B, Cronin J, Keogh J, et al. The salivary testosterone and cortisol response to three loading schemes. J Strength Cond Res. 2008;22(1):250–5.
62. 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.
63. Linnamo V, Pakarinen A, Komi PV, et al. Acute hormonal responses to submaximal and maximal heavy resistance and explosive exercises in men and women. J Strength Cond Res. 2005;19(3):566–71.
64. 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.
65. Smilios I, Pilianidis T, Karamouzis M, et al. Hormonal responses after various resistance exercise protocols. Med Sci Sports Exerc. 2003;35(4):644–54.
66. Uchida MC, Crewther BT, Ugrinowitsch C, et al. Hormonal responses to different resistance exercise schemes of similar total volume. J Strength Cond Res. 2009;23(7):2003–8.
67. 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.
68. 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.
69. West DW, Burd NA, Staples AW, et al. Human exercise-mediated skeletal muscle hypertrophy is an intrinsic process. Int J Biochem Cell Biol. 2010;42(9):1371–5.
70. 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(21):5239–47.
71. Goldberg AL, Etlinger JD, Goldspink DF, et al. Mechanism of work-induced hypertrophy of skeletal muscle. Med Sci Sports. 1974;7(3):185–98.
72. Brian M, Bilgen E, Diane CF. Regulation and function of ribosomal protein S6 kinase (S6K) within mTOR signalling networks. Biochem J. 2012;441(1):1–21.
73. Drummond MJ, Fry CS, Glynn EL, et al. Rapamycin administration in humans blocks the contraction-induced increase in skeletal muscle protein synthesis. J Physiol. 2009;587(7):1535–46.
74. Hornberger TA, Sukhija KB, Chien S. Regulation of mTOR by mechanically induced signaling events in skeletal muscle. Cell Cycle. 2006;5(13):1391–6.
75. Goodman CA. The role of mTORC1 in regulating protein synthesis and skeletal muscle mass in response to various mechanical stimuli. Rev Physiol Biochem Pharmacol. 2014;166:43–95.
76. Bodine SC, Stitt TN, Gonzalez M, et al. Akt/mTOR pathway is a crucial regulator of skeletal muscle hypertrophy and can prevent muscle atrophy in vivo. Nat Cell Biol. 2001;3(11):1014–9.
77. Laplante M, Sabatini DM. mTOR signaling in growth control and disease. Cell. 2012;149(2):274–93.
78. Anthony JC, Yoshizawa F, Anthony TG, et al. Leucine stimulates translation initiation in skeletal muscle of postabsorptive rats via a rapamycin-sensitive pathway. J Nutr. 2000;130(10):2413–9.
79. Kubica N, Bolster DR, Farrell PA, et al. Resistance exercise increases muscle protein synthesis and translation of eukaryotic initiation factor 2bϵ mRNA in a mammalian target of rapamycin-dependent manner. J Biol Chem. 2005;280(9):7570–80.
80. Gundermann DM, Walker DK, Reidy PT, et al. Activation of mTORC1 signaling and protein synthesis in human muscle following blood flow restriction exercise is inhibited by rapamycin. Am J Physiol Endocrinol Metab. 2014;306(10):E1198–204.
81. 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.
82. Kumar V, Selby A, Rankin D, et al. Age-related differences in the dose–response relationship of muscle protein synthesis to resistance exercise in young and old men. J Physiol. 2009;587(1):211–7.
83. Burd NA, Holwerda AM, Selby KC, et al. Resistance exercise volume affects myofibrillar protein synthesis and anabolic signalling molecule phosphorylation in young men. J Physiol. 2010;588(16):3119–30.
84. Baar K, Esser K. Phosphorylation of p70s6k correlates with increased skeletal muscle mass following resistance exercise. Am J Physiol Cell Physiol. 1999;276(1):C120–7.

