INVITED REVIEW

A focused review of myokines as a potential contributor to muscle hypertrophy from resistance-based exercise

Stephen M. Cornish[1] · Eric M. Bugera[1] · Todd A. Duhamel[1,2] · Jason D. Peeler[3] · Judy E. Anderson[4]

Abstract

Purpose Resistance exercise induces muscle growth and is an important treatment for age-related losses in muscle mass and strength. Myokines are hypothesized as a signal conveying physiological information to skeletal muscle, possibly to "fine-tune" other regulatory pathways. While myokines are released from skeletal muscle following contraction, their role in increasing muscle mass and strength in response to resistance exercise or training is not established. Recent research identified both local and systemic release of myokines after an acute bout of resistance exercise. However, it is not known whether myokines with putative anabolic function are mechanistically involved in producing muscle hypertrophy after resistance exercise. Further, nitric oxide (NO), an important mediator of muscle stem cell activation, upregulates the expression of certain myokine genes in skeletal muscle.

Method In the systemic context of complex hypertrophic signaling, this review: (1) summarizes literature on several well-recognized, representative myokines with anabolic potential; (2) explores the potential mechanistic role of myokines in skeletal muscle hypertrophy; and (3) identifies future research required to advance our understanding of myokine anabolism specifically in skeletal muscle.

Result This review establishes a link between myokines and NO production, and emphasizes the importance of considering systemic release of potential anabolic myokines during resistance exercise as complementary to other signals that promote hypertrophy.

Conclusion Investigating adaptations to resistance exercise in aging opens a novel avenue of interdisciplinary research into myokines and NO metabolites during resistance exercise, with the longer-term goal to improve muscle health in daily living, aging, and rehabilitation.

Keywords Muscle · Myokine · Cytokine · Nitric oxide · Anabolism · Skeletal muscle hypertrophy

Communicated by Michael Lindinger.

✉ Stephen M. Cornish
Stephen.Cornish@umanitoba.ca

1 Faculty of Kinesiology and Recreation Management, University of Manitoba, 117 Frank Kennedy Centre, Winnipeg, MB R3T 2N2, Canada

2 Institute of Cardiovascular Sciences, St. Boniface General Hospital Albrechtsen Research Centre, Winnipeg, MB, Canada

3 Department of Human Anatomy and Cell Science, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada

4 Department of Biological Sciences, Faculty of Science, University of Manitoba, Winnipeg, MB, Canada

Abbreviations

4E-BP1	4E binding protein-1
BFR	Blood flow restricted
CNS	Central nervous system
FABP-3	Fatty acid binding protein-3
FGF-2	Fibroblast growth factor-2
HGF	Hepatocyte growth factor
IGF-1	Insulin-like growth factor-1
IL-4	Interleukin-4
IL-6	Interleukin-6
IL-7	Interleukin-7
IL-15	Interleukin-15
LH	Luteinizing hormone
LHRH	Luteinizing hormone-releasing hormone
LIF	Leukemia inhibitory factor
MGF	Mechano-growth factor
mRNA	Messenger ribonucleic acid

|	
mTOR	Mechanistic target of rapamycin
NO	Nitric oxide
p70S6K	p70 ribosomal S6 kinase
PNS	Peripheral nervous system
SPARC	Secreted protein acidic and rich in cysteine
STAT3	Signal transducer and activator of transcription-3

Introduction

Resistance exercise protocols designed to elicit skeletal muscle hypertrophy commonly focus on generating mechanical tension, metabolic stress, and muscle damage (Schoenfeld 2010). Although these three stimuli appear to initiate signaling through a complex labyrinth of hypertrophy pathways in muscle, upon entering recovery, many underlying mechanisms that ultimately produce hypertrophic adaptations are identified (Bamman et al. 2018). As such, much more research is required before a comprehensive understanding of the mechanisms of muscle hypertrophy can be fully appreciated, particularly since prevention or treatment of skeletal muscle atrophy in aging and disuse is a major challenge to individuals and society. While stimulation of myogenic pathways, endocrine and other systemic and local influences, and myogenic stem cells (called satellite cells) all provide unique and overlapping contributions to muscle hypertrophy (Schoenfeld 2010), recent research has also identified a potential role for muscle-derived myokines in this process (Pedersen 2011; So et al. 2014; Bamman et al. 2018; Lee and Jun 2019). Myokines are proteins produced by skeletal muscle during contraction that may act locally or at some distance, on muscle and also non-muscle cells and tissues (Pedersen 2011; Pedersen and Febbraio 2012; Iizuka et al. 2014; Lee and Jun 2019).

There are six mechanistic paradigms that predominate our current understanding of signaling pathways mediating hypertrophic stimuli. These paradigms include: (1) satellite cells; (2) mRNA transcriptional and protein translational control; (3) mechanotransduction; (4) autocrine, paracrine, and endocrine factors; (5) sensorimotor control; and (6) non-myogenic cells in muscle (see Fig. 1). Satellite cells are thought to be involved in muscle hypertrophy when they move from a quiescent state to an activated and then a proliferative state from which they can differentiate and fully commit to forming new, multinucleated myotubes (Fukada 2018) and/or contribute to fiber hypertrophy by adding new myonuclei through fusion with existing fibers (Englund et al. 2019). This process is thought to be mediated by muscle damage produced by resistance exercise (especially eccentric type muscle actions) (Guilhem et al. 2010; Damas et al. 2018), although muscle loading is known to play a role in fiber hypertrophy, particularly following atrophy of muscle, and it is well established that muscle hypertrophy can occur independent of satellite cell activity (Bruusgaard et al. 2010; Leiter et al. 2011, 2012; Eftestøl et al. 2016; Psilander et al. 2019).

Transcriptional and translational control of muscle hypertrophy follows a sequential process whereby mRNA transcripts are generated and then translated inside cells to produce new muscle proteins. The main kinase that is involved in the generation of new muscle protein is the mechanistic target of rapamycin (mTOR) (Yoon 2017). Recent reviews of this topic have identified that there may be rapamycin-sensitive and rapamycin-insensitive pathways and that both lead to increased muscle protein synthesis (Ogasawara et al. 2019; Goodman 2019). Mechanotransduction turns loading signals from the execution of resistance exercises into biochemical/biological processes whereby the addition of newly synthesized muscle protein both within muscle fibers and in the muscle tissue will result in skeletal muscle hypertrophy

Fig. 1 Six paradigms and their relationship/interrelationship with producing skeletal muscle hypertrophy
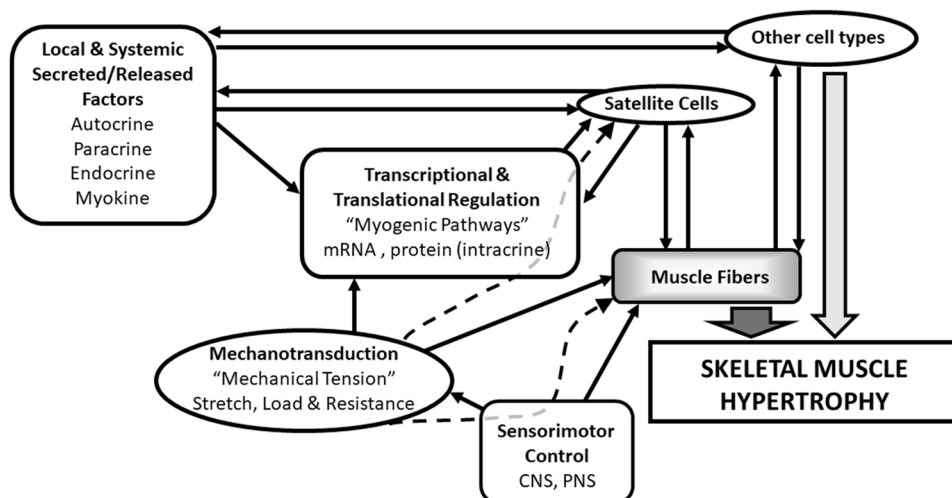
(Toigo and Boutellier 2006). As well, the type of stretch stimulus (static or dynamic) can influence the responses to resistance training by muscle growth and strength (Ferreira-Júnior et al. 2019).

Protein levels and other nutritional factors including vitamin D3 and various supplements (such as collagen, creatine, and omega-3s), influence the impact of exercise or training on muscle growth (McGlory and Phillips 2015; Antoniak and Greig 2017; Shamim et al. 2018; Morton et al. 2018; Candow et al. 2019a, b; McGlory et al. 2019; Oertzen-Hagemann et al. 2019). Additional non-myogenic cells within skeletal muscle such as bone, vessels, and the connective tissue matrix, also operate metabolically and/or non-mechanically in sustaining and promoting muscle tissue health and responsiveness to hypertrophic stimulation (Hausman 2012; Isaacson and Brotto 2014; Girgis 2015; Tarantino et al. 2015; Brotto and Bonewald 2015; Smythe 2016; Levinger et al. 2017; Grygiel-Górniak and Puszczewicz 2017; Huey 2018; Leal et al. 2018; Roberts et al. 2018; Stanford and Goodyear 2018; Olsen et al. 2019). Analytical systems biology (Smith et al. 2013) and experimental approaches using the modern technical "acuity" of proteomics, transcriptomics and next-generation sequencing are advancing the power to investigate the broader (increasingly complex) interplay of signaling at various levels of molecular mechanisms in tissues and even the gut microbiome (Donovan 2017) that impact muscle growth and muscle and overall health.

Sensorimotor control of skeletal muscle, through the central nervous system (CNS) regulation of spinal neurons and peripheral nervous system (PNS) input to and stimuli from muscle and tendons, is the basis of voluntary contraction. However, in-depth consideration of nerve–muscle excitation–contraction coupling, motor unit physiology and pathology, and the interplay between the corticospinal (pyramidal) and extrapyramidal pathways at the level of the spinal cord motor-pattern generators (MacIntosh et al. 2006) are beyond the scope of this review, even though they will certainly influence the muscle response to resistance training (Sterczala et al. 2018). Nonetheless, it is useful to remember the important role(s) of neurotrophic factors produced by muscle and myotrophic factors produced by peripheral nerve that influence nerve and muscle, respectively, via signaling at the neuromuscular junction region; these both change with aging and are influenced by exercise training (Nishimune et al. 2014). Such trophic factors maintain the health of neuromuscular junction synapses (Tsujihata et al. 1987; Nishimune et al. 2014) and higher-order nerve–nerve synapses in the motor-control system (Verhovshek and Sengelaub 2010). As well, passive exercise can promote muscle growth in the absence of input from the CNS (Phadke et al. 2019) or the PNS (Salvini et al. 2012) and both the CNS and muscle show adaptive responses to eccentric stretching during exercise (Hedayatpour and Falla 2015). Interestingly, the

distinction of nerve-derived versus muscle-derived pathologies, for instance detected using ultrasound, relates to the impact on muscle strength, structure, and texture, of losing trophic influences from each source (Sogawa et al. 2017).

Finally, and most relevant to the primary focus of this review, a large variety of autocrine, paracrine, and endocrine factors are demonstrated or hypothesized to promote or mediate muscle hypertrophy, as shown by their increased levels following a session of resistance exercise (Adams and Bamman 2012; Bamman et al. 2018; Lee and Jun 2019; Han et al. 2019). Such factors reportedly include byproducts of metabolism (termed myobolites) that may act as paracrine or systemic signaling molecules (Ibrahim et al. 2017). Notably, age influences the extent of the responsiveness to exercise and mechanical stretching as stimuli to hypertrophy (Li et al. 2006; Leiter et al. 2011; McGlory and Phillips 2015), at least in part because muscle satellite cells that are resident on stretched fibers become increasingly refractory to mechanical tension with increasing age: more stretching (as a proportion of muscle length) is required to activate satellite cells on healthy muscle of older animals (Leiter and Anderson 2010; Fujimaki et al. 2015) and humans (Kandalla et al. 2011; Snijders et al. 2014; Boers et al. 2018; Riddle et al. 2018). Some of these factors have long been known as intricately involved in producing muscle hypertrophy (such as the hormones testosterone and growth hormone), although the dogma that these two hormones are sufficient to restore the capacity for exercise-induced muscle hypertrophy in muscle of older individuals has been challenged in the research literature (Schroeder et al. 2013; Morton et al. 2016).

The possibility exists that more tentatively researched factors which seemingly promote muscle hypertrophy, such as myokines, may also play a role in the process of building muscle; however, it is highly likely that all of the above related processes either work in concert or contribute in some way to the physiological hypertrophy of muscle. The challenge for current researchers is to clarify the role of each of these paradigms in the greater cybernetic network of adaptive pathways, fleshing out the complexities of potential synergies and redundancies with the theoretical hierarchies of influence between the above more well-established mechanistic signaling responses to resistance exercise.

