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The Molecular Bases of Training Adaptation

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Abstract

Skeletal muscle is a malleable tissue capable of altering the type and amount of protein in response to disruptions to cellular homeostasis. The process of exercise-induced adaptation in skeletal muscle involves a multitude of signalling mechanisms initiating replication of specific DNA genetic sequences, enabling subsequent translation of the genetic message and ultimately generating a series of amino acids that form new proteins. The functional consequences of these adaptations are determined by training volume, intensity and frequency, and the half-life of the protein. Moreover, many features of the training adaptation are specific to the type of stimulus, such as the mode of exercise. Prolonged endurance training elicits a variety of metabolic and morphological changes, including mitochondrial biogenesis, fast-to-slow fibre-type transformation and substrate metabolism. In contrast, heavy resistance exercise stimulates synthesis of contractile proteins responsible for muscle hypertrophy and increases in maximal contractile force output. Concomitant with the vastly different functional outcomes induced by these diverse exercise modes, the genetic and molecular mechanisms

of adaptation are distinct. With recent advances in technology, it is now possible to study the effects of various training interventions on a variety of signalling proteins and early-response genes in skeletal muscle. Although it cannot presently be claimed that such scientific endeavours have influenced the training practices of elite athletes, these new and exciting technologies have provided insight into how current training techniques result in specific muscular adaptations, and may ultimately provide clues for future and novel training methodologies. Greater knowledge of the mechanisms and interaction of exercise-induced adaptive pathways in skeletal muscle is important for our understanding of the aetiology of disease, maintenance of metabolic and functional capacity with aging, and training for athletic performance. This article highlights the effects of exercise on molecular and genetic mechanisms of training adaptation in skeletal muscle.

1. The Specificity of Exercise Responses

Skeletal muscle is a malleable tissue capable of altering the type and amount of protein in response to disruptions to cellular homeostasis. The complex process of exercise-induced adaptation in skeletal muscle involves specific signalling mechanisms initiating replication of DNA genetic sequences that enable subsequent translation of the genetic code into a series of amino acids to create new proteins.[1] The functional consequences of these adaptations are determined by training volume, intensity and frequency, and the half-life of the protein. Moreover, many features of the training adaptation are specific to the type of stimulus, such as the mode of exercise.[2,3]

Contraction generates transient increases in the quantity of messenger RNA (mRNA) that, for a multitude of genes, typically peaks 3–12 hours post-exercise and returns to basal levels within 24 hours.[4-6] This directional change in mRNA is generally the same as the encoded protein during adaptation to a new steady-state level.[7] Therefore, frequent bouts of exercise result in acute increases in transcriptional activity and subsequent protein synthesis. Consequently, long-term adaptation to training is probably due to the cumulative effects of each short-term exercise bout leading to a change in the steady-state level of specific proteins and a new functional threshold.[3]

Prolonged endurance training elicits a variety of metabolic and morphological changes, including mitochondrial biogenesis,[8] fast-to-slow fibre-type transformation[9] and substrate metabolism.[10] In contrast, heavy resistance exercise stimulates adaptive machinery responsible for muscle hypertrophy[11] and maximal contractile force output.[12] Concomitant with the vastly different functional outcomes induced via these diverse exercise modes, the genetic and molecular mechanisms of adaptation are distinct. Each mode of exercise results in activation and/or repression of specific pathways and subsets of genes. Performing multiple bouts of each training mode in isolation will ultimately generate a developmental history in the muscle fibres, producing a specific exercise-induced phenotype associated with long-term training.[13] Therefore, aerobic endurance and heavy resistance training represent opposite ends of an adaptation continuum. Greater knowledge of the mechanisms and interaction of exercise-induced adaptive pathways in skeletal muscle is important for our understanding of the aetiology of disease, maintenance of metabolic and functional capacity with aging, and training for athletic performance.