85. Terzis G, Georgiadis G, Stratakos G, et al. Resistance exercise-induced increase in muscle mass correlates with p70s6 kinase phosphorylation in human subjects. Eur J Appl Physiol. 2008;102(2):145–52.
86. Mayhew DL, J-s Kim, Cross JM, et al. Translational signaling responses preceding resistance training-mediated myofiber hypertrophy in young and old humans. J Appl Physiol. 2009;107(5):1655–62.
87. Goodman CA, Frey JW, Mabrey DM, et al. The role of skeletal muscle mTOR in the regulation of mechanical load-induced growth. J Physiol. 2011;589(22):5485–501.
88. Marcotte GR, West DW, Baar K. The molecular basis for load-induced skeletal muscle hypertrophy. Calc Tiss Int. 2014;96(3):196–210.
89. Sato T, Nakashima A, Guo L, et al. Specific activation of mTORC1 by Rheb G-protein in vitro involves enhanced recruitment of its substrate protein. J Biol Chem. 2009;284(19):12783–91.
90. Tee AR, Manning BD, Roux PP, et al. Tuberous sclerosis complex gene products, tuberin and hamartin, control mTOR signaling by acting as a GTPase-activating protein complex toward Rheb. Curr Biol. 2003;13(15):1259–68.
91. Menon S, Dibble CC, Talbott G, et al. Spatial control of the TSC complex integrates insulin and nutrient regulation of mTORC1 at the lysosome. Cell. 2014;156(4):771–85.
92. Sandri M. Signaling in muscle atrophy and hypertrophy. Physiology. 2008;23(3):160–70.
93. Jacobs BL, You J-S, Frey JW, et al. Eccentric contractions increase the phosphorylation of tuberous sclerosis complex-2 (TSC2) and alter the targeting of TSC2 and the mechanistic target of rapamycin to the lysosome. J Physiol. 2013;591(18):4611–20.
94. Hornberger T, Stuppard R, Conley K, et al. Mechanical stimuli regulate rapamycin-sensitive signalling by a phosphoinositide 3-kinase-, protein kinase B- and growth factor-independent mechanism. Biochem J. 2004;380:795–804.
95. Deldicque L, Atherton P, Patel R, et al. Effects of resistance exercise with and without creatine supplementation on gene expression and cell signaling in human skeletal muscle. J Appl Physiol. 2008;104(2):371–8.
96. Deldicque L, Atherton P, Patel R, et al. Decrease in Akt/PKB signalling in human skeletal muscle by resistance exercise. Eur J Appl Physiol. 2008;104(1):57–65.
97. Hornberger T, Chu W, Mak Y, et al. The role of phospholipase D and phosphatidic acid in the mechanical activation of mTOR signaling in skeletal muscle. Proc Natl Acad Sci. 2006;103(12):4741–6.
98. You J-S, Lincoln HC, Kim C-R, et al. The role of diacylglycerol kinase ζ and phosphatidic acid in the mechanical activation of mammalian target of rapamycin (mTOR) signaling and skeletal muscle hypertrophy. J Biol Chem. 2014;289(3):1551–63.
99. Tang W, Yuan J, Chen X, et al. Identification of a novel human lysophosphatidic acid acyltransferase, LPAAT-theta, which activates mTOR pathway. J Biochem Mol Biol. 2006;39(5):626.
100. Ávila-Flores A, Santos T, Rincón E, et al. Modulation of the mammalian target of rapamycin pathway by diacylglycerol kinase-produced phosphatidic acid. J Biol Chem. 2005;280(11):10091–9.
101. Fang Y, Vilella-Bach M, Bachmann R, et al. Phosphatidic acid-mediated mitogenic activation of mTOR signaling. Science. 2001;294(5548):1942–5.
102. Chen J, Fang Y. A novel pathway regulating the mammalian target of rapamycin (mTOR) signaling. Biochem Pharmacol. 2002;64(7):1071–7.