Aging is associated with the loss of muscle mass (sarcopenia) and muscle strength (dynapenia) (Candow et al. 2012, 2019a, b). Finding strategies to ameliorate or reverse the progression of these functional and structural declines with age is considered crucial for the aging population. In addition, finding such strategies would also serve as a platform from which to highlight potential mechanistic underpinnings of skeletal muscle hypertrophy, and then apply those mechanisms in other conditions such as rehabilitation, where muscle growth is desirable. As such, resistance training that was designed to enhance skeletal muscle hypertrophy and

strength has now evolved to include many unique exercise techniques (such as blood flow restriction resistance exercise), and is currently viewed as an effective exercise strategy to slow and minimize the age-related loss of muscle strength and size. While each particular resistance training protocol presents users with training stimuli that foster muscle remodeling and functional adaptation by muscle fibers, satellite cells, and other types of cells within a muscle, the approach is not uniformly successful. Strategically controlled resistance training interventions performed on a research basis by well-documented specific populations of users (e.g., older-aged individuals who sustain different levels of activity, with or without additional health problems, or younger-aged individuals with a variety of disuse conditions including obesity) and well-defined modalities of physical activity in particular muscle groups may provide further nuance to our understanding of the interplay of emerging and previously established muscle hypertrophy mechanisms.

Thus, the purpose of this review is to explore the idea that myokines may serve as a contributing mechanism for muscle hypertrophy associated with resistance exercise. The review will attempt to contextualize the potential contribution of myokines in an increasingly complex network of muscle-hypertrophy mechanisms. This review is also focused on the effects that nitric oxide and its metabolites have on systemic myokine release with resistance exercise. The review then identifies some of the interesting findings from research on blood flow restricted (BFR) resistance exercise in comparison to more standard resistance exercise protocols used to enhance muscle hypertrophy, and the potential application of these BFR resistance training methodologies to counter the loss of skeletal muscle mass in our aging population and how myokines may influence this. Finally, the review identifies the need for continued research to elucidate myokine involvement in the regulation of skeletal muscle hypertrophy.

Cytokines and myokines

Cytokines are intercellular messengers that comprise a large family of polypeptides and proteins. A cytokine response is inducible by a wide variety of stimuli and can be secreted by several cell types in the human body. While their primary function is typically associated with an immune response, many cytokines are also responsible for the mediation of other biological functions including energy metabolism. As such, cytokines can be described as pleiotropic in function. A particular cytokine may confer different mediating effects depending upon the initial stimulus, target cell, or other cytokines released in conjunction. Cytokines are also capable of acting in local (autocrine or paracrine) or systemic

(endocrine) fashion depending on the target tissue (Peake et al. 2015b).

Certain cytokines (termed "myokines") are proteins released by skeletal muscle fibers (multinucleated muscle cells) that can have local effects on muscle, as well as systemic effects on other tissues. The extent of the myokine-release response after muscular contraction varies with the intensity, mode, and volume of exercise an individual performs (Peake et al. 2015b). Some myokines may be anabolic and have direct growth-promoting effects (Lee and Jun 2019) (see Fig. 2). Still others generate signals which may mediate some of the health benefits of resistance exercise (Hoffmann and Weigert 2017). Since their discovery in 2000 (Steensberg et al. 2000), myokines have continued to generate increasing interest. Since they were hypothesized to be important mediators in systemic metabolism, ongoing research has largely focused on possible cellular signaling events that could enhance muscle growth through anabolic pathways (direct or indirect) in muscle (Dankel et al. 2017; Hoffmann and Weigert 2017). Such pathways are particularly intriguing as they explore the potential mediators (such as myokines) of the impact of resistance exercise and training protocols, an area of growing interest with the burgeoning population of adults over 55 years of age (Tieland et al. 2018).

Certain myokines are upregulated in resistance exercise; these include leukemia inhibitory factor (LIF); interleukins such as interleukin-4 (IL-4), IL-6, IL-7, IL-15; decorin; and irisin (Pedersen and Febbraio 2012; Kanzleiter et al. 2014; Huh et al. 2014). These particular myokines have the
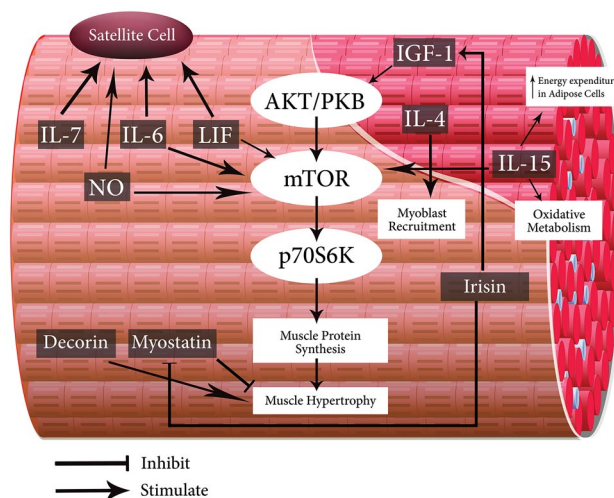
Fig. 2 Potential roles of some main myokines in influencing skeletal muscle protein synthesis/skeletal muscle hypertrophy. Akt/PKB: protein kinase B; IGF-1: insulin-like growth factor-1; IL-4: interleukin-4; IL-6: interleukin-6; IL-7: interleukin-7; IL-15: interleukin-15; LIF: leukemia inhibitory factor; mTOR: mechanistic target of rapamycin; NO: nitric oxide; p70S6K: ribosomal protein S6 kinase

potential to reduce muscle atrophy and promote growth by fiber hypertrophy, due to their induced release by contraction during resistance exercise. Additional growth factors such as hepatocyte growth factor (HGF) and insulin-like growth factor (IGF-1) and the gaseous signaling molecule nitric oxide (NO), are released by exercise and mechanical stretching (Anderson 2000; Tatsumi et al. 2006; Wozniak and Anderson 2007). Moreover, NO is known to upregulate certain myokines such as IL-6 (Steensberg et al. 2007). HGF and NO also have the potential to promote muscle growth by activating skeletal muscle stem cells (called satellite cells) that are typically quiescent in sedentary adults or in age-related atrophy. Interestingly, the capability for satellite cells to respond to mechanical stretch or exercise decreases with increasing age, and satellite cells become refractory to levels of stretch that would normally activate stem cells in muscle from younger individuals, at least in a mouse model (Leiter and Anderson 2010). In mice, this observation is congruent with findings that exercise-induced muscle growth is muscle specific and age dependent (Leiter et al. 2011). It is also demonstrated that age-related atrophy in old female mice can be reversed by treatment with a nitric oxide donor drug (Leiter et al. 2012). HGF and NO are able to initiate cycling of muscle satellite cells, as well as inducing the migration of satellite cells (Anderson 2000; Siegel et al. 2009, 2011) and mediating the speed and direction of such movement in interactions with the extracellular matrix proteins fibronectin and collagen in experimental microfluidics devices (Roveimiab, Lin, and Anderson, personal communications) (Roveimiab et al. 2019). Satellite cells stimulated by IGF-1 will induce their proliferation, along with other growth factors including fibroblast growth factor (FGF-2) and mechano-growth factor (MGF), specifically MGF-E (Kandalla et al. 2011), a mechanically released form of IGF. The following section highlights a number of the key findings from research which has examined myokines with hypertrophic potential in muscle.

Leukemia inhibitory factor

LIF is part of the IL-6 superfamily of cytokines and plays many physiological roles (Pedersen and Febbraio 2012). Research indicates that LIF can act as a myokine as it is produced when cultures of human muscle (myotubes) are electrically stimulated (Broholm et al. 2008). An increase in LIF mRNA expression by human skeletal muscle follows an acute bout of resistance exercise although it did not result in any increase in LIF protein content (Broholm et al. 2008) or an increase in circulating levels of LIF (Broholm and Pedersen 2010). In vitro study of LIF indicated a role for LIF in stimulating human satellite cell activity (Spangenburg and Booth 2002) which is important for muscle growth and hypertrophy. As well, in LIF knockout

mice, the hypertrophic response to functional overloading was blunted; restoration of physiological concentrations of LIF in those knockout mice reestablished the hypertrophic response by muscle, indicating specific involvement of LIF in muscle hypertrophy (Spangenburg and Booth 2002). In other research, incubation of LIF in myotube cultures caused a significant increase in mechanistic target of rapamycin (mTOR) which, in turn, induces an anabolic muscle response to increase protein synthesis (Gao et al. 2017). These reports support an important assertion that LIF plays a role in inducing a hypertrophic response in skeletal muscle.

Interleukin-4

IL-4 is a cytokine that is predominantly produced by T-helper type-2 leukocytes and is primarily considered an anti-inflammatory cytokine (Prokopchuk et al. 2007; Della Gatta et al. 2014). However, in a culture of myotubes, IL-4 was involved in myoblast recruitment to fuse into the myotubes, and secretion of IL-4 was necessary for growth of the cultured muscle (Horsley et al. 2003). The first in vivo experiment focused on IL-4 in human skeletal muscle demonstrated that expression of the mRNA and protein of IL-4 and the IL-4 receptor-α was higher in human muscle after 6 weeks of high-intensity strength training (Prokopchuk et al. 2007). This result indicated IL-4 was involved in skeletal muscle hypertrophy; although, the direct evidence for this still requires further exploration.

Interleukin-6

IL-6 is considered one of the main myokines that increases in muscle tissue after contraction and is released systemically. IL-6 plays many roles in physiology and pathology in muscle (Pedersen and Febbraio 2012; Peake et al. 2015a), and it may stimulate hypertrophic signaling in muscle (Toth et al. 2011; Mitchell et al. 2013). In a rat model of exercise, IL-6 protein in muscle was increased after 8 weeks of training in young- and middle-aged rats; although, the extent of the increase was lower than in middle aged animals (Jung et al. 2015). IL-6 production has also been found to stimulate muscle satellite cell proliferation and myogenic differentiation in a rat model; these changes were associated with muscle hypertrophy over a 10-week training program (Begue et al. 2013). In a human study, a completion of a 16-week resistance exercise protocol resulted in a systemic IL-6 response after an initial single bout of resistance exercise and was significantly correlated with the degree of muscle hypertrophy in young men (Mitchell et al. 2013). Another study in humans used muscle lengthening (eccentric muscle contraction) to induce muscle damage, and IL-6 was shown to induce signaling by the signal transducer and activator of transcription 3 protein (STAT3) in the nuclei of satellite

cells available from muscle biopsies, which likely indicates a role for IL-6 in muscle growth involving stem cell proliferation and fusion into muscle fibers (Toth et al. 2011). There is in vitro evidence linking IL-6 to myoblast proliferation and differentiation (Baeza-Raja and Muñoz-Cánoves 2004; Serrano et al. 2008) and myotube protein synthesis through upregulation of the mTOR pathway (Gao et al. 2017). Thus, it seems that IL-6 may play an important role in promoting skeletal muscle adaptation and could be required to initiate muscle hypertrophy in response to resistance exercise.

Interleukin-7

Currently, there is limited research on the hypertrophic potential of IL-7; although, some preliminary evidence suggests IL-7 may be locally upregulated in exercised skeletal muscle and be involved in muscle satellite cell activation (Pedersen and Febbraio 2012). Human models of investigation which examined the effects of an 11-week strength training program suggest that IL-7 mRNA expression was significantly higher at rest in the vastus lateralis and trapezius muscles of young men than at the start of the study (Haugen et al. 2010). Also, in vitro incubation of myotubes with recombinant IL-7 in culture has been demonstrated to increase the migration of myoblasts (Haugen et al. 2010), which would foster myotube formation in vivo.

Interleukin-15

Several lines of evidence suggest IL-15 may be involved in muscle hypertrophy. Research in culture studies have demonstrated the anabolic potential of the myokine IL-15 as it induced myosin heavy chain accumulation (Quinn et al. 1995; Furmanczyk and Quinn 2003), and stimulated myogenic differentiation (Quinn et al. 1997), and muscle protein synthesis while inhibiting protein degradation (Quinn et al. 2002; Busquets et al. 2005). In animal models, IL-15 mRNA was increased in both unloaded and aged skeletal muscle compared to loaded and younger muscle, findings, which suggest its possible role in promoting hypertrophy or at least counteracting decreases in loss of muscle mass (Pistilli et al. 2007). Other research from the same group also indicated that systemic elevation by recombinant IL-15 infusion produced an increase in apoptosis in skeletal muscle of young adult and aged rats and attenuated the accretion of muscle mass compared to controls (Pistilli and Alway 2008). Further research indicated that IL-15 transgenic mice that overexpressed and secreted high levels of IL-15 from muscle into the systemic circulation had lower adiposity and greater bone mineral content with no effect on skeletal muscle (Quinn et al. 2009). Research showed that aging mice have decreased levels of both serum and skeletal muscle IL-15 that correlated with a decrease in soluble IL-15 receptor-α,

which may have implications for understanding increases in adiposity and decreased muscularity with age (Quinn et al. 2010). In normal and streptozotocin-induced diabetic rats with muscle atrophy, IL-15 levels in both serum and muscle were upregulated after resistance-based training in both fast- and slow-twitch muscle and that fast muscle morphology was maintained as normal in the trained diabetic rats (Molanouri Shamsi et al. 2014, 2015). In humans, plasma IL-15 was significantly elevated following an acute session of resistance exercise, both before and after a 10-week resistance training program. However, this acute increase in IL-15 was not associated with morphological changes or hypertrophy in skeletal muscle (Riechman et al. 2004). Another report found that resting plasma IL-15 concentration increased after an 8-week program of moderate or heavy intensity resistance training in young adult males, and that there was a corresponding increase in lean body mass and a decrease in percent body fat in the group that completed the heavy resistance training (Yeo et al. 2012). Human muscle biopsies after an acute resistance exercise session in humans demonstrated increased IL-15 mRNA expression (Nielsen et al. 2007) and 12 weeks of endurance training in males enhanced the protein content of IL-15 by 40% in resting muscle without any change in plasma IL-15 or its mRNA suggesting that the IL-15 myokine is primarily involved in skeletal muscle metabolism (Rinnov et al. 2014). Other reviews have suggested that IL-15 serves as a signaling molecule in the mTOR pathway, that it may play a greater role in oxidative metabolism than previously hypothesized, and that IL-15 may be intricately involved in providing feedback from muscle to adipose tissue to increase energy expenditure as a protective mechanism in overweight or obese individuals (Tamura et al. 2011; Raschke and Eckel 2013; Pistilli and Quinn 2013; Ye 2015; Nadeau and Aguer 2019). In summary, it appears that IL-15 may play many roles physiologically in response to a single bout of exercise or training; however, its effects on muscle hypertrophy appear debatable.