2. Signal Transduction Pathways in Skeletal Muscle

The process of converting a mechanical signal generated during contraction to a molecular event that promotes adaptation in a muscle cell involves the upregulation of primary and secondary messengers that initiate a cascade of events that result in activation and/or repression of specific signalling pathways regulating exercise-induced gene expression and protein synthesis/degradation.[14]

2.1 Putative Primary Messengers

Elucidation of the precise mechanisms that enable skeletal muscle cells to interpret and respond to contraction has proved elusive. Indeed, the complexity of this process is complicated by (i) the proposed mechanoreceptors that connect the neuronal, mechanical and biochemical events; and (ii) the numerous cellular candidates as potential primary messengers that transduce the mechanical signal. In addition, it is unlikely that these primary signalling messengers act in isolation, and probably results in an intricate multifaceted signal with redundancy and cross-talk. Nevertheless, there are numerous putative messengers emerging, including, but not limited to, mechanical stretch, calcium flux, redox state and phosphorylation state.

2.1.1 Mechanical Stretch

Mechanical stimuli modulate cell function and directly affect tissue form and function.[15] Technical limitations currently prevent accurate measurement of the effect of mechanical stimuli on mechanotransduction *in vivo*. However, the use of passive stretch on muscle *in vitro* and *in situ* demonstrates that mechanical stimuli induce numerous adaptive processes. Mechanical perturbation of skeletal muscle mediates activation of the calcineurin, mitogen activated protein kinase (MAPK) and insulin-like growth factor (IGF) signalling cascades.[16,17] Moreover, it has become apparent that muscle cells can distinguish between mechanical forces acting on the cell. Work by Kumar and colleagues[16] revealed that axial versus transverse stress produced activation of distinct signalling intermediates despite the same magnitude of mechanical stress applied to the muscle fibre. Similarly, Hornberger and co-workers[17] observed unique activation of signalling proteins when comparing cyclic uni- and multi-axial stretch. The rapid and differentiated mechanochemical conversion induced by distinct models of mechanical stress strongly suggests the existence of mechanotransduction specificity. Therefore, the signalling events initiated by mechanical load with exercise (i.e. frequency and intensity of contraction) are likely to contribute to the specificity of exercise-induced adaptation, and implicates mechanical stress/tension as a significant primary messenger (figure 1).

2.1.2 Calcium

Neural activation of skeletal muscle generates an action potential that results in Ca^{2+} release from the sarcoplasmic reticulum, while cessation of the action potential initiates the transport of Ca^{2+} out of the cytosol back to the sarcoplasmic reticulum. The rate and capacity of Ca^{2+} release and uptake is

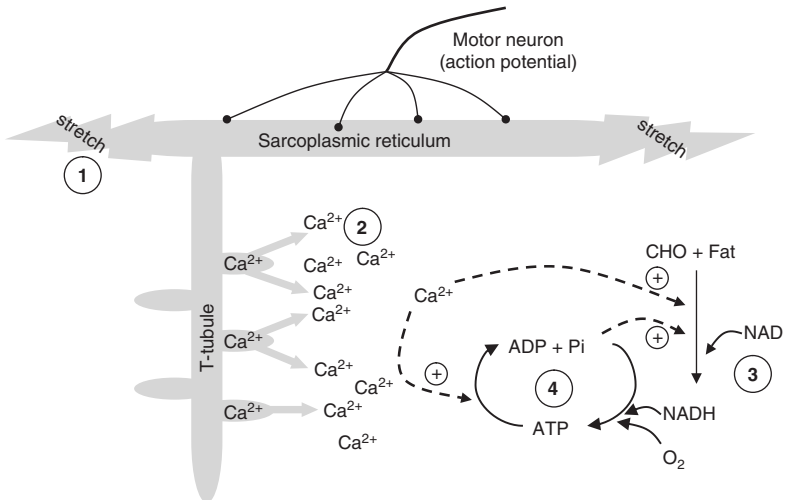

Fig. 1. Metabolic and mechanical signals believed to play key roles as primary messengers in mechanotransduction: (**1**) mechanical stretch; (**2**) Ca^{2+} flux; (**3**) redox potential; and (**4**) phosphorylation potential (reproduced from Spriet,[18] with permission from Lippincott, Williams & Wilkins). **ADP** = adenosine diphosphate; **ATP** = adenosine triphosphate; **Ca^{2+}** = calcium; **CHO** = carbohydrate; **NAD** = nicotinamide adenine dinucleotide; **NADH** = reduced form of NAD; **Pi** = inorganic phosphate.