103. Sun Y, Fang Y, Yoon M-S, et al. Phospholipase D1 is an effector of Rheb in the mTOR pathway. Proc Natl Acad Sci. 2008;105(24):8286–91.
104. Wang X, Devaiah SP, Zhang W, et al. Signaling functions of phosphatidic acid. Progr Lipid Res. 2006;45(3):250–78.
105. Foster DA, Salloum D, Menon D, et al. Phospholipase D and the maintenance of phosphatidic acid levels for regulation of mammalian target of rapamycin (mTOR). J Biol Chem. 2014;289(33):22583–8.
106. Joy JM, Gundermann DM, Lowery RP, et al. Phosphatidic acid enhances mTOR signaling and resistance exercise induced hypertrophy. Nutr Metab. 2014;11(1):29.
107. Shepherd P, Withers D, Siddle K. Phosphoinositide 3-kinase: the key switch mechanism in insulin signalling. Biochem J. 1998;333:471–90.
108. Alessi DR, Cohen P. Mechanism of activation and function of protein kinase B. Curr Opin Gen Dev. 1998;8(1):55–62.
109. Alessi DR, James SR, Downes CP, et al. Characterization of a 3-phosphoinositide-dependent protein kinase which phosphorylates and activates protein kinase B. Curr Biol. 1997;7(4):261–9.
110. Inoki K, Li Y, Zhu T, et al. TSC2 is phosphorylated and inhibited by Akt and suppresses mTOR signalling. Nat Cell Biol. 2002;4(9):648–57.
111. Vander Haar E, Lee S-I, Bandhakavi S, et al. Insulin signalling to mTOR mediated by the Akt/PKB substrate pras40. Nat Cell Biol. 2007;9(3):316–23.
112. Veldhuis JD, Roemmich JN, Richmond EJ, et al. Endocrine control of body composition in infancy, childhood, and puberty. Endocr Rev. 2005;26(1):114–46.
113. Solomon A, Bouloux P. Modifying muscle mass–the endocrine perspective. J Endocrinol. 2006;191(2):349–60.
114. Schroeder ET, Villanueva M, West D, et al. Are acute post-resistance exercise increases in testosterone, growth hormone, and IGF-1 necessary to stimulate skeletal muscle anabolism and hypertrophy? Med Sci Sports Exerc. 2013;45(11):2044–51.
115. McCall GE, Byrnes WC, Fleck SJ, et al. Acute and chronic hormonal responses to resistance training designed to promote muscle hypertrophy. Can J Appl Physiol. 1999;24(1):96–107.
116. 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.
117. Kraemer WJ, Ratamess NA. Hormonal responses and adaptations to resistance exercise and training. Sports Med. 2005;35(4):339–61.
118. Wilkinson SB, Tarnopolsky MA, Grant EJ, et al. Hypertrophy with unilateral resistance exercise occurs without increases in endogenous anabolic hormone concentration. Eur J Appl Physiol. 2006;98(6):546–55.
119. Spiering BA, Kraemer WJ, Anderson JM, et al. Effects of elevated circulating hormones on resistance exercise-induced Akt signaling. Med Sci Sports Exerc. 2008;40(6):1039–48.
120. Griggs RC, Kingston W, Jozefowicz RF, et al. Effect of testosterone on muscle mass and muscle protein synthesis. J Appl Physiol. 1989;66(1):498–503.
121. Ferrando AA, Tipton KD, Doyle D, et al. Testosterone injection stimulates net protein synthesis but not tissue amino acid transport. Am J Physiol Endocrinol Metab. 1998;275(5):E864–71.
122. Bhasin S, Storer TW, Berman N, et al. The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. N Engl J Med. 1996;335(1):1–7.
123. Bhasin S, Woodhouse L, Casaburi R, et al. Testosterone dose-response relationships in healthy young men. Am J Physiol Endocrinol Metab. 2001;281(6):E1172–81.