Decorin

Decorin has long been proposed as a myokine involved in muscle hypertrophy (Brandan et al. 1991; Kanzleiter et al. 2014). Myotubes secrete decorin (Kanzleiter et al. 2014) and decorin upregulates protein synthesis in vitro (Sun et al. 2013). In vivo evidence from murine skeletal muscle further indicates that decorin overexpression can upregulate several factors involved in inhibiting myostatin, itself a potent myokine that increases protein degradation, which attenuates muscle cell growth and differentiation (Guiraud et al. 2012; Kanzleiter et al. 2014). Inhibition of myostatin by decorin is believed to open a molecular pathway in which decorin may be involved in anabolic activity in skeletal muscle. Further research suggests that an acute bout of resistance

exercise results in systemic decorin release, with the degree of fat-free mass being positively associated with the extent of decorin released after an acute bout of resistance exercise (Kanzleiter et al. 2014). Further to this point, we have also demonstrated that various types of acute resistance exercise (low load, blood flow restricted low load, and high load) resulted in a systemic release of decorin indicating that this myokine may be involved in the hypertrophic response to resistance exercise (Bugera et al. 2018).

Irisin

Irisin is a myokine known predominantly for its effect on the "browning" or transformation of white adipose tissue to brown adipose tissue, providing increased capacity to generate heat and thus increase the energy expenditure of muscle (Shan et al. 2013). However, in addition to its role in muscle–adipose crosstalk, there is emerging evidence to suggest that irisin may have a role in regulating muscle and bone hypertrophy (Huh et al. 2014; Colaianni et al. 2015). Irisin increases significantly in the muscle of mice exposed to 3 weeks of wheel running compared to levels in resting control animals, and osteoblast cultures were more differentiated when culture media were prepared from mouse muscle with higher levels of irisin protein (Colaianni et al. 2014). Beyond this, in cultured human myocytes, in vitro treatment with irisin upregulated insulin-like growth factor-1 (IGF-1) and downregulated myostatin, suggesting that it may play a role in skeletal muscle hypertrophy (Huh et al. 2014).

Other myokines

Other novel myokines of interest for research on promoting skeletal muscle hypertrophy include: apelin, fatty acid binding protein-3 (FABP-3), fibroblast growth factor-21 (FGF-21), fractalkine, follistatin-related protein-1, oncostatin-M, osteocrin, and secreted protein acidic and rich in cysteine (SPARC). While these known myokines influence a wide variety of physiological processes, their roles also hold promise in mediating muscle hypertrophy, as they may influence the main molecular pathway for the new protein synthesis in muscle that is regulated by targeting the mTOR pathway that signals p70 ribosomal S6 kinase (p70S6K) and activates the downstream product, 4E binding protein 1 (4E-BP1). The 4E-BP1 signal results in increased expression and ultimately synthesis of a variety of muscle proteins. For instance, repair of damaged skeletal muscle tissue may be aided by myokines such as fractalkine (Strömberg et al. 2016) which is thought to be beneficial for muscle adaptation to resistance exercise. Higher-level interactions between pituitary hormones and muscle were also investigated in relation to the capacity for ongoing repair and growth of damaged muscle in *mdx* mouse muscular dystrophy

(Anderson et al. 1994). Also, follistatin-related protein-1 binds myostatin, resulting in increased muscle mass; follistatin-related protein-1 may help induce muscle adaptation to resistance exercise (Brandt et al. 2015). As well, when LIF and oncostatin-M bind their receptors, muscle growth is promoted (Hunt and White 2016). Further, apelin is reported to be released systemically to a larger degree in response to an acute resistance exercise session in trained as compared to untrained individuals (Fortunato et al. 2018); restoration of apelin levels in older adult humans increases muscle mass and as one ages, it helps to improve functional ability (Vinel et al. 2018). Finally, osteocrin may exert a direct influence on muscle (Moffatt and Thomas 2009) and SPARC is known to induce muscle atrophy in muscle (Son et al. 2016).

Myokines and pleiotropy

Skeletal muscle is considered to be an endocrine organ, with myokines serving as a major component of the muscle secretome (Pedersen and Febbraio 2008; Giudice and Taylor 2017). Certain myokines are known to play a role in muscle–fat crosstalk and are, thus, described as adipo-myokines; this term is used to indicate that the higher-level complexity of their signaling role depends on the original stimulus for their secretion and the particular cellular and extracellular milieu in which they are active (Raschke and Eckel 2013; Li et al. 2017).

This multi-functional and context-dependent variation by individual molecules is termed pleiotropy, an important feature of complex signaling pathways that span multiple tissues and organ systems. For example, tissue secretomes, including those from renal, hepatic and other tissues, play important roles in fine-tuning the complex crosstalk of signals between bone and muscle and ultimately modulate the primary biomechanical interactions of those two tissues (Karasik and Kiel 2010; Bonewald 2019; Trajanoska et al. 2019). Anabolic hormones have long been viewed as the dominant exercise-induced signaling molecule (Kraemer and Ratamess 2005) but the discovery of myokines, in particular their release from muscle after resistance exercise, suggested the existence of a more complex cascade of signals involved in skeletal muscle adaptation than previously thought (Steensberg et al. 2000). Thus, it is important that research determines distinct and overlapping characteristics among signaling molecules, and further, if possible, a hierarchy of biological relevance—clarifying the synergy, redundancy, and dominance among signals.

The complexity of studying and understanding the dynamic interplay among signaling molecules following resistance exercise cannot be understated. Current research on the anabolic hormone responses to resistance exercise, for example, may help to establish our understanding of myokines. Briefly, anabolic hormone release induced by

resistance exercise function in a canonical (classical) stimulus–response, ligand–receptor fashion. In response to muscle tissue contraction, damage, or metabolic demand, the levels of several hormones will increase in systemic circulation—many of those hormones appear to be functionally pleiotropic yet also have additional synergistic effects that promote "supercompensation" of the exercise-affected tissues and also restore homeostasis after exercise (Kraemer et al. 2017). Once released, these hormones require receptors to bind to in order to produce their effect. Such receptors also have potential for site-specific upregulation of hypertrophic signaling pathways in response to exercise stimulus (Kraemer et al. 2017), suggesting that the direction of adaptation is coordinated across cell types, tissues, and organ systems. Further, some anabolic hormones (for example, growth hormone or IGF-1) appear in different isoforms, a feature that confers additional specificity to the signaling cascades, depending on the original exercise stimulus and the tissue that is targeted (Kraemer et al. 2003, 2017). Methodologies such as genome-wide association studies and the use of computational biology and genetic algorithms to analyze complex interactions are beginning to dissect the multidimensional interactions of signals involved in pleiotropic bone–muscle signaling by exploring the contributions of gene loci expressed in specific tissues during particular types of activity (Trajanoska et al. 2019).

By contrast, myokines display even more functional pleiotropy than hormones. As with hormones, resistance exercise initiates the systemic appearance of several myokines (Riechman et al. 2004; Mitchell et al. 2013; Kanzleiter et al. 2014; Bugera et al. 2018). Some studies also suggest there is a corresponding upregulation of receptor molecules in the target tissue(s) (Reihmane and Dela 2014). Notably, however, certain myokines and their receptors are ubiquitously expressed. For example, IL-6 is an extensively studied exercise-induced myokine that is involved in several different skeletal muscle-adaptation pathways (Toth et al. 2011; Mitchell et al. 2013). It also helps to recall that hormone receptors can be down-regulated secondary to increases in the levels of the ligand; this type of feedback mechanism in regulating the effects of the steroid testosterone is now used as a treatment modality to suppress testosterone (Kvorning et al. 2015).

When viewed from a global endocrine perspective, the seemingly ubiquitous nature of the IL-6 molecule and the expression of its multiple receptor types (Wolf et al. 2014; Baran et al. 2018) make it extremely difficult to confidently characterize the scope of IL-6 actions at any given time, from a simple blood level measured in the systemic circulation. IL-6 affects anabolic, metabolic, and pro- and anti-inflammatory effects, and the magnitude of each of those effects is difficult to determine without extensive controls (Muñoz-Cánoves et al. 2013; Karstoft and Pedersen 2016).

This is particularly the case when considering potential (or likely) confounding hypertrophic effects of other signaling mechanisms noted above.

Many myokines such as IL-15 (Pistilli and Quinn 2013), which were initially thought to have a major role in anabolic signaling were recently re-characterized as metabolically derived "adipo-myokines". Even the change in terminology highlights the currently understood complexity of these pleiotropic molecules and the need for further research to fully understand their role (Li et al. 2017) and how that role depends on the nature of the exercise that stimulates their production and release. Finally, the skeletal muscle secretome is described as encompassing over 300 unique molecules to date (Giudice and Taylor 2017). The level of research on each of those molecules varies, and there is limited research available from in vivo trials using well-controlled studies of interventions with resistance exercise protocols. These observations make it clear that our understanding of this topic is in its infancy. Revisiting research developments on the hormones, including myokines, that are induced by resistance exercise, is a logical next step in bolstering our understanding of myokines, particularly when attempts to untangle the role of each myokine and its potential for pleiotropy.

Determining myokine influence in anabolic cellular signaling

Many previous studies indicated that major hormones such as testosterone, the growth hormones (including growth hormone and insulin), and IGF-1 and its isoform mechanical growth factor (MGF) are upregulated following acute resistance exercise, either systemically or locally in skeletal muscle (Hickson et al. 1994; Bamman et al. 2001; Tremblay et al. 2004; Hackney and Lane 2015; Mangine et al. 2017; Kraemer et al. 2017). The upregulation and release of such hormones during recovery from resistance exercise indicates that such a response is likely essential for restoring body homeostasis. Work in both animal models and humans with low testosterone has indicated that low testosterone suppresses both the synthesis of myofibrillar proteins by muscle and the accrual of lean body mass (White et al. 2013; Kvorning et al. 2013). A recent review indicated that testosterone interacts in two ways with its receptors to upregulate protein synthesis: genomically, through its interaction with the androgen receptor and nuclear DNA; and non-genomically, through its interaction with a membrane-bound receptor that triggers intracellular signaling (Hooper et al. 2017).

Interestingly, acute resistance exercise is reported to concurrently increase growth hormone and cortisol levels; furthermore, the increase in cortisol was sufficient to inhibit p70S6K signaling, which actually reduced the initiation of translation and ultimately reduced protein synthesis in

muscle (Spiering et al. 2008). From descriptions of only a few hormones in the above examples, it is obvious that a vast network of signaling occurs during recovery from strenuous acute resistance exercise and which enhances resilience to additional stresses (e.g., mechanical, inflammatory, or metabolic) placed on the system by future exercise and demands for adaptation. As indicated earlier in this review, there are multiple paradigms that characterize the mechanisms of muscle hypertrophy. The myokine response to the stress and stimulus of resistance exercise is only one of the myriad responses that may synergize or be redundant with the other signals generated during the skeletal muscle adaptations that produce hypertrophy.

While many systems play a role in mediating skeletal muscle hypertrophy, the impact and relative strength and/or timing of signals that produce that hypertrophy also vary depending on the particular conditions in an experiment (Bamman et al. 2018). Typically, anabolic hormones (e.g., testosterone and growth hormones) are credited with a potent hypertrophic influence, given their acute increases after a bout of resistance exercise (Kraemer and Ratamess 2005). However, the literature identifies additional evidence that anabolic hormones do not account for all the features of hypertrophy by skeletal muscle.

Interestingly, early seminal work on muscle hypertrophy using a rat model showed that muscle loading still produced a strong muscle-hypertrophy response despite removal of the pituitary gland and resulting severely reduced levels of circulating growth hormone, insulin like growth factor-1, and thyroid hormones (Goldberg 1967). A later human study that combined resistance training with exogenous growth hormone administration concluded that the combined intervention was no more effective than resistance training alone, in increasing muscle strength and size, and the rate of protein synthesis by muscle (Yarasheski et al. 1992). Conversely, supraphysiologic levels of testosterone administration promoted a dose-dependent rise in muscle cross-sectional area, an index of muscle mass, plus increases in the number of satellite cells, muscle precursors needed for muscle growth, in both younger and older men (Sinha-Hikim et al. 2003, 2006). A more recent study further examined the impact of suppressing testosterone using goserelin, an agonist of luteinizing hormone-releasing hormone (LHRH) that downregulates LH receptors. Notably, after testosterone suppression with goserelin in young men, 8 weeks of resistance training reduced the differentiation of satellite cells into myonuclei and attenuated the exercise-related rise in lean leg mass compared to placebo administration (Kvorning et al. 2015). These studies suggest that overall, testosterone signaling dominates skeletal muscle hypertrophy compared to other signals.