altered by contractile activity (figure 1). Prolonged moderate-intensity (≈60–70% of maximal oxygen uptake [$\dot{V}O_{2max}$]) exercise increases sarcoplasmic reticulum Ca^{2+} uptake and the number of active pumps re-sequestering Ca^{2+}.[19] In contrast, a single bout of high-intensity (>100% $\dot{V}O_{2max}$) or fatiguing exercise generates a 20–50% transient decrease in Ca^{2+} uptake and release, returning to basal levels after 60 minutes' recovery.[20] These acute alterations in cytosolic calcium concentration ($[Ca^{2+}]$) may also elicit secondary events following a return to resting/basal values. Interestingly, repeated bouts of exercise have been shown to induce an adaptive response, resulting in less perturbation in Ca^{2+} release and uptake, and subsequently improved Ca^{2+} cycling and resistance to fatigue.[21] Taken together, these findings suggest that the amplitude and duration of Ca^{2+} flux is regulated by the duration and frequency of the contractile stimulus. For example, endurance exercise likely results in extended periods of moderately elevated $[Ca^{2+}]$, while resistance exercise would generate short cycles of significantly higher intracellular $[Ca^{2+}]$.[22] It is plausible to suggest that the specific cytosolic Ca^{2+} transient will also determine subsequent downstream events such as gene expression and protein synthesis.[23] Therefore, Ca^{2+} is an important regulator in the specificity of exercise-induced adaptive events, and its effects are likely to be altered by the mode, intensity and volume of exercise.

2.1.3 Redox Potential

The redox mechanism (nicotinamide adenine dinucleotide [NAD] : reduced form of NAD [NADH] ratio) is predominantly a result of the catabolic reactions occurring with glycolytic and lipolytic metabolism in the mitochondria (figure 1; for review see Smith and Reid[24]). The maintenance of redox potential produces volatile free oxygen molecules (e.g. reactive oxygen species [ROS]), and this oxidant activity is buffered by multiple antioxidant systems in skeletal muscle such as glutathione peroxidase, manganese superoxide dismutase and catalase.[25] Because of the increase in demand for oxygen and activity of metabolic pathways, exercise represents a stimulus capable of generating high levels of ROS. Although a direct cause-and-effect relationship has not been established, indirect evidence suggests that oxidative stress may modulate exercise-induced adaptive signalling.[26]

Redox potential and resultant free-radical synthesis during and after exercise may regulate adaptive pathways in two ways. In the first instance, redox state may act as a primary messenger through a direct effect on transcriptional regulation and DNA binding specificity of transcription factors, including nuclear factor kappa B (NFκB) and activator protein 1 (AP1).[26,27] In addition, because of the apparent effect of ROS on numerous elements of cellular function, redox state may act indirectly on signalling machinery via its effect on mitochondrial metabolism and a decrease in myofilament Ca^{2+} sensitivity.[24]

2.1.4 Phosphorylation Potential

Resynthesis of adenosine triphosphate (ATP) via restoration of its high energy phosphate bonds is generated by oxidative phosphorylation and/or glycolysis. Subsequently, concentrations of metabolites related to the maintenance of muscle phosphorylation potential, i.e. [ATP]/[ADP][Pi] (where ADP = adenosine diphosphate and Pi = inorganic phosphate) provide feedback signals to balance ATP production with ATP consumption.[28] Indeed, intracellular concentrations of free adenosine monophosphate (AMP) are an important regulator of energy consumption and regenerating pathways.[29] Strong evidence exists to demonstrate an inverse relationship between metabolite concentrations and contractile intensity and duration during exercise *in vivo*.[30-32]

Any cellular stress that inhibits ATP synthesis or accelerates ATP consumption (e.g. exercise-induced contraction) and subsequently increases the AMP : ATP ratio initiates numerous downstream molecular events in skeletal muscle.[33] As a primary messenger for adaptive signalling, phosphorylation state appears to exert its effect principally via a potent secondary messenger, the 5′adenosine monophosphate activated protein kinase (AMPK).[33] Therefore, phosphorylation potential and subsequent AMPK activation may ultimately regulate multiple cell signalling cascades for such diverse processes as glucose uptake, fatty acid oxidation, hypertrophy and gene expression.[34] This

ubiquitous kinase is discussed in detail in section 2.2.1.