124. Tenover JS. Effects of testosterone supplementation in the aging male. J Clin Endocrinol Metab. 1992;75(4):1092–8.
125. Tenover JL. Experience with testosterone replacement in the elderly. Mayo Clin Proc. 2000;75(Suppl): S77–81 **(discussion S82)**.

126. Morley JE, Perry H, Kaiser F, et al. Effects of testosterone replacement therapy in old hypogonadal males: a preliminary study. J Am Geriatr Soc. 1993;41(2):149–52.
127. Sih R, Morley JE, Kaiser FE, et al. Testosterone replacement in older hypogonadal men: a 12-month randomized controlled trial. J Clin Endocrinol Metab. 1997;82(6):1661–7.
128. Snyder PJ, Peachey H, Hannoush P, et al. Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. J Clin Endocrinol Metab. 1999;84(8):2647–53.
129. Ferrando AA, Sheffield-Moore M, Yeckel CW, et al. Testosterone administration to older men improves muscle function: Molecular and physiological mechanisms. Am J Physiol Endocrinol Metab. 2002;282(3):E601–7.
130. McGlory C, Phillips SM. Exercise and the regulation of skeletal muscle hypertrophy. Progr Mol Biol Trans Sci. 2015;135:153–73.
131. Goodman CA, Miu MH, Frey JW, et al. A phosphatidylinositol 3-kinase/protein kinase B-independent activation of mammalian target of rapamycin signaling is sufficient to induce skeletal muscle hypertrophy. Mol Biol Cell. 2010;21(18):3258–68.
132. Ahtiainen JP, Pakarinen A, Alen M, et al. Short vs. long rest period between the sets in hypertrophic resistance training: Influence on muscle strength, size, and hormonal adaptations in trained men. J Strength Cond Res. 2005;19(3):572–82.
133. Boroujerdi SS, Rahimi R. Acute GH and IGF-I responses to short vs. long rest period between sets during forced repetitions resistance training system. S Afr J Res Sport Phys Educ Recreat. 2008;30(2):31–8.
134. Beaven CM, Gill ND, Cook CJ. Salivary testosterone and cortisol responses in professional rugby players after four resistance exercise protocols. J Strength Cond Res. 2008;22(2):426–32.
135. Goto K, Sato K, Takamatsu K. A single set of low intensity resistance exercise immediately following high intensity resistance exercise stimulates growth hormone secretion in men. J Phys Fit Sports Med. 2003;43(2):243–9.
136. 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.
137. Kraemer WJ, Häkkinen K, Newton RU, et al. Effects of heavy-resistance training on hormonal response patterns in younger vs. older men. J Appl Physiol. 1999;87(3):982–92.
138. Villanueva MG, Villanueva MG, Lane CJ, et al. Influence of rest interval length on acute testosterone and cortisol responses to volume-load–equated total body hypertrophic and strength protocols. J Strength Cond Res. 2012;26(10):2755–64.
139. Raastad T, Bjøro T, Hallen J. Hormonal responses to high-and moderate-intensity strength exercise. Eur J Appl Physiol. 2000;82(1–2):121–8.
140. West DW, Phillips SM. Associations of exercise-induced hormone profiles and gains in strength and hypertrophy in a large cohort after weight training. Eur J Appl Physiol. 2012;112(7):2693–702.
141. Mitchell CJ, Churchward-Venne TA, Parise G, et al. Acute post-exercise myofibrillar protein synthesis is not correlated with resistance training-induced muscle hypertrophy in young men. PLoS One. 2014;9(2):e89431.
142. Sheffield-Moore M. Androgens and the control of skeletal muscle protein synthesis. Ann Med. 2000;32(3):181–6.
143. Willoughby DS, Taylor L. Effects of sequential bouts of resistance exercise on androgen receptor expression. Med Sci Sports Exerc. 2004;36(9):1499–506.
144. Bricout V, Germain P, Serrurier B, et al. Changes in testosterone muscle receptors: effects of an androgen treatment on physically trained rats. Cell Mol Biol. 1994;40(3):291–4.