However, it is important to note that even in castrated rats, in which there is a substantial reduction of circulating testosterone levels, the plantaris muscle was still able to hypertrophy in compensation for excess loading produced after removal of the gastrocnemius muscle (Hickson et al. 1983). Together, these reports further suggest that in the absence of the dominant signal from testosterone, compensatory hypertrophic responses are still possible via other, non-testosterone-dependent mechanisms (Hickson et al. 1983). It is possible that the myokine response was still intact and, thus, may have been why the compensatory hypertrophy occurred.

Even more recently, administration of growth hormone, but not testosterone, was identified to induce a significant increase in systemic levels of the anabolic myokine, decorin (see above); interestingly, this result was specific to men and did not occur in women (Bahl et al. 2018). This evidence indicates the possibility of growth hormone-stimulated increases in a myokine that is known to influence muscle hypertrophy. Further research on myokines is needed to understand the potency of myokine responses to resistance exercise stimuli and indeed, whether such responses are unique, complementary, or redundant to other signals that have been heavily researched.

Therefore, while anabolic hormones are primary endocrine stimuli that produce muscle hypertrophy, and their loss or reduction (e.g., with aging) significantly contributes to reduced muscle mass, there is debate in the literature as to whether testosterone is sufficient to regulate hypertrophy. This debate continues despite the fact that myokines are released from muscle and appear to stimulate distinct hypertrophic pathways that are redundant to hypertrophic signals from anabolic steroids (West et al. 2010; West and Phillips 2010). Systemic endocrine stimuli cannot account for the totality of responses (or lack of responses) during muscle adaptation, either anabolic or catabolic (West and Phillips 2010), or local responses via myokines in the muscle, itself. Given these observations of systemic endocrine signaling in specific response to resistance training or other forms of exercise, one or more myokines may provide a sufficiently potent signal to induce muscle hypertrophy or modulate its magnitude. Remarkably, a recent study in a mouse model found that irisin injection significantly increased muscle hypertrophy and muscle function/strength, while also promoting muscle regeneration and hypertrophy in response to muscle injury (Reza et al. 2017). Clearly, the possibility that myokines can improve muscle repair and also promote functional hypertrophy still needs investigation. A better understanding of local and systemic signaling via myokines could provide clues that foster new ways to treat or counteract atrophy by promoting muscle hypertrophy.

Nitric oxide (NO)

Nitric oxide (NO) production upregulates IL-6 and IL-8 mRNA expression in exercising human skeletal muscle (Steensberg et al. 2007). NO is also a key signaling molecule that activates muscle satellite cells into proliferation and growth (Anderson 2000). Further, NO and peroxynitrite (a metabolite of NO) mediate protein synthesis in skeletal muscle via stimulation of the mTOR pathway (Ito et al. 2013). Research indicates that exercise during blood flow restriction dilates arterial vessels, which is also stimulated by NO production (Rudic et al. 1998; Hunt et al. 2012, 2013) and BFR resistance exercise induces satellite cell proliferation in skeletal muscle and increases protein synthesis in muscle (Nielsen et al. 2012; Wernbom et al. 2013). In a rat model of overload-induced hypertrophy, NO signaling was essential in causing skeletal muscle hypertrophy (Smith et al. 2002). Further, within a mouse model where hind-limb suspension was used to induce muscle atrophy, treatment with an NO donor (isosorbide dinitrate) prevented and attenuated the suspension-induced decrease in muscle satellite cell proliferation in young and adult mice compared to suspended controls that did not receive treatment (Anderson et al. 2018). Notably, the same NO-donor treatment enabled exercise-induced muscle hypertrophy accompanied by increased satellite cell proliferation in old female mice, a feature that is typically lost in aged animals serving as controls without treatment (Leiter et al. 2012). Thus, there is strong evidence that supports the involvement of NO and possibly its metabolites in skeletal muscle hypertrophy via both satellite cell proliferation and fusion into muscle fibers and the growth of fibers through anabolic pathways. Future explorations of the relationship between NO metabolites and the putative anabolic myokines will be interesting.

Chronic resistance training is also linked with increases in satellite cell proliferation in muscle (Nielsen et al. 2012; Bellamy et al. 2014). This suggests a plausible link between NO production and myokine release. However, it is not known whether the systemic release of potential anabolic myokines is associated with the appearance of, or changes in a systemic level of NO or peroxynitrite after resistance exercise. These ideas encourage research to evaluate the systemic response of putative anabolic myokines and peroxynitrite to an acute bout of resistance exercise. It will also be important to determine whether resistance training can differentially modify that systemic response in younger, middle-aged, and older adults. It is interesting to note that insulin acts as a vasodilator through the nitric oxide synthase (NOS) pathway but, in older adults, the vasodilatory effects of insulin are diminished and may adversely affect muscle blood flow and

thus, muscle protein synthesis in this population (Dickinson et al. 2013). However, increasing vasodilation by pharmacological administration of sodium nitroprusside and co-administering insulin to older adults restored muscle protein synthesis suggesting that enhancing the vasodilatory effect may enhance muscle protein anabolism (Timmerman et al. 2010). Thus, examining the association between anabolic myokines and NO production will help determine if this is a possible mechanism for muscle hypertrophy. Such research would help to validate the role of myokines as a mechanism that accounts for the health benefits associated with exercise, would help to clarify the role of resistance exercise to sustain muscle mass and strength in aging and rehabilitation, and would validate whether anabolic myokines, as proposed above, serve as part of the underlying mechanism that accounts for the musculoskeletal health benefits frequently observed with resistance training exercises.

Blood flow restricted resistance exercise

One particular training method that underscores the necessity to broaden our understanding of hypertrophic mechanisms is blood flow restricted (BFR) resistance training. BFR resistance training involves the application of a cuff around the most proximal portion of an exercising limb (arm or leg), inflating the cuff to a pressure predetermined to restrict venous return while keeping arterial flow unimpeded, and completing a low load, high repetition, low rest training protocol under this mild restriction of vascular flow (Pope et al. 2013; Wilk et al. 2018). As publications using this model have emerged, greater research interest in BFR resistance training has focused on BFR exercise as tool for enhancing skeletal muscle hypertrophy and strength in athletes, older-age, or clinical populations (Abe et al. 2006; Scott et al. 2016; Kambič et al. 2019; Wernbom and Aagaard 2019).

An interesting divergence in protocols arises when comparing a standard hypertrophy-training protocol and the BFR resistance training technique. For example, standard exercise parameters designed to elicit muscular hypertrophy in novice to intermediate trainees include loading schemes between 70 and 85% of the trainee's 1-repetition maximum (1RM), 1–3 total sets per exercise with 8–12 repetitions per set, and 1–2 min of rest between each set (American College of Sports Medicine 2009). Conversely, commonly prescribed BFR resistance training parameters involve a loading range of 20–40% 1RM, one set of 30 repetitions followed by three additional sets of 15 repetitions, and 30 s of rest between sets (Scott et al. 2015). Despite this disparity in training protocols, both approaches result in muscular hypertrophy (American College of Sports Medicine 2009; Martín-Hernández

et al. 2013; Slysz et al. 2016). Research involving individuals, either with or without resistance training experience, demonstrated that low-load, high-repetition resistance exercise provides gains in muscle mass that are similar to those from high-load, lower-repetition resistance exercise when resistance exercise is done to fatigue (Mitchell et al. 2012; Morton et al. 2016). Further, BFR resistance training results in superior hypertrophic responses compared to unrestricted, volume-matched low-intensity resistance training (Takarada et al. 2004; Loenneke et al. 2012).

These observations continue to generate further research into BFR resistance exercise in relation to the main initiators of hypertrophy: mechanical loading, metabolic stress, and muscle damage (Loenneke et al. 2012, 2015; Takada et al. 2012; Sudo et al. 2015; Dankel et al. 2017), in an attempt to understand the seemingly unique adaptation process. However, few studies report the role of potential underlying hypertrophic mechanisms, such as myokines and the relationship myokines may have in certain clinical conditions as potential biomarkers of disease/dysfunction (Coelho-Junior et al. 2019). Moreover, the difference between BFR and more standardized training protocols serves to highlight that the mechanisms of action underlying resistance exercise adaptations are not fully understood.

Age-related muscle atrophy

Muscle atrophy associated with aging (termed age-related sarcopenia) results in progressive weakness and disability. Weakness and disability, in turn, have been associated with significantly higher risk of falls and serious fractures, and often lead to loss of function and personal autonomy. A recent study reported that over 80% of individuals over 65 years of age were hospitalized in Canada from injuries directly related to a fall (Canadian Institute for Health Information 2019). The reduced quality of life and escalating costs of providing health care to an aging population serve to highlight the importance and urgency for determining forms of exercise that can best be used to safely prevent the loss of muscle mass and strength which occurs due to disability, obesity, injury, or age. In particular, greater understanding is required of anabolic resistance that occurs with age, in which a decrease in muscle mass happens in older adults, especially if resistance exercise and nutrition are not adequate (Dickinson et al. 2013). Furthermore, there is an impairment of the signaling cascades that stimulate muscle protein synthesis in older ages, such as mTOR signaling, which may indicate a decreased ability to enhance muscle protein synthesis more than muscle protein breakdown (Dickinson et al. 2013). However, we and others have shown that progressive resistance exercise training over 12 weeks can and does enhance whole body lean tissue mass, muscle

strength measures, and functional ability even in older individuals (Cornish and Chilibeck 2009; Cornish et al. 2018). It is, therefore, important to understand whether secretion of these myokines with proposed anabolic activity could be a mechanism that underlies the effectiveness of regular resistance exercise as part of one's lifestyle to sustain or even increase muscle mass and strength during aging.

Maintaining skeletal muscle health (mass and strength) through exercise or normal activity is increasingly difficult as we age, particularly after an injury that requires rehabilitation. Resistance training is effective in maintaining and can even be effective in increasing muscle mass in both younger and older adults. However, older adults do not respond as robustly to chronic resistance exercise training stimuli compared to younger adults (Farnfield et al. 2012). BFR resistance training may be an effective modality to help older adults achieve increases in strength and muscle mass (Patterson and Ferguson 2011; Yasuda et al. 2015); these two studies demonstrated that BFR resistance training is effective in increasing muscle mass and improving muscle strength more than the same degree of muscle loading without BFR. However, the mechanism by which BFR resistance exercise enhances skeletal muscle mass and strength remains elusive. Given the impact of sarcopenia and muscle atrophy that follows from our modern, increasingly sedentary lifestyle, research to investigate the possibility of systemically released, putatively anabolic myokines and/or nitric oxide metabolites (such as peroxynitrite) following an acute bout of BFR resistance exercise in untrained individuals could be effective in maintaining or growing muscle mass across the age spectrum. Such research will help to clarify the basis of the significant functional effects of BFR exercise, an intervention that would be easily implemented in regular exercise activities. An additional impact of participation in a regular resistance training program may also include effects on the magnitude or pattern of systemic release of anabolic myokines. The aim of future research should be more directly focused on exploring details of the cellular and molecular mechanisms that could be used to improve muscle health in rehabilitation and gerontology.

Future directions

There are limitations associated with each type of experimental approach when trying to unravel the mechanism(s) regulating muscle hypertrophy. There are also numerous methodologies used to elucidate these mechanisms, from cell culture to animal models, and further to applied research on human participants. Every method and model system has its limitations, including the powerful tools available in molecular biology research (Ash et al. 2013).

In general, chronic resistance training adaptations producing muscle hypertrophy can happen (i.e., an increase in muscle size), although unfortunately, researchers appear to assume that a single, acute bout of resistance exercise represents the range of biological processes that occur during repeated stimulation toward chronic adaptations. While this may hold true in general, it is beneficial to understand the different physiological and biological effects of resistance exercise activity when completing an intervention to an unaccustomed versus accustomed exercise stimulus. For example, the muscle response of individuals who are trained in that particular activity may differ from that of untrained individuals and such differences may explain some of the variability observed in research datasets and results (Fernandez-Gonzalo et al. 2013). Since myokines have been studied very little in the context of muscle hypertrophy, increasing interest and support for this type of research as collaborations among basic scientists and applied physiologists will go a long way to illuminate the mechanisms of muscle hypertrophy associated with myokine production (Lee and Jun 2019).

Designing well-controlled in vivo animal and human exercise experiments to address the mechanistic complexity represented by previous research on the six established paradigms of resistance exercise-induced muscle hypertrophy is necessary to fully appreciate the biological relevance of myokines. While certain myokines like IL-6 have been more intensively researched, data on the hypertrophic potential of myokines in response to in vivo human exercise trials are still relatively sparse and difficult to interpret. This is especially the case when the research aims to consider and evaluate the potentially confounding effects of other mechanisms underlying skeletal muscle hypertrophic in a given population and after a particular type of exercise intervention. A comprehensive series of experiments modeled after newly emerging literature on the most recently established mechanisms of hypertrophic signaling pathways, particularly those mediated by hormones and nitric oxide, would be helpful in delineating the potential for myokines to contribute to functionally important levels of skeletal muscle hypertrophy.