2.2 Secondary Messengers

Following initiation of the primary signal, additional kinases/phosphatases are activated to mediate the exercise-induced signal. Numerous signalling cascades exist in mammalian cells and these pathways are highly regulated at multiple levels, with substantial cross-talk between pathways producing a highly sensitive, complex transduction network. This article is restricted to consideration of the AMPK, calmodulin/calcineurin, IGF and NFκB-tumour necrosis factor-α (TNFα) signalling pathways in skeletal muscle.

2.2.1 Adenosine Monophosphate Activated Protein Kinase-Mediated Signalling

The role of AMPK in skeletal muscle continues to be the subject of intense scientific enquiry, and the reader is referred to several recent reviews detailing the mechanisms of activation and the specific role of AMPK isoforms in skeletal muscle.[33,35] Briefly, AMPK is directly activated by AMP and consequently is sensitive to changes in cellular AMP : ATP ratios.[34] Acute activation of AMPK in response to cellular energy depletion (e.g. skeletal muscle contraction) initiates actions to both conserve and generate ATP.[34] AMPK is implicated in enhancing ATP production by stimulating insulin-independent glucose uptake[36-38] and increasing fat oxidation.[39,40] Additional effects of contraction-mediated AMPK activation are less clear, but may result in multiple adaptive events, including altered protein synthesis and gene expression. AMPK has been linked to the control of gene expression by activating transcription factors associated with mitochondrial fatty acid oxidation, and with the inhibition of protein synthesis by downregulating components of the insulin/IGF signalling pathway.[40-43]

Current evidence suggests that isoform-specific AMPK activation occurs in a time-, intensity- and fibre-type-specific manner, and exercise-induced contraction of skeletal muscle *in vivo* has been clearly shown to upregulate AMPK activity.[44-53] Findings *in vivo* following treadmill running support the contention that AMPK activation is greater in red oxidative than in white glycolytic muscle.[47,54] Importantly, interpretation of the available literature with regard to fibre-type-specific AMPK activity is limited because many studies have incorporated exercise protocols unlikely to significantly recruit white muscle (i.e. endurance running or swimming). Consequently, our current understanding of fibre-type specific AMPK responses is unresolved.

Commensurate with its proposed role as an 'energy sensing' kinase, increased AMPK activation has been shown with submaximal aerobic exercise and increasing treadmill speed and cycling power.[54-56] Indeed, endurance exercise-induced activation of AMPK is predictable, given its ability to increase ATP regeneration via fat oxidation to meet the demands of prolonged low-intensity contraction. Interestingly, this exercise response seems to be dependent on the adaptive state of the muscle, as short- and long-term aerobic training reduces the acute AMPK response to prolonged and intermittent submaximal exercise undertaken at the same (pre-training) absolute work rate.[50,53] However, the AMPK response in endurance-trained athletes may be conserved with adequate overload. In this regard, intense (≈90% $\dot{V}O_{2max}$) interval training has been shown to increase AMPK activity in highly trained cyclists.[57] Furthermore, AMPK phosphorylation is also significantly upregulated following short duration (≈30 seconds) supramaximal sprint cycling, probably because of to the extensive and rapid reduction in cellular ATP.[58]

Few studies that have investigated AMPK signalling in humans have incorporated resistance training as a stimulus. Hence, our knowledge of AMPK signalling following this mode of contractile activity is limited. Of those studies that have employed resistance training protocols, several reported increased AMPK phosphorylation and gene expression following both a single bout and repeated bouts of exercise.[45,59,60] Resistance exercise-induced changes in AMPK phosphorylation may reflect an increase in insulin-independent cellular glucose uptake and transport. However, the physiological significance of increased AMPK following resistance training has yet to be determined.