145. Lu Y, Tong Q, He L. The effect of exercise on the androgen receptor binding capacity and the level of testosterone in the skeletal muscle. Chin J Appl Physiol. 1997;13(3):198–201.
146. Bamman MM, Shipp JR, Jiang J, et al. Mechanical load increases muscle IGF-I and androgen receptor mRNA concentrations in humans. Am J Physiol Endocrinol Metab. 2001;280(3):E383–90.
147. Deschenes MR, Maresh CM, Armstrong LE, et al. Endurance and resistance exercise induce muscle fiber type specific responses in androgen binding capacity. J Steroid Biochem Mol Biol. 1994;50(3):175–9.
148. Kadi F, Bonnerud P, Eriksson A, et al. The expression of androgen receptors in human neck and limb muscles: effects of training and self-administration of androgenic-anabolic steroids. Histochem Cell Biol. 2000;113(1):25–9.
149. Ratamess NA, Kraemer WJ, Volek JS, et al. Androgen receptor content following heavy resistance exercise in men. J Steroid Biochem Mol Biol. 2005;93(1):35–42.
150. Vingren JL, Kraemer WJ, Hatfield DL, et al. Effect of resistance exercise on muscle steroid receptor protein content in strength-trained men and women. Steroids. 2009;74(13):1033–9.
151. Vingren JL, Kraemer WJ, Ratamess NA, et al. Testosterone physiology in resistance exercise and training. Sports Med. 2010;40(12):1037–53.
152. Inoue K, Yamasaki S, Fushiki T, et al. Androgen receptor antagonist suppresses exercise-induced hypertrophy of skeletal muscle. Eur J Appl Physiol Occup Physiol. 1994;69(1):88–91.
153. Kvorning T, Andersen M, Brixen K, et al. Suppression of testosterone does not blunt mRNA expression of myoD, myogenin, IGF, myostatin or androgen receptor post strength training in humans. J Physiol. 2007;578(2):579–93.
154. 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.
155. Rønnestad 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.
156. West DW, Cotie LM, Mitchell CJ, et al. Resistance exercise order does not determine postexercise delivery of testosterone, growth hormone, and IGF-1 to skeletal muscle. Appl Physiol Nutr Metab. 2012;38(2):220–6.
157. Apró W, Blomstrand E. Influence of supplementation with branched-chain amino acids in combination with resistance exercise on p70s6 kinase phosphorylation in resting and exercising human skeletal muscle. Acta Physiol. 2010;200(3):237–48.
158. Deldicque L, De Bock K, Maris M, et al. Increased p70s6k phosphorylation during intake of a protein–carbohydrate drink following resistance exercise in the fasted state. Eur J Appl Physiol. 2010;108(4):791–800.
159. Farnfield MM, Carey KA, Gran P, et al. Whey protein ingestion activates mTOR-dependent signalling after resistance exercise in young men: a double-blinded randomized controlled trial. Nutrients. 2009;1(2):263–75.
160. Hulmi JJ, Tannerstedt J, Selänne H, et al. Resistance exercise with whey protein ingestion affects mTOR signaling pathway and myostatin in men. J Appl Physiol. 2009;106(5):1720–9.
161. Karlsson HK, Nilsson P-A, Nilsson J, et al. Branched-chain amino acids increase p70s6k phosphorylation in human skeletal muscle after resistance exercise. Am J Physiol Endocrinol Metab. 2004;287(1):E1–7.
162. Dreyer HC, Fujita S, Cadenas JG, et al. Resistance exercise increases AMPK activity and reduces 4E-BP1 phosphorylation and protein synthesis in human skeletal muscle. J Physiol. 2006;576(2):613–24.
163. Dreyer HC, Fujita S, Glynn EL, et al. Resistance exercise increases leg muscle protein synthesis and mTOR signalling independent of sex. Acta Physiol. 2010;199(1):71–81.