Some current human studies are offering valuable insights regarding the in vivo response of muscle to myokines and how those molecules may be involved in targeting the mTOR pathway of skeletal muscle hypertrophy. However, even comparing research findings from younger and older adults, there is little clarity and a distinct lack of information on whether the anabolic myokines with hypertrophic potential may have differential responses to exercise, or understanding the details of the mechanistic interaction of myokines with the mTOR and Wnt signaling pathways. Although invasive, muscle biopsy research from human participants would open the potential to reveal more about myokine effects on the mTOR or other pathways involved in skeletal muscle cell

growth and hypertrophy, similar to the basic science investigations of satellite cell responsiveness to nitric oxide in biopsy samples from participants with rotator-cuff injury (Gigliotti et al. 2015, 2016, 2017).

Ultimately, it will be important to determine whether myokines might be effective in treatment for atrophy of many types in many age groups, which will require separate study from the question of whether myokines might be a useful intervention in preventing age-related atrophy. It is interesting to note that the influence of myokines from contracting skeletal muscle is a temporal phenomenon in which acute bouts of exercise cause a significant increase in myokines, either locally or systemically, for brief periods of time (Peake et al. 2015a). This response to acute exercise is viewed as beneficial. However, paradoxically, a chronic increase in many pro-inflammatory cytokines that are also myokines and would be released in the same timeframe, can add another layer to the complexity of these signaling pathways, as they would function to oppose or attenuate the growth of skeletal muscle through a chronic low-grade inflammatory response that promotes muscle catabolism (Degens 2010). Thus, an important direction of future research is to clarify whether the myokine response to resistance exercise is similar between younger and older individuals, since older individuals frequently experience chronic low-grade inflammation (Xia et al. 2016) that could counteract any benefit of myokines released after resistance exercise.

It is also important for future research to evaluate the potential or even likely differences in the myokine response to resistance exercise between untrained and trained individuals, given there are clear differences in resistance training parameters recommended for novice and highly trained individuals (American College of Sports Medicine 2009). Thus, it would be interesting to evaluate whether the local myokine response is dependent on the level of training. A difference between untrained and highly resistance-trained individuals could help to explain time-dependent sequence of changes in the mechanisms of hypertrophy during the experience of resistance training, itself.

Further suggestions for research include establishing data on the time-course and magnitude of the appearance of myokines in local tissue (assessed via muscle biopsy) and the appearance of myokines and hormones in the systemic circulation in response to resistance exercise. Additionally, understanding the magnitude of hypertrophic effects stimulated by each myokine, including for example, the rate of muscle protein synthesis via mTOR activation, inhibition of myostatin or potential myokine synergies with nitric oxide pathways, or quantifying the mobilization and integration of satellite cells comparing their stimulation by myokines versus their responses to the other signaling mechanisms. Further, basic research to clarify the location and regulation

of myokine receptors, and their potential for upregulation by exercise will greatly advance our potential to understand and integrate the concurrent, pleiotropic effects of each myokine. These research avenues will help determine the relative significance of myokines in comparison to the other established muscle hypertrophic signaling pathways.

Conclusion

Since the anabolic resistance observed in older age results in loss of skeletal muscle mass, it is important to gain a better understanding of the range of mechanisms, including myokines, that regulate or mediate muscle hypertrophy and gains in strength. Such knowledge will help us identify how best to combat the rising health-care costs that result from declines in musculoskeletal function associated with the aging process. Finding specific and measureable methods of maintaining or enhancing skeletal muscle mass as a person ages, through application of training techniques such as blood flow restricted resistance exercise, will help us to elucidate the mechanisms that could be valuable in enhancing skeletal muscle hypertrophy in the older adult population. That myokines have a role in muscle hypertrophy is clear, even though the degree of their influence requires further exploration before we have a solid base of knowledge about these small signaling proteins. More focused research on the hypertrophic potential of myokines from collaborations of basic and applied scientists and clinicians will extend our current speculations and explain the role of myokines in producing adaptations in skeletal muscle.

From the perspective of foundational skeletal muscle biology, our knowledge about the regulation of muscle stem cells from models of development, health, aging, and disease have provided researchers with a very broad and rich range of disciplines and approaches. Future research on myokines needs to take leverage from the interconnections between basic skeletal muscle biology, often explored in animal models and human tissue culture studies, and the applied physiology of skeletal muscle to advance our understanding of mechanisms underlying skeletal muscle adaptation to resistance exercise and training. Further integration of these disciplines, particularly explorations that utilize the benefit of direct application in humans (best provided through multidisciplinary collaboration and enhanced by biopsy studies), will augment our ability to put science into application by developing evidence-based treatment strategies; such strategies will be the best approach to improving skeletal muscle health and the quality of life of our aging population and those in rehabilitation.

Determining the role of myokines, particularly those with anabolic potential, and their interplay with NO and its metabolites in regulating or mediating skeletal muscle

hypertrophy will be an important topic for future investigations. Moreover, determining the role of anabolic myokines in producing the effects of BFR resistance training could bring the possibility of inducing muscle growth during or before the onset of age-related atrophy in healthy men and women, and in those challenged by injury or illness requiring short- or longer-term rehabilitation. Understanding the complex and interacting relationships among the numerous hypertrophy pathways in skeletal muscle and acting upon it from systemic influences is essential in developing evidence-based interventions that are effective and realistic interventions to improve overall muscle health in our aging population worldwide.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

Abe T, Kearns CF, Sato Y (2006) Muscle size and strength are increased following walk training with restricted venous blood flow from the leg muscle, Kaatsu-walk training. J Appl Physiol Bethesda Md 100:1460–1466. https://doi.org/10.1152/japplphysiol.01267.2005

Adams GR, Bamman MM (2012) Characterization and regulation of mechanical loading-induced compensatory muscle hypertrophy. Compr Physiol 2:2829–2870. https://doi.org/10.1002/cphy.c110066

American College of Sports Medicine (2009) American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. Med Sci Sports Exerc 41:687–708. https://doi.org/10.1249/MSS.0b013e3181915670

Anderson JE (2000) A role for nitric oxide in muscle repair: nitric oxide-mediated activation of muscle satellite cells. Mol Biol Cell 11:1859–1874

Anderson JE, Liu L, Kardami E, Murphy LJ (1994) The pituitary-muscle axis in mdx dystrophic mice. J Neurol Sci 123:80–87. https://doi.org/10.1016/0022-510x(94)90207-0

Anderson JE, Zhu A, Mizuno TM (2018) Nitric oxide treatment attenuates muscle atrophy during hind limb suspension in mice. Free Radic Biol Med 115:458–470. https://doi.org/10.1016/j.freeradbiomed.2017.12.021

Antoniak AE, Greig CA (2017) The effect of combined resistance exercise training and vitamin D3 supplementation on musculoskeletal health and function in older adults: a systematic review and meta-analysis. BMJ Open 7:e014619. https://doi.org/10.1136/bmjopen-2016-014619

Ash GI, Eicher JD, Pescatello LS (2013) The promises and challenges of the use of genomics in the prescription of exercise for hypertension: the 2013 update. Curr Hypertens Rev 9:130–147

Baeza-Raja B, Muñoz-Cánoves P (2004) p38 MAPK-induced nuclear factor-kappaB activity is required for skeletal muscle

differentiation: role of interleukin-6. Mol Biol Cell 15:2013–2026. https://doi.org/10.1091/mbc.e03-08-0585

Bahl N, Stone G, McLean M et al (2018) Decorin, a growth hormone-regulated protein in humans. Eur J Endocrinol 178:145–152. https://doi.org/10.1530/EJE-17-0844

Bamman MM, Shipp JR, Jiang J et al (2001) Mechanical load increases muscle IGF-I and androgen receptor mRNA concentrations in humans. Am J Physiol Endocrinol Metab 280:E383–E390. https://doi.org/10.1152/ajpendo.2001.280.3.E383

Bamman MM, Roberts BM, Adams GR (2018) Molecular regulation of exercise-induced muscle fiber hypertrophy. Cold Spring Harb Perspect Med. https://doi.org/10.1101/cshperspect.a029751

Baran P, Hansen S, Waetzig GH et al (2018) The balance of interleukin (IL)-6, IL-6·soluble IL-6 receptor (sIL-6R), and IL-6·sIL-6R·sgp130 complexes allows simultaneous classic and trans-signaling. J Biol Chem 293:6762–6775. https://doi.org/10.1074/jbc.RA117.001163

Begue G, Douillard A, Galbes O et al (2013) Early activation of rat skeletal muscle IL-6/STAT1/STAT3 dependent gene expression in resistance exercise linked to hypertrophy. PLoS ONE 8:e57141. https://doi.org/10.1371/journal.pone.0057141

Bellamy LM, Joanisse S, Grubb A et al (2014) The acute satellite cell response and skeletal muscle hypertrophy following resistance training. PLoS ONE 9:e109739. https://doi.org/10.1371/journal.pone.0109739

Boers HE, Haroon M, Le Grand F et al (2018) Mechanosensitivity of aged muscle stem cells. J Orthop Res Off Publ Orthop Res Soc 36:632–641. https://doi.org/10.1002/jor.23797

Bonewald L (2019) Use it or lose it to age: a review of bone and muscle communication. Bone 120:212–218. https://doi.org/10.1016/j.bone.2018.11.002

Brandan E, Fuentes ME, Andrade W (1991) The proteoglycan decorin is synthesized and secreted by differentiated myotubes. Eur J Cell Biol 55:209–216

Brandt C, Hansen RH, Hansen JB et al (2015) Over-expression of Follistatin-like 3 attenuates fat accumulation and improves insulin sensitivity in mice. Metabolism 64:283–295. https://doi.org/10.1016/j.metabol.2014.10.007

Broholm C, Pedersen BK (2010) Leukaemia inhibitory factor–an exercise-induced myokine. Exerc Immunol Rev 16:77–85

Broholm C, Mortensen OH, Nielsen S et al (2008) Exercise induces expression of leukaemia inhibitory factor in human skeletal muscle. J Physiol 586:2195–2201. https://doi.org/10.1113/jphysiol.2007.149781

Brotto M, Bonewald L (2015) Bone and muscle: interactions beyond mechanical. Bone 80:109–114. https://doi.org/10.1016/j.bone.2015.02.010

Bruusgaard JC, Johansen IB, Egner IM et al (2010) Myonuclei acquired by overload exercise precede hypertrophy and are not lost on detraining. Proc Natl Acad Sci U S A 107:15111–15116. https://doi.org/10.1073/pnas.0913935107

Bugera EM, Duhamel TA, Peeler JD, Cornish SM (2018) The systemic myokine response of decorin, interleukin-6 (IL-6) and interleukin-15 (IL-15) to an acute bout of blood flow restricted exercise. Eur J Appl Physiol. https://doi.org/10.1007/s00421-018-3995-8

Busquets S, Figueras MT, Meijsing S et al (2005) Interleukin-15 decreases proteolysis in skeletal muscle: a direct effect. Int J Mol Med 16:471–476

Canadian Institute for Health Information (2019) Slips, trips and falls: Our newest data reveals causes of injury hospitalizations and ER visits in Canada. https://www.cihi.ca/en/slips-trips-and-falls-our-newest-data-reveals-causes-of-injury-hospitalizations-and-er-visits-in

Candow DG, Forbes SC, Little JP et al (2012) Effect of nutritional interventions and resistance exercise on aging muscle mass and strength. Biogerontology 13:345–358. https://doi.org/10.1007/s10522-012-9385-4

Candow DG, Forbes SC, Chilibeck PD et al (2019a) Variables influencing the effectiveness of creatine supplementation as a therapeutic intervention for sarcopenia. Front Nutr 6:124. https://doi.org/10.3389/fnut.2019.00124

Candow DG, Forbes SC, Chilibeck PD et al (2019b) Effectiveness of creatine supplementation on aging muscle and bone: focus on falls prevention and inflammation. J Clin Med. https://doi.org/10.3390/jcm8040488

Coelho-Junior HJ, Picca A, Calvani R et al (2019) If my muscle could talk: myokines as a biomarker of frailty. Exp Gerontol 127:110715. https://doi.org/10.1016/j.exger.2019.110715

Colaianni G, Cuscito C, Mongelli T et al (2014) Irisin enhances osteoblast differentiation in vitro. Int J Endocrinol 2014:902186. https://doi.org/10.1155/2014/902186

Colaianni G, Cuscito C, Mongelli T et al (2015) The myokine irisin increases cortical bone mass. Proc Natl Acad Sci U S A 112:12157–12162. https://doi.org/10.1073/pnas.1516622112

Cornish SM, Chilibeck PD (2009) Alpha-linolenic acid supplementation and resistance training in older adults. Appl Physiol Nutr Metab Physiol Appl Nutr Metab 34:49–59. https://doi.org/10.1139/H08-136

Cornish SM, Myrie SB, Bugera EM et al (2018) Omega-3 supplementation with resistance training does not improve body composition or lower biomarkers of inflammation more so than resistance training alone in older men. Nutr Res N Y N 60:87–95. https://doi.org/10.1016/j.nutres.2018.09.005

Damas F, Libardi CA, Ugrinowitsch C (2018) The development of skeletal muscle hypertrophy through resistance training: the role of muscle damage and muscle protein synthesis. Eur J Appl Physiol 118:485–500. https://doi.org/10.1007/s00421-017-3792-9

Dankel SJ, Mattocks KT, Jessee MB et al (2017) Do metabolites that are produced during resistance exercise enhance muscle hypertrophy? Eur J Appl Physiol 117:2125–2135. https://doi.org/10.1007/s00421-017-3690-1