Differences in AMPK responses between endurance and resistance training have not been extensively investigated. However, recent work by Atherton et al.[46] using an animal model indicates mode-

specific AMPK activation with acute bouts of 'endurance-like' and 'resistance-like' contraction. Using electrical stimulation to mimic endurance or resistance loading, these workers showed increased AMPK phosphorylation immediately and 3 hours post-exercise following 'endurance-like', but not 'resistance-like', contraction in slow-twitch soleus and fast-twitch extensor digitorum longus muscle. However, we have recently reported a blunting of the AMPK response when highly trained cyclists and power-lifters undertook exercise in their habitual discipline.[61] Conversely, when these athletes 'crossed over' and performed a bout of unfamiliar exercise (i.e. resistance training and cycling, respectively), we observed an increase in AMPK phosphorylation in both groups,[61] suggesting that the adaptive phenotype and overload stimulus rather than mode of exercise *per se* alters the AMPK signalling response. Nonetheless, given the dissimilar functional adaptive outcomes with long-term endurance versus resistance training, the possibility exists that AMPK signalling may emerge as a key intermediate for the divergent adaptation with these different exercise modes.

2.2.2 Ca^{2+} Calmodulin-Dependent Kinase/ Calcineurin Signalling

The Ca^{2+}-calmodulin-dependent serine/threonine kinases (CaMK), a group of single and multifunctional kinases, detect and respond to $[Ca^{2+}]$.[23] The specific kinases from the CaMK family found in skeletal muscle are not well defined, but evidence indicates that CaMKII and IV are expressed in skeletal muscle.[62,63] CaMKII and IV have been linked with activation of gene expression of contractile and mitochondrial proteins, respectively.[63,64] CaMKII activity has been shown to increase with stretch overload and wheel running animal models[64] and with cycling exercise in humans.[62] Indeed, it appears that CaMKII is the predominant multifunctional CaMK in response to endurance exercise, and is rapidly upregulated after commencing exercise in an intensity-dependent manner.[65] Conclusive mechanistic data linking the effect of CaMK activation to cellular adaptation are currently lacking, but it has been suggested that downstream effects may be mediated, at least in part, through nuclear factor of activated T cells (NFAT) signalling and histone deacetylase nuclear extrusion via calcium signalling (figure 2).[23,66]

Prolonged, low-amplitude intracellular calcium transients have been shown to increase calcineurin activity that dephosphorylates and activates the transcriptional promoter NFAT to upregulate gene expression.[67] Calcineurin has been implicated in several adaptive responses inducing muscle fibre growth/regeneration and slow fibre-type gene expression.[68-70] Calcineurin appears to act as a co-regulator of muscle hypertrophy with IGF and may also contribute to myogenic proliferation and differentiation of satellite cells during skeletal muscle regeneration.[68-71] Use of calcium/calmodulin inhibitors suppresses growth of overloaded muscle fibres, while calcineurin over expression reduces disuse atrophy.[70,72] In addition, calcineurin is involved in fibre-type plasticity and fast-to-slow phenotype transformation.[67,73-75] Indeed, it has been proposed that calcineurin-induced gene expression of slow fibre and oxidative genes may result in the acquisition of a more metabolically efficient phenotype.[67,76,77] Such diverse calcineurin-regulated adaptive pathways appear paradoxical (i.e. hypertrophy vs oxidative phenotype), but may represent alternating adaptive responses that are specific to the intensity and duration of contractile activity.

While research investigating Ca^{2+}-calmodulin-calcineurin-dependent signalling has provided

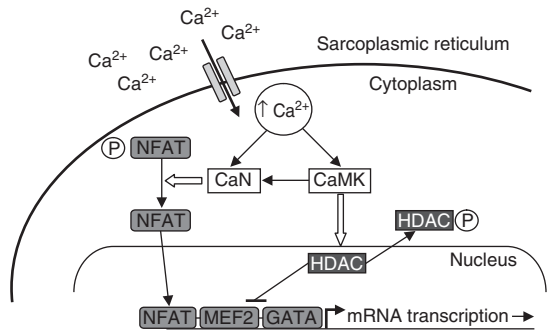

Fig. 2. Proposed mechanisms for calcium-dependent increases in gene expression with skeletal muscle contractile activity. Bars denote inhibition and arrows denote activation. **Ca^{2+}** = calcium; **CaMK** = calmodulin kinase; **CaN** = calcineurin; **GATA** = glutamyl-tRNA amidotransferase; **HDAC** = histone deacetylase; **MEF2** = myocyte enhancer factor 2; **mRNA** = messenger RNA; **NFAT** = nuclear factor of activated T cells; **P** = phosphorylation; ↑ indicates increase.

mechanistic insight into the role of this pathway in skeletal muscle, it should be noted that our current understanding appears to be limited to results from cell culture and transgenic animal models. Importantly, few studies have investigated the role of Ca^{2+}-dependent signalling in humans, and the effect of exercise on calmodulin-calcineurin pathways remains to be established.