164. Roschel H, Ugrinowistch C, Barroso R, et al. Effect of eccentric exercise velocity on Akt/mTOR/p70s6k signaling in human skeletal muscle. Appl Physiol Nutr Metab. 2011;36(2):283–90.
165. Areta JL, Burke LM, Ross ML, et al. Timing and distribution of protein ingestion during prolonged recovery from resistance exercise alters myofibrillar protein synthesis. J Physiol. 2013;591(9):2319–31.
166. Glover EI, Oates BR, Tang JE, et al. Resistance exercise decreases eIF2B phosphorylation and potentiates the feeding-induced stimulation of p70s6k1 and rpS6 in young men. Am J Phys Reg Integr Compar Physiol. 2008;295(2):R604–10.
167. Terzis G, Spengos K, Mascher H, et al. The degree of p70s6k and s6 phosphorylation in human skeletal muscle in response to resistance exercise depends on the training volume. Eur J Appl Physiol. 2010;110(4):835–43.
168. Hulmi J, Walker S, Ahtiainen J, et al. Molecular signaling in muscle is affected by the specificity of resistance exercise protocol. Scand J Med Sci Sports. 2012;22(2):240–8.
169. Oishi Y, Tsukamoto H, Yokokawa T, et al. Mixed lactate and caffeine compound increases satellite cell activity and anabolic signals for muscle hypertrophy. J Appl Physiol. 2015;118(6):742–9.
170. Gundermann DM, Dickinson JM, Fry CS, et al. Inhibition of glycolysis and mTORC1 activation in human skeletal muscle with blood flow restriction exercise. FASEB J. 1076;2012(26):3.
171. Moore DR, Phillips SM, Babraj JA, et al. Myofibrillar and collagen protein synthesis in human skeletal muscle in young men after maximal shortening and lengthening contractions. Am J Physiol Endocrinol Metab. 2005;288(6):E1153–9.
172. Cuthbertson DJ, Babraj J, Smith K, et al. Anabolic signaling and protein synthesis in human skeletal muscle after dynamic shortening or lengthening exercise. Am J Physiol Endocrinol Metab. 2006;290(4):E731–8.
173. Eliasson J, Elfegoun T, Nilsson J, et al. Maximal lengthening contractions increase p70 s6 kinase phosphorylation in human skeletal muscle in the absence of nutritional supply. Am J Physiol Endocrinol Metab. 2006;291(6):E1197–205.
174. Rahbek SK, Farup J, Møller AB, et al. Effects of divergent resistance exercise contraction mode and dietary supplementation type on anabolic signalling, muscle protein synthesis and muscle hypertrophy. Amino Acids. 2014;46(10):2377–92.
175. Moore DR, Young M, Phillips SM. Similar increases in muscle size and strength in young men after training with maximal shortening or lengthening contractions when matched for total work. Eur J Appl Physiol. 2012;112(4):1587–92.
176. Davidsen PK, Gallagher IJ, Hartman JW, et al. High responders to resistance exercise training demonstrate differential regulation of skeletal muscle mRNA expression. J Appl Physiol. 2011;110(2):309–17.
177. Phillips SM. A brief review of critical processes in exercise-induced muscular hypertrophy. Sports Med. 2014;44(1):71–7.
178. Ogasawara R, Kobayashi K, Tsutaki A, et al. mTOR signaling response to resistance exercise is altered by chronic resistance training and detraining in skeletal muscle. J Appl Physiol. 2013;114(7):934–40.
179. Hoffman J, Maresh C, Armstrong L, et al. Effects of off-season and in-season resistance training programs on a collegiate male basketball team. J Hum Muscle Perform. 1991;1(2):48–55.
180. Häkkinen K, Komi PV, Alén M, et al. EMG, muscle fibre and force production characteristics during a 1 year training period in elite weight-lifters. Eur J Appl Physiol Occup Physiol. 1987;56(4):419–27.