Degens H (2010) The role of systemic inflammation in age-related muscle weakness and wasting. Scand J Med Sci Sports 20:28–38. https://doi.org/10.1111/j.1600-0838.2009.01018.x

Della Gatta PA, Garnham AP, Peake JM, Cameron-Smith D (2014) Effect of exercise training on skeletal muscle cytokine expression in the elderly. Brain Behav Immun 39:80–86. https://doi.org/10.1016/j.bbi.2014.01.006

Dickinson JM, Volpi E, Rasmussen BB (2013) Exercise and nutrition to target protein synthesis impairments in aging skeletal muscle. Exerc Sport Sci Rev 41:216–223. https://doi.org/10.1097/JES.0b013e3182a4e699

Donovan SM (2017) Introduction to the special focus issue on the impact of diet on gut microbiota composition and function and future opportunities for nutritional modulation of the gut microbiome to improve human health. Gut Microb 8:75–81. https://doi.org/10.1080/19490976.2017.1299309

Eftestøl E, Egner IM, Lunde IG et al (2016) Increased hypertrophic response with increased mechanical load in skeletal muscles receiving identical activity patterns. Am J Physiol Cell Physiol 311:C616–C629. https://doi.org/10.1152/ajpcell.00016.2016

Englund DA, Peck BD, Murach KA et al (2019) Resident muscle stem cells are not required for testosterone-induced skeletal muscle hypertrophy. Am J Physiol Cell Physiol 317:C719–C724. https://doi.org/10.1152/ajpcell.00260.2019

Farnfield MM, Breen L, Carey KA et al (2012) Activation of mTOR signalling in young and old human skeletal muscle in response to combined resistance exercise and whey protein ingestion. Appl Physiol Nutr Metab Physiol Appl Nutr Metab 37:21–30. https://doi.org/10.1139/h11-132

Fernandez-Gonzalo R, Lundberg TR, Tesch PA (2013) Acute molecular responses in untrained and trained muscle subjected to aerobic and resistance exercise training versus resistance training alone. Acta Physiol Oxf Engl 209:283–294. https://doi.org/10.1111/apha.12174

Ferreira-Júnior JB, Benine RPC, Chaves SFN et al (2019) Effects of static and dynamic stretching performed before resistance training on muscle adaptations in untrained men. J Strength Cond Res. https://doi.org/10.1519/JSC.0000000000003283

Fortunato AK, Pontes WM, De Souza DMS et al (2018) Strength training session induces important changes on physiological, immunological, and inflammatory biomarkers. J Immunol Res 2018:9675216. https://doi.org/10.1155/2018/9675216

Fujimaki S, Wakabayashi T, Takemasa T et al (2015) The regulation of stem cell aging by Wnt signaling. Histol Histopathol 30:1411–1430. https://doi.org/10.14670/HH-11-657

Fukada S-I (2018) The roles of muscle stem cells in muscle injury, atrophy and hypertrophy. J Biochem (Tokyo) 163:353–358. https://doi.org/10.1093/jb/mvy019

Furmanczyk PS, Quinn LS (2003) Interleukin-15 increases myosin accretion in human skeletal myogenic cultures. Cell Biol Int 27:845–851

Gao S, Durstine JL, Koh H-J et al (2017) Acute myotube protein synthesis regulation by IL-6-related cytokines. Am J Physiol Cell Physiol 313:C487–C500. https://doi.org/10.1152/ajpcell.00112.2017

Gigliotti D, Leiter JRS, Macek B et al (2015) Atrophy, inducible satellite cell activation, and possible denervation of supraspinatus muscle in injured human rotator-cuff muscle. Am J Physiol Cell Physiol 309:C383–C391. https://doi.org/10.1152/ajpcell.00143.2015

Gigliotti D, Leiter JRS, MacDonald PB et al (2016) Altered satellite cell responsiveness and denervation implicated in progression of rotator-cuff injury. PLoS ONE 11:e0162494. https://doi.org/10.1371/journal.pone.0162494

Gigliotti D, Xu MC, Davidson MJ et al (2017) Fibrosis, low vascularity, and fewer slow fibers after rotator-cuff injury. Muscle Nerve 55:715–726. https://doi.org/10.1002/mus.25388

Girgis CM (2015) Integrated therapies for osteoporosis and sarcopenia: from signaling pathways to clinical trials. Calcif Tissue Int 96:243–255. https://doi.org/10.1007/s00223-015-9956-x

Giudice J, Taylor JM (2017) Muscle as a paracrine and endocrine organ. Curr Opin Pharmacol 34:49–55. https://doi.org/10.1016/j.coph.2017.05.005

Goldberg AL (1967) Work-induced growth of skeletal muscle in normal and hypophysectomized rats. Am J Physiol 213:1193–1198. https://doi.org/10.1152/ajplegacy.1967.213.5.1193

Goodman CA (2019) Role of mTORC1 in mechanically induced increases in translation and skeletal muscle mass. J Appl Physiol Bethesda Md 127:581–590. https://doi.org/10.1152/japplphysiol.01011.2018

Grygiel-Górniak B, Puszczewicz M (2017) A review on irisin, a new protagonist that mediates muscle-adipose-bone-neuron connectivity. Eur Rev Med Pharmacol Sci 21:4687–4693

Guilhem G, Cornu C, Guével A (2010) Neuromuscular and muscle-tendon system adaptations to isotonic and isokinetic eccentric exercise. Ann Phys Rehabil Med 53:319–341. https://doi.org/10.1016/j.rehab.2010.04.003

Guiraud S, van Wittenberghe L, Georger C et al (2012) Identification of decorin derived peptides with a zinc dependent anti-myostatin activity. Neuromuscul Disord NMD 22:1057–1068. https://doi.org/10.1016/j.nmd.2012.07.002

Hackney AC, Lane AR (2015) Exercise and the Regulation of Endocrine Hormones. Prog Mol Biol Transl Sci 135:293–311. https://doi.org/10.1016/bs.pmbts.2015.07.001

Han X, Møller LLV, De Groote E et al (2019) Mechanisms involved in follistatin-induced hypertrophy and increased insulin action in skeletal muscle. J Cachexia Sarcopenia Muscle. https://doi.org/10.1002/jcsm.12474

Haugen F, Norheim F, Lian H et al (2010) IL-7 is expressed and secreted by human skeletal muscle cells. Am J Physiol Cell Physiol 298:C807–C816. https://doi.org/10.1152/ajpcell.00094.2009

Hausman GJ (2012) Meat science and muscle biology symposium: the influence of extracellular matrix on intramuscular and extramuscular adipogenesis. J Anim Sci 90:942–949. https://doi.org/10.2527/jas.2011-4616

Hedayatpour N, Falla D (2015) Physiological and neural adaptations to eccentric exercise: mechanisms and considerations for training. Biomed Res Int 2015:193741. https://doi.org/10.1155/2015/193741

Hickson RC, Galassi TM, Kurowski TT et al (1983) Skeletal muscle cytosol [3H]methyltrienolone receptor binding and serum androgens: effects of hypertrophy and hormonal state. J Steroid Biochem 19:1705–1712. https://doi.org/10.1016/0022-4731(83)90347-3

Hickson RC, Hidaka K, Foster C et al (1994) Successive time courses of strength development and steroid hormone responses to heavy-resistance training. J Appl Physiol Bethesda Md 76:663–670. https://doi.org/10.1152/jappl.1994.76.2.663

Hoffmann C, Weigert C (2017) Skeletal muscle as an endocrine organ: the role of myokines in exercise adaptations. Cold Spring Harb Perspect Med. https://doi.org/10.1101/cshperspect.a029793

Hooper DR, Kraemer WJ, Focht BC et al (2017) Endocrinological roles for testosterone in resistance exercise responses and adaptations. Sports Med Auckl NZ 47:1709–1720. https://doi.org/10.1007/s40279-017-0698-y

Horsley V, Jansen KM, Mills ST, Pavlath GK (2003) IL-4 acts as a myoblast recruitment factor during mammalian muscle growth. Cell 113:483–494

Huey KA (2018) Potential roles of vascular endothelial growth factor during skeletal muscle hypertrophy. Exerc Sport Sci Rev 46:195–202. https://doi.org/10.1249/JES.0000000000000152

Huh JY, Dincer F, Mesfum E Mantzoros CS (2014) Irisin stimulates muscle growth-related genes and regulates adipocyte differentiation and metabolism in humans. Int J Obes 38:1538–1544. https://doi.org/10.1038/ijo.2014.42

Hunt LC, White J (2016) The role of leukemia inhibitory factor receptor signaling in skeletal muscle growth, injury and disease. Adv Exp Med Biol 900:45–59. https://doi.org/10.1007/978-3-319-27511-6_3

Hunt JEA, Walton LA, Ferguson RA (2012) Brachial artery modifications to blood flow-restricted handgrip training and detraining. J Appl Physiol Bethesda Md 112:956–961. https://doi.org/10.1152/japplphysiol.00905.2011

Hunt JEA, Galea D, Tufft G et al (2013) Time course of regional vascular adaptations to low load resistance training with blood flow restriction. J Appl Physiol Bethesda Md 115:403–411. https://doi.org/10.1152/japplphysiol.00040.2013

Ibrahim A, Neinast M, Arany ZP (2017) Myobolites: muscle-derived metabolites with paracrine and systemic effects. Curr Opin Pharmacol 34:15–20. https://doi.org/10.1016/j.coph.2017.03.007

Iizuka K, Machida T, Hirafuji M (2014) Skeletal muscle is an endocrine organ. J Pharmacol Sci 125:125–131

Isaacson J, Brotto M (2014) Physiology of mechanotransduction: how do muscle and bone "talk" to one another? Clin Rev Bone Miner Metab 12:77–85. https://doi.org/10.1007/s12018-013-9152-3

Ito N, Ruegg UT, Kudo A et al (2013) Activation of calcium signaling through Trpv1 by nNOS and peroxynitrite as a key trigger of skeletal muscle hypertrophy. Nat Med 19:101–106. https://doi.org/10.1038/nm.3019

Jung S, Ahn N, Kim S et al (2015) The effect of ladder-climbing exercise on atrophy/hypertrophy-related myokine expression in middle-aged male Wistar rats. J Physiol Sci JPS 65:515–521. https://doi.org/10.1007/s12576-015-0388-1

Kambič T, Novaković M, Tomažin K et al (2019) Blood flow restriction resistance exercise improves muscle strength and hemodynamics, but not vascular function in coronary artery disease patients: a pilot randomized controlled trial. Front Physiol 10:656. https://doi.org/10.3389/fphys.2019.00656

Kandalla PK, Goldspink G, Butler-Browne G, Mouly V (2011) Mechano growth factor E peptide (MGF-E), derived from an isoform of IGF-1, activates human muscle progenitor cells and induces an increase in their fusion potential at different ages. Mech Ageing Dev 132:154–162. https://doi.org/10.1016/j.mad.2011.02.007

Kanzleiter T, Rath M, Görgens SW et al (2014) The myokine decorin is regulated by contraction and involved in muscle hypertrophy. Biochem Biophys Res Commun 450:1089–1094. https://doi.org/10.1016/j.bbrc.2014.06.123

Karasik D, Kiel DP (2010) Evidence for pleiotropic factors in genetics of the musculoskeletal system. Bone 46:1226–1237. https://doi.org/10.1016/j.bone.2010.01.382

Karstoft K, Pedersen BK (2016) Skeletal muscle as a gene regulatory endocrine organ. Curr Opin Clin Nutr Metab Care 19:270–275. https://doi.org/10.1097/MCO.0000000000000283

Kraemer WJ, Ratamess NA (2005) Hormonal responses and adaptations to resistance exercise and training. Sports Med Auckl NZ 35:339–361. https://doi.org/10.2165/00007256-200535040-00004

Kraemer WJ, Rubin MR, Häkkinen K et al (2003) Influence of muscle strength and total work on exercise-induced plasma growth hormone isoforms in women. J Sci Med Sport 6:295–306. https://doi.org/10.1016/s1440-2440(03)80023-3

Kraemer WJ, Ratamess NA, Nindl BC (2017) Recovery responses of testosterone, growth hormone, and IGF-1 after resistance exercise. J Appl Physiol Bethesda Md 122:549–558. https://doi.org/10.1152/japplphysiol.00599.2016

Kvorning T, Christensen LL, Madsen K et al (2013) Mechanical muscle function and lean body mass during supervised strength training and testosterone therapy in aging men with low-normal testosterone levels. J Am Geriatr Soc 61:957–962. https://doi.org/10.1111/jgs.12279

Kvorning T, Kadi F, Schjerling P et al (2015) The activity of satellite cells and myonuclei following 8 weeks of strength training in young men with suppressed testosterone levels. Acta Physiol Oxf Engl 213:676–687. https://doi.org/10.1111/apha.12404

Leal LG, Lopes MA, Batista ML (2018) Physical exercise-induced myokines and muscle-adipose tissue crosstalk: a review of current knowledge and the implications for health and metabolic diseases. Front Physiol 9:1307. https://doi.org/10.3389/fphys.2018.01307

Lee JH, Jun H-S (2019) Role of myokines in regulating skeletal muscle mass and function. Front Physiol 10:42. https://doi.org/10.3389/fphys.2019.00042

Leiter JRS, Anderson JE (2010) Satellite cell activation via passive stretch and nitric oxide is perturbed with age in whole-muscle cultures. Int J Biochem Cell Biol 42:132–136