2.2.3 Insulin/Insulin-Like Growth Factor Signalling Pathway

The insulin/IGF signalling pathway incorporates many of the molecular components critical to our current understanding of muscle proteolysis and regulation of hypertrophy and atrophy processes.[78] Moreover, many of these components have additional roles for the regulation of glucose uptake, glycogen synthesis, and cell growth and differentiation.[79] The expression and importance of IGF-1 in skeletal muscle has been demonstrated in a variety of models from cell culture to human *in vivo*.[69,80-84] Contractile activity in skeletal muscle stimulates the secretion of IGF-1, which acts as an autocrine/paracrine growth factor, binding to its membrane receptor and initiating a cascade of molecular events (figure 3).[78,85] The following sections focus on IGF signalling intermediaries Akt and its associated substrate targets.

Akt/Protein Kinase B

There are three isoforms of the serine/threonine Akt family, two of which (Akt1 and 2) are primarily expressed in skeletal muscle.[86] Furthermore, the different Akt isoforms appear to have distinct functions: Akt1 has been associated with muscle hypertrophy, whereas Akt2 has been implicated in signalling to glucose transport.[79] Following translocation to the cell membrane, Akt is phosphorylated by 3′-phosphoinositide-dependent protein kinase 1 (PDK1) at threonine^{308}, but requires secondary phosphorylation at serine^{473} for full activation.[87]

Akt has numerous molecular targets commensurate with its varied physiological functions, including those involved in (i) protein synthesis (mammalian target of rapamycin [mTOR], tuberous sclerosis complex 2 [TSC2], glycogen synthase kinase 3 [GSK3]); (ii) atrophy (forkhead box O1 [FoxO1]); and (iii) glucose transport (Akt substrate of 160 kDa

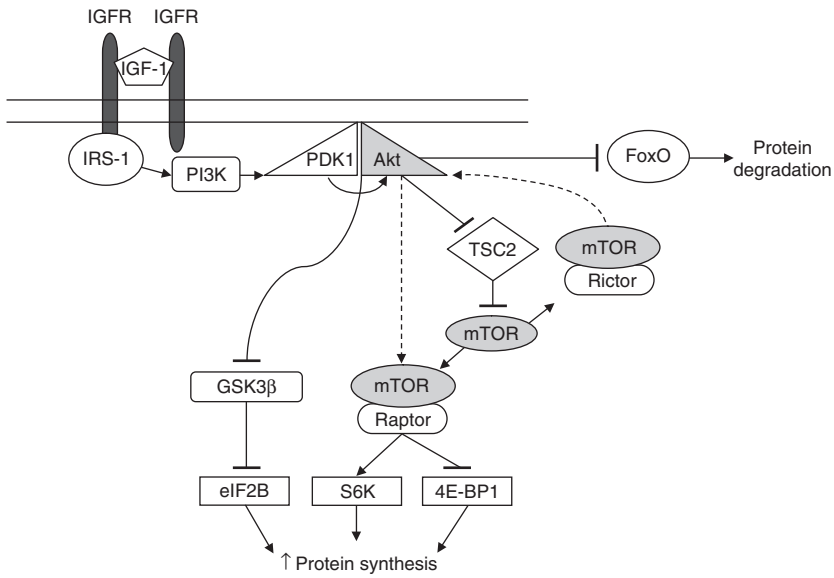

Fig. 3. Simplified insulin-like growth factor (IGF)-1 signalling pathway from receptor binding to protein synthesis. Arrows designate that phosphorylation activates the substrate (dashed line represents putative direct activation) and bars denote inhibition. **4E-BP1** = eukaryotic initiation factor 4E-binding protein; **eIF2B** = eukaryotic initiation factor 2B; **FoxO** = forkhead box O; **GSK3**β = glycogen synthase kinase 3β; **IGF-1** = insulin-like growth factor-1; **IGFR** = insulin-like growth factor receptor; **IRS-1** = insulin receptor substrate-1; **mTOR** = mammalian target of rapamycin; **PDK1** = 3′-phosphoinositide-dependent protein kinase 1; **PI3K** = phosphatidylinositol-3-OH kinase; **S6K** = ribosomal protein S6 kinase; **TSC2** = tuberous sclerosis complex 2; ↑ indicates increase.