Leiter JRS, Peeler J, Anderson JE (2011) Exercise-induced muscle growth is muscle-specific and age-dependent. Muscle Nerve 43:828–838. https://doi.org/10.1002/mus.21965

Leiter JRS, Upadhaya R, Anderson JE (2012) Age-related atrophy and cytoskeletal remodelling in mice reversed by treatment with NO-donor in combination with voluntary exercise. Am J Physiol Cell Physiol 302:C1306–C1315

Levinger I, Brennan-Speranza TC, Zulli A et al (2017) Multifaceted interaction of bone, muscle, lifestyle interventions and metabolic and cardiovascular disease: role of osteocalcin. Osteoporos Int

J Establ Result Coop Eur Found Osteoporos Natl Osteoporos Found USA 28:2265–2273. https://doi.org/10.1007/s00198-017-3994-3

Li P, Akimoto T, Zhang M et al (2006) Resident stem cells are not required for exercise-induced fiber-type switching and angiogenesis but are necessary for activity-dependent muscle growth. Am J Physiol Cell Physiol 290:C1461–C1468. https://doi.org/10.1152/ajpcell.00532.2005

Li F, Li Y, Duan Y et al (2017) Myokines and adipokines: involvement in the crosstalk between skeletal muscle and adipose tissue. Cytokine Growth Factor Rev 33:73–82. https://doi.org/10.1016/j.cytogfr.2016.10.003

Loenneke JP, Wilson JM, Marín PJ et al (2012) Low intensity blood flow restriction training: a meta-analysis. Eur J Appl Physiol 112:1849–1859. https://doi.org/10.1007/s00421-011-2167-x

Loenneke JP, Kim D, Fahs CA et al (2015) Effects of exercise with and without different degrees of blood flow restriction on torque and muscle activation. Muscle Nerve 51:713–721. https://doi.org/10.1002/mus.24448

MacIntosh BR, Gardiner PF, McComas AJ (2006) Skeletal muscle: form and function, 2nd edn. Human Kinetics, Champaign

Mangine GT, Hoffman JR, Gonzalez AM et al (2017) Exercise-induced hormone elevations are related to muscle growth. J Strength Cond Res 31:45–53. https://doi.org/10.1519/JSC.0000000000001491

Martín-Hernández J, Marín PJ, Menéndez H et al (2013) Muscular adaptations after two different volumes of blood flow-restricted training. Scand J Med Sci Sports 23:e114–e120. https://doi.org/10.1111/sms.12036

McGlory C, Phillips SM (2015) Exercise and the regulation of skeletal muscle hypertrophy. Prog Mol Biol Transl Sci 135:153–173. https://doi.org/10.1016/bs.pmbts.2015.06.018

McGlory C, Calder PC, Nunes EA (2019) The influence of omega-3 fatty acids on skeletal muscle protein turnover in health, disuse, and disease. Front Nutr 6:144. https://doi.org/10.3389/fnut.2019.00144

Mitchell CJ, Churchward-Venne TA, West DWD et al (2012) Resistance exercise load does not determine training-mediated hypertrophic gains in young men. J Appl Physiol Bethesda Md 113:71–77. https://doi.org/10.1152/japplphysiol.00307.2012

Mitchell CJ, Churchward-Venne TA, Bellamy L et al (2013) Muscular and systemic correlates of resistance training-induced muscle hypertrophy. PLoS ONE 8:e78636. https://doi.org/10.1371/journal.pone.0078636

Moffatt P, Thomas GP (2009) Osteocrin-beyond just another bone protein? Cell Mol Life Sci CMLS 66:1135–1139. https://doi.org/10.1007/s00018-009-8716-3

Molanouri Shamsi M, Hassan ZH, Gharakhanlou R et al (2014) Expression of interleukin-15 and inflammatory cytokines in skeletal muscles of STZ-induced diabetic rats: effect of resistance exercise training. Endocrine 46:60–69. https://doi.org/10.1007/s12020-013-0038-4

Molanouri Shamsi M, Hassan ZM, Quinn LS et al (2015) Time course of IL-15 expression after acute resistance exercise in trained rats: effect of diabetes and skeletal muscle phenotype. Endocrine 49:396–403. https://doi.org/10.1007/s12020-014-0501-x

Morton RW, Oikawa SY, Wavell CG et al (2016) Neither load nor systemic hormones determine resistance training-mediated hypertrophy or strength gains in resistance-trained young men. J Appl Physiol Bethesda Md 121:129–138. https://doi.org/10.1152/japplphysiol.00154.2016

Morton RW, Murphy KT, McKellar SR et al (2018) A systematic review, meta-analysis and meta-regression of the effect of protein supplementation on resistance training-induced gains in muscle mass and strength in healthy adults. Br J Sports Med 52:376–384. https://doi.org/10.1136/bjsports-2017-097608

Muñoz-Cánoves P, Scheele C, Pedersen BK, Serrano AL (2013) Interleukin-6 myokine signaling in skeletal muscle: a double-edged sword? FEBS J 280:4131–4148. https://doi.org/10.1111/febs.12338

Nadeau L, Aguer C (2019) Interleukin-15 as a myokine: mechanistic insight into its effect on skeletal muscle metabolism. Appl Physiol Nutr Metab Physiol Appl Nutr Metab 44:229–238. https://doi.org/10.1139/apnm-2018-0022

Nielsen AR, Mounier R, Plomgaard P et al (2007) Expression of interleukin-15 in human skeletal muscle effect of exercise and muscle fibre type composition. J Physiol 584:305–312. https://doi.org/10.1113/jphysiol.2007.139618

Nielsen JL, Aagaard P, Bech RD et al (2012) Proliferation of myogenic stem cells in human skeletal muscle in response to low-load resistance training with blood flow restriction. J Physiol 590:4351–4361. https://doi.org/10.1113/jphysiol.2012.237008

Nishimune H, Stanford JA, Mori Y (2014) Role of exercise in maintaining the integrity of the neuromuscular junction. Muscle Nerve 49:315–324. https://doi.org/10.1002/mus.24095

Oertzen-Hagemann V, Kirmse M, Eggers B et al (2019) Effects of 12 weeks of hypertrophy resistance exercise training combined with collagen peptide supplementation on the skeletal muscle proteome in recreationally active men. Nutrients. https://doi.org/10.3390/nu11051072

Ogasawara R, Jensen TE, Goodman CA, Hornberger TA (2019) Resistance exercise-induced hypertrophy: a potential role for rapamycin-insensitive mTOR. Exerc Sport Sci Rev 47:188–194. https://doi.org/10.1249/JES.0000000000000189

Olsen LA, Nicoll JX, Fry AC (2019) The skeletal muscle fiber: a mechanically sensitive cell. Eur J Appl Physiol 119:333–349. https://doi.org/10.1007/s00421-018-04061-x

Patterson SD, Ferguson RA (2011) Enhancing strength and post-occlusive calf blood flow in older people with training with blood-flow restriction. J Aging Phys Act 19:201–213

Peake JM, Della Gatta P, Suzuki K, Nieman DC (2015) Cytokine expression and secretion by skeletal muscle cells: regulatory mechanisms and exercise effects. Exerc Immunol Rev 21:8–25

Pedersen BK (2011) Muscles and their myokines. J Exp Biol 214:337–346. https://doi.org/10.1242/jeb.048074

Pedersen BK, Febbraio MA (2008) Muscle as an endocrine organ: focus on muscle-derived interleukin-6. Physiol Rev 88:1379–1406. https://doi.org/10.1152/physrev.90100.2007

Pedersen BK, Febbraio MA (2012) Muscles, exercise and obesity: skeletal muscle as a secretory organ. Nat Rev Endocrinol 8:457–465. https://doi.org/10.1038/nrendo.2012.49

Phadke CP, Vierira L, Mathur S et al (2019) Impact of passive leg cycling in persons with spinal cord injury: a systematic review. Top Spinal Cord Inj Rehabil 25:83–96. https://doi.org/10.1310/sci18-00020

Pistilli EE, Alway SE (2008) Systemic elevation of interleukin-15 in vivo promotes apoptosis in skeletal muscles of young adult and aged rats. Biochem Biophys Res Commun 373:20–24. https://doi.org/10.1016/j.bbrc.2008.05.188

Pistilli EE, Quinn LS (2013) From anabolic to oxidative: reconsidering the roles of IL-15 and IL-15Rα in skeletal muscle. Exerc Sport Sci Rev 41:100–106. https://doi.org/10.1097/JES.0b013e318275d230

Pistilli EE, Siu PM, Alway SE (2007) Interleukin-15 responses to aging and unloading-induced skeletal muscle atrophy. Am J Physiol Cell Physiol 292:C1298–C1304. https://doi.org/10.1152/ajpcell.00496.2006

Pope ZK, Willardson JM, Schoenfeld BJ (2013) Exercise and blood flow restriction. J Strength Cond Res 27:2914–2926. https://doi.org/10.1519/JSC.0b013e3182874721

Prokopchuk O, Liu Y, Wang L et al (2007) Skeletal muscle IL-4, IL-4Ralpha, IL-13 and IL-13Ralpha1 expression and response to strength training. Exerc Immunol Rev 13:67–75

Psilander N, Eftestøl E, Cumming KT et al (2019) Effects of training, detraining, and retraining on strength, hypertrophy, and myonuclear number in human skeletal muscle. J Appl Physiol Bethesda Md 126:1636–1645. https://doi.org/10.1152/japplphysiol.00917.2018

Quinn LS, Haugk KL, Grabstein KH (1995) Interleukin-15: a novel anabolic cytokine for skeletal muscle. Endocrinology 136:3669–3672. https://doi.org/10.1210/endo.136.8.7628408

Quinn LS, Haugk KL, Damon SE (1997) Interleukin-15 stimulates C2 skeletal myoblast differentiation. Biochem Biophys Res Commun 239:6–10. https://doi.org/10.1006/bbrc.1997.7414

Quinn LS, Anderson BG, Drivdahl RH et al (2002) Overexpression of interleukin-15 induces skeletal muscle hypertrophy in vitro: implications for treatment of muscle wasting disorders. Exp Cell Res 280:55–63

Quinn LS, Anderson BG, Strait-Bodey L et al (2009) Oversecretion of interleukin-15 from skeletal muscle reduces adiposity. Am J Physiol Endocrinol Metab 296:E191–E202. https://doi.org/10.1152/ajpendo.90506.2008

Quinn LS, Anderson BG, Strait-Bodey L, Wolden-Hanson T (2010) Serum and muscle interleukin-15 levels decrease in aging mice: correlation with declines in soluble interleukin-15 receptor alpha expression. Exp Gerontol 45:106–112. https://doi.org/10.1016/j.exger.2009.10.012

Raschke S, Eckel J (2013) Adipo-myokines: two sides of the same coin—mediators of inflammation and mediators of exercise. Mediat Inflamm 2013:320724. https://doi.org/10.1155/2013/320724

Reihmane D, Dela F (2014) Interleukin-6: possible biological roles during exercise. Eur J Sport Sci 14:242–250. https://doi.org/10.1080/17461391.2013.776640

Reza MM, Subramaniyam N, Sim CM et al (2017) Irisin is a pro-myogenic factor that induces skeletal muscle hypertrophy and rescues denervation-induced atrophy. Nat Commun 8:1104. https://doi.org/10.1038/s41467-017-01131-0

Riddle ES, Bender EL, Thalacker-Mercer AE (2018) Expansion capacity of human muscle progenitor cells differs by age, sex, and metabolic fuel preference. Am J Physiol Cell Physiol 315:C643–C652. https://doi.org/10.1152/ajpcell.00135.2018

Riechman SE, Balasekaran G, Roth SM, Ferrell RE (2004) Association of interleukin-15 protein and interleukin-15 receptor genetic variation with resistance exercise training responses. J Appl Physiol Bethesda Md 97:2214–2219. https://doi.org/10.1152/japplphysiol.00491.2004

Rinnov A, Yfanti C, Nielsen S et al (2014) Endurance training enhances skeletal muscle interleukin-15 in human male subjects. Endocrine 45:271–278. https://doi.org/10.1007/s12020-013-9969-z

Roberts MD, Haun CT, Mobley CB et al (2018) Physiological differences between low versus high skeletal muscle hypertrophic responders to resistance exercise training: current perspectives and future research directions. Front Physiol 9:834. https://doi.org/10.3389/fphys.2018.00834

Roveimiab Z, Lin F, Anderson JE (2019) Emerging development of microfluidics-based approaches to improve studies of muscle cell migration. Tissue Eng Part B Rev 25:30–45. https://doi.org/10.1089/ten.TEB.2018.0181

Rudic RD, Shesely EG, Maeda N et al (1998) Direct evidence for the importance of endothelium-derived nitric oxide in vascular remodeling. J Clin Invest 101:731–736. https://doi.org/10.1172/JCI1699

Salvini TF, Durigan JLQ, Peviani SM, Russo TL (2012) Effects of electrical stimulation and stretching on the adaptation of denervated skeletal muscle: implications for physical therapy. Rev Bras Fisioter Sao Carlos Sao Paulo Braz 16:175–183

Schoenfeld BJ (2010) The mechanisms of muscle hypertrophy and their application to resistance training. J Strength Cond Res 24:2857–2872. https://doi.org/10.1519/JSC.0b013e3181e840f3