[AS160]).[82,84,88-91] There is strong evidence that the Akt-mTOR pathway mediates hypertrophy in skeletal muscle via activation of translation initiation and increased ribosomal protein content.[84,88,92,93] In addition, Akt regulation of AMPK activity and direct phosphorylation of TSC2 and GSK3β may suppress their role as inhibitors of protein synthesis.[84,90,91,94,95] AMPK phosphorylates TSC2, which subsequently inhibits the hypertrophic actions of mTOR, while GSK3β prevents activation of eukaryotic initiation factor (eIF) 2B.[94,96] Thus, in addition to $mTOR^{ser2448}$ phosphorylation, Akt may also indirectly enhance translation initiation and protein synthesis through inhibition of AMPK-TSC2 and GSK3β. Similarly, phosphorylation of the nuclear transcription factor FoxO by phosphatidylinositol-3-OH kinase (PI3K)-Akt has been shown to sequester FoxO from the nucleus to the cytosol, preventing transcription of atrophy genes responsible for degradation of contractile protein, thereby mediating a protective effect on skeletal muscle by downregulating pathways of protein degradation.[81,82,97]

There are conflicting data regarding Akt responses to exercise in skeletal muscle (see table I). Moreover, *in vivo* contraction after running and resistance training has produced conflicting findings where Akt has been reported to increase or remain unchanged in response to exercise. Notably, Bolster et al.[98] examined the time-course of Akt response to resistance exercise in rodent muscle and observed peak Akt phosphorylation 5–15 minutes following a bout of resistance training. Conversely, Dreyer and colleagues[59] have recently shown an increase in Akt phosphorylation 60 minutes after an acute bout of resistance training in humans. In addition, work by others[99-101] has shown that moderate duration (30–60 minutes) low-intensity (≈70% $\dot{V}O_{2max}$) and high-intensity (≈125% $\dot{V}O_{2max}$) cycling exercise is sufficient to increase Akt phosphorylation in humans. In contrast, Widegren and co-workers[102] found no change in Akt activity 15 minutes post-exercise after 60 minutes of cycling at 70% $\dot{V}O_{2max}$. Similarly, others[59,103,104] have reported a significant increase in Akt phosphorylation following resis-

Table I. Summary of research investigating Akt responses to exercise in skeletal muscle

Study	Stimulus	Results
Human		
Leger et al.[104]	Resistance 2–3 days/week × 8 weeks	P – 1.4-fold increase
Dreyer et al.[59]	Resistance 10 × 10 leg extensions, 70% 1RM	P – 100% increase
Eliasson et al.[105]	Resistance (i) 4 × 6 ECC; (ii) 4 × 6 CON	P – no change
Coffey et al.[61]	Cycle (i) 60 min (≈70% $\dot{V}O_{2max}$); (ii) resistance 8 × 5 maximal leg extensions	P – (i) 50% increase; (ii) no change
Wilson et al.[99]	Cycle 60 min, ≈70% $\dot{V}O_{2max}$	P – 50% increase
Creer et al.[103]	Resistance 3 × 10, ≈70% 1RM	P – 1.5-fold increase
Sakamoto et al.[100]	Cycle (i) 30 min, ≈75% $\dot{V}O_{2max}$; (ii) 6 × 60 sec, 125% $\dot{V}O_{2max}$	A – increase (i) 75% $\dot{V}O_{2max}$ = 40%; (ii) 125% $\dot{V}O_{2max}$ = 110%
Thorell et al.[101]	Cycle 60 min, ≈70% $\dot{V}O_{2max}$	P – 180% increase
Widegren et al.[102]	Cycle 60 min one-leg, ≈70% $\dot{V}O_{2max}$	A – no change
Rat		
Williamson et al.[106]	Treadmill 10% grade, 26 m/min for 10, 20, 30 min	P – no change
Reynolds et al.[107]	Voluntary wheel running (3 months)	P + T – 45–50% increase
Krisan et al.[108]	Resistance 3 × 10, 75% 1RM 3/week (12 weeks)	A + T – no change
Bolster et al.[98]	Resistance 1 × 50 each day for 4 days	P – ≈200% increase
Sakamoto et al.[109]	Treadmill (i) 60 min, 20 m/min + 12% grade; (ii) 16 m/min, grade increased 1% every 2 min to fatigue	A – increase (i) 60 min = 80–150%; (ii) fatigue = 150–150%
Markuns et al.[110]	Treadmill 5, 10, 30, 60 min, 25 m/min (10% grade)	A + P = no change
Mouse		
Wojtaszewski et al.[111]	Treadmill 60 min, 22 m/min (10% grade)	P – no effect