Schroeder ET, Villanueva M, West DDW, Phillips SM (2013) 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 45:2044–2051. https://doi.org/10.1249/MSS.0000000000000147

Scott BR, Loenneke JP, Slattery KM, Dascombe BJ (2015) Exercise with blood flow restriction: an updated evidence-based approach for enhanced muscular development. Sports Med Auckl NZ 45:313–325. https://doi.org/10.1007/s40279-014-0288-1

Scott BR, Loenneke JP, Slattery KM, Dascombe BJ (2016) Blood flow restricted exercise for athletes: a review of available evidence. J Sci Med Sport 19:360–367. https://doi.org/10.1016/j.jsams.2015.04.014

Serrano AL, Baeza-Raja B, Perdiguero E et al (2008) Interleukin-6 is an essential regulator of satellite cell-mediated skeletal muscle hypertrophy. Cell Metab 7:33–44. https://doi.org/10.1016/j.cmet.2007.11.011

Shamim B, Hawley JA, Camera DM (2018) Protein availability and satellite cell dynamics in skeletal muscle. Sports Med Auckl NZ 48:1329–1343. https://doi.org/10.1007/s40279-018-0883-7

Shan T, Liang X, Bi P, Kuang S (2013) Myostatin knockout drives browning of white adipose tissue through activating the AMPK-PGC1α-Fndc5 pathway in muscle. FASEB J Off Publ Fed Am Soc Exp Biol 27:1981–1989. https://doi.org/10.1096/fj.12-225755

Siegel AL, Atchison K, Fisher KE et al (2009) 3D timelapse analysis of muscle satellite cell motility. Stem Cells Dayt Ohio 27:2527–2538. https://doi.org/10.1002/stem.178

Siegel AL, Kuhlmann PK, Cornelison DDW (2011) Muscle satellite cell proliferation and association: new insights from myofiber time-lapse imaging. Skelet Muscle 1:7. https://doi.org/10.1186/2044-5040-1-7

Sinha-Hikim I, Roth SM, Lee MI, Bhasin S (2003) Testosterone-induced muscle hypertrophy is associated with an increase in satellite cell number in healthy, young men. Am J Physiol Endocrinol Metab 285:E197–E205. https://doi.org/10.1152/ajpendo.00370.2002

Sinha-Hikim I, Cornford M, Gaytan H et al (2006) Effects of testosterone supplementation on skeletal muscle fiber hypertrophy and satellite cells in community-dwelling older men. J Clin Endocrinol Metab 91:3024–3033. https://doi.org/10.1210/jc.2006-0357

Slysz J, Stultz J, Burr JF (2016) The efficacy of blood flow restricted exercise: a systematic review & meta-analysis. J Sci Med Sport 19:669–675. https://doi.org/10.1016/j.jsams.2015.09.005

Smith LW, Smith JD, Criswell DS (2002) Involvement of nitric oxide synthase in skeletal muscle adaptation to chronic overload. J Appl Physiol Bethesda Md 92:2005–2011. https://doi.org/10.1152/japplphysiol.00950.2001

Smith LR, Meyer G, Lieber RL (2013) Systems analysis of biological networks in skeletal muscle function. Wiley Interdiscip Rev Syst Biol Med 5:55–71. https://doi.org/10.1002/wsbm.1197

Smythe G (2016) Role of growth factors in modulation of the microvasculature in adult skeletal muscle. Adv Exp Med Biol 900:161–183. https://doi.org/10.1007/978-3-319-27511-6_7

Snijders T, Verdijk LB, Smeets JSJ et al (2014) The skeletal muscle satellite cell response to a single bout of resistance-type exercise is delayed with aging in men. Age Dordr Neth 36:9699. https://doi.org/10.1007/s11357-014-9699-z

So B, Kim H-J, Kim J, Song W (2014) Exercise-induced myokines in health and metabolic diseases. Integr Med Res 3:172–179. https://doi.org/10.1016/j.imr.2014.09.007

Sogawa K, Nodera H, Takamatsu N et al (2017) Neurogenic and myogenic diseases: quantitative texture analysis of muscle US data for differentiation. Radiology 283:492–498. https://doi.org/10.1148/radiol.2016160826

Son JS, Kim JH, Kim H-J et al (2016) Effect of resistance ladder training on sparc expression in skeletal muscle of hindlimb immobilized rats. Muscle Nerve 53:951–957. https://doi.org/10.1002/mus.24940

Spangenburg EE, Booth FW (2002) Multiple signaling pathways mediate LIF-induced skeletal muscle satellite cell proliferation. Am J Physiol Cell Physiol 283:C204–C211. https://doi.org/10.1152/ajpcell.00574.2001

Spiering BA, Kraemer WJ, Anderson JM et al (2008) Effects of elevated circulating hormones on resistance exercise-induced Akt signaling. Med Sci Sports Exerc 40:1039–1048. https://doi.org/10.1249/MSS.0b013e31816722bd

Stanford KI, Goodyear LJ (2018) Muscle-adipose tissue cross talk. Cold Spring Harb Perspect Med. https://doi.org/10.1101/cshperspect.a029801

Steensberg A, van Hall G, Osada T et al (2000) Production of interleukin-6 in contracting human skeletal muscles can account for the exercise-induced increase in plasma interleukin-6. J Physiol 529(Pt 1):237–242. https://doi.org/10.1111/j.1469-7793.2000.00237.x

Steensberg A, Keller C, Hillig T et al (2007) Nitric oxide production is a proximal signaling event controlling exercise-induced mRNA expression in human skeletal muscle. FASEB J Off Publ Fed Am Soc Exp Biol 21:2683–2694. https://doi.org/10.1096/fj.06-7477com

Sterczala AJ, Miller JD, Trevino MA et al (2018) Differences in the motor unit firing rates and amplitudes in relation to recruitment thresholds during submaximal contractions of the first dorsal interosseous between chronically resistance-trained and physically active men. Appl Physiol Nutr Metab Physiol Appl Nutr Metab 43:759–768. https://doi.org/10.1139/apnm-2017-0646

Strömberg A, Olsson K, Dijksterhuis JP et al (2016) CX3CL1-a macrophage chemoattractant induced by a single bout of exercise in human skeletal muscle. Am J Physiol Regul Integr Comp Physiol 310:R297–R304. https://doi.org/10.1152/ajpregu.00236.2015

Sudo M, Ando S, Poole DC, Kano Y (2015) Blood flow restriction prevents muscle damage but not protein synthesis signaling following eccentric contractions. Physiol Rep. https://doi.org/10.14814/phy2.12449

Sun L, Lu K, Liu H et al (2013) The effects of endoplasmic reticulum stress response on duck decorin stimulate myotube hypertrophy in myoblasts. Mol Cell Biochem 377:151–161. https://doi.org/10.1007/s11010-013-1581-2

Takada S, Okita K, Suga T et al (2012) Low-intensity exercise can increase muscle mass and strength proportionally to enhanced metabolic stress under ischemic conditions. J Appl Physiol Bethesda Md 113:199–205. https://doi.org/10.1152/japplphysiol.00149.2012

Takarada Y, Tsuruta T, Ishii N (2004) Cooperative effects of exercise and occlusive stimuli on muscular function in low-intensity resistance exercise with moderate vascular occlusion. Jpn J Physiol 54:585–592

Tamura Y, Watanabe K, Kantani T et al (2011) Upregulation of circulating IL-15 by treadmill running in healthy individuals: is IL-15 an endocrine mediator of the beneficial effects of endurance exercise? Endocr J 58:211–215

Tarantino U, Piccirilli E, Fantini M et al (2015) Sarcopenia and fragility fractures: molecular and clinical evidence of the bone-muscle interaction. J Bone Joint Surg Am 97:429–437. https://doi.org/10.2106/JBJS.N.00648

Tatsumi R, Liu X, Pulido A et al (2006) Satellite cell activation in stretched skeletal muscle and the role of nitric oxide and

hepatocyte growth factor. Am J Physiol Cell Physiol 290:C1487–C1494. https://doi.org/10.1152/ajpcell.00513.2005

Tieland M, Trouwborst I, Clark BC (2018) Skeletal muscle performance and ageing. J Cachexia Sarcopenia Muscle 9:3–19. https://doi.org/10.1002/jcsm.12238

Timmerman KL, Lee JL, Fujita S et al (2010) Pharmacological vasodilation improves insulin-stimulated muscle protein anabolism but not glucose utilization in older adults. Diabetes 59:2764–2771. https://doi.org/10.2337/db10-0415

Toigo M, Boutellier U (2006) New fundamental resistance exercise determinants of molecular and cellular muscle adaptations. Eur J Appl Physiol 97:643–663. https://doi.org/10.1007/s00421-006-0238-1

Toth KG, McKay BR, De Lisio M et al (2011) IL-6 induced STAT3 signalling is associated with the proliferation of human muscle satellite cells following acute muscle damage. PLoS ONE 6:e17392. https://doi.org/10.1371/journal.pone.0017392

Trajanoska K, Rivadeneira F, Kiel DP, Karasik D (2019) Genetics of Bone and Muscle Interactions in Humans. Curr Osteoporos Rep 17:86–95. https://doi.org/10.1007/s11914-019-00505-1

Tremblay MS, Copeland JL, Van Helder W (2004) Effect of training status and exercise mode on endogenous steroid hormones in men. J Appl Physiol Bethesda Md 96:531–539. https://doi.org/10.1152/japplphysiol.00656.2003

Tsujihata M, Kinoshita I, Mori M et al (1987) Ultrastructural study of the motor end-plate in botulism and Lambert-Eaton myasthenic syndrome. J Neurol Sci 81:197–213. https://doi.org/10.1016/0022-510x(87)90096-7

Verhovshek T, Sengelaub DR (2010) Trophic effects of brain-derived neurotrophic factor blockade in an androgen-sensitive neuromuscular system. Endocrinology 151:5337–5348. https://doi.org/10.1210/en.2010-0799

Vinel C, Lukjanenko L, Batut A et al (2018) The exerkine apelin reverses age-associated sarcopenia. Nat Med 24:1360–1371. https://doi.org/10.1038/s41591-018-0131-6

Wernbom M, Aagaard P (2019) Muscle fibre activation and fatigue with low-load blood flow restricted resistance exercise-An integrative physiology review. Acta Physiol Oxf Engl. https://doi.org/10.1111/apha.13302

Wernbom M, Apro W, Paulsen G et al (2013) Acute low-load resistance exercise with and without blood flow restriction increased protein signalling and number of satellite cells in human skeletal muscle. Eur J Appl Physiol 113:2953–2965. https://doi.org/10.1007/s00421-013-2733-5

West DWD, Phillips SM (2010) Anabolic processes in human skeletal muscle: restoring the identities of growth hormone and testosterone. Phys Sportsmed 38:97–104. https://doi.org/10.3810/psm.2010.10.1814

West DWD, Burd NA, Tang JE et al (2010) Elevations in ostensibly anabolic hormones with resistance exercise enhance neither training-induced muscle hypertrophy nor strength of the elbow flexors. J Appl Physiol Bethesda Md 108:60–67. https://doi.org/10.1152/japplphysiol.01147.2009

White JP, Gao S, Puppa MJ et al (2013) Testosterone regulation of Akt/mTORC1/FoxO3a signaling in skeletal muscle. Mol Cell Endocrinol 365:174–186. https://doi.org/10.1016/j.mce.2012.10.019

Wilk M, Krzysztofik M, Gepfert M et al (2018) Technical and training related aspects of resistance training using blood flow restriction in competitive sport—a review. J Hum Kinet 65:249–260. https://doi.org/10.2478/hukin-2018-0101

Wolf J, Rose-John S, Garbers C (2014) Interleukin-6 and its receptors: a highly regulated and dynamic system. Cytokine 70:11–20. https://doi.org/10.1016/j.cyto.2014.05.024

Wozniak AC, Anderson JE (2007) Nitric oxide-dependence of satellite stem cell activation and quiescence on normal skeletal muscle fibers. Dev Dyn Off Publ Am Assoc Anat 236:240–250. https://doi.org/10.1002/dvdy.21012

Xia S, Zhang X, Zheng S et al (2016) An update on inflamm-aging: mechanisms, prevention, and treatment. J Immunol Res 2016:8426874. https://doi.org/10.1155/2016/8426874

Yarasheski KE, Campbell JA, Smith K et al (1992) Effect of growth hormone and resistance exercise on muscle growth in young men. Am J Physiol 262:E261–E267. https://doi.org/10.1152/ajpendo.1992.262.3.E261

Yasuda T, Fukumura K, Uchida Y et al (2015) Effects of low-load, elastic band resistance training combined with blood flow restriction on muscle size and arterial stiffness in older adults. J Gerontol A Biol Sci Med Sci 70:950–958. https://doi.org/10.1093/gerona/glu084

Ye J (2015) Beneficial metabolic activities of inflammatory cytokine interleukin 15 in obesity and type 2 diabetes. Front Med 9:139–145. https://doi.org/10.1007/s11684-015-0377-z

Yeo NH, Woo J, Shin KO et al (2012) The effects of different exercise intensity on myokine and angiogenesis factors. J Sports Med Phys Fitness 52:448–454

Yoon M-S (2017) mTOR as a key regulator in maintaining skeletal muscle mass. Front Physiol 8:788. https://doi.org/10.3389/fphys.2017.00788