A = activity; **CON** = concentric; **ECC** = eccentric; **P =** phosphorylation; **RM** = repetition maximum; **T** = total protein; **$\dot{V}O_{2max}$** = maximal oxygen uptake.

tance training, while we[61] and others[105] have seen a distinct lack of response to this mode of exercise in humans. Indeed, work from our laboratory has shown diverse Akt activation with endurance and resistance exercise in athletes with divergent training history.[61] Thus, establishing the exercise-specific response and associated time-course of Akt activation remains elusive. These conflicting results bring into question our current understanding of the specific role and functions of Akt in contraction-mediated training responses. Differences in the contractile stimulus, timing of muscle tissue collection and isoform-specific response may have contributed to the diverse and conflicting findings. Moreover, experimental design, mixed fibre-type samples, and mode and intensity/duration of contractile activity may partly explain some of these discordant findings.

While there is strong evidence for Akt as a critical regulator of adaptation in skeletal muscle, defining and validating its isoform-specific role with *in vivo* exercise models remains elusive. Heavy resistance training increases muscle tension and hypertrophy, while endurance training increases substrate turnover and utilisation. Therefore, the increase in Akt observed with diverse exercise modes described previously may be expected considering Akt's putative regulation of protein synthesis and glucose transport, respectively. Indeed, Akt appears to be a primary signalling mediator of training-specific adaptation to both endurance and resistance training in skeletal muscle.

Mammalian Target of Rapamycin

Protein complexes involving mTOR are capable of sensing diverse signals, and produce a multitude of responses including mRNA translation, ribosomal biogenesis and nutrient metabolism.[112] Two mTOR protein complexes exist where mTOR binds with a G-β-L protein and either a rapamycin-sensitive raptor or a rictor protein.[87,113,114] mTOR-raptor complex is a positive regulator of cell growth, while mTOR-rictor appears to have a key role in Akt activation and actin cytoskeleton regulation (figure 3).[114-117]

In addition to Akt, upstream regulators of mTOR-raptor include the Ras homologue enriched in brain (Rheb) G protein.[118] Rheb is in turn regulated upstream by the TSC1/2 complex and has been shown to regulate mTOR signalling and its subsequent downstream targets.[96,119] Primary downstream targets of mTOR-raptor include p70 ribosomal protein S6 kinase (p70 S6K), eIF4E-binding protein (4E-BP1) and eIF4B, which links mTOR with mRNA translation and increased protein synthesis and cell size.[120-122]

Overloaded plantaris muscle following surgical removal of synergist muscles has been shown to increase mTOR phosphorylation and total protein content in rodent skeletal muscle.[123,124] Work by Parkington et al.[125,126] and Atherton et al.[46] has used intermittent high-frequency electrical stimulation (60 × 3 seconds, 100Hz) and induced significant increases in mTOR phosphorylation in a number of different muscle groups. Conversely, no change in mTOR phosphorylation was seen following sustained low-frequency electrical stimulation (3 hours, 10Hz), suggesting a tension-specific contractile response.[46] It should be noted that these contractile stimuli may not represent physiological loading, as voluntary wheel running and resistance training in rodents have both been shown to increase mTOR phosphorylation.[98,107] It is difficult to reconcile an increase in mTOR activity following an endurance exercise stimulus such as voluntary wheel running, although emerging evidence suggests that mTOR may be involved in regulating mitochondrial function.[127] In contrast, increased mTOR activation following resistance training seems plausible, given its proposed role in protein synthesis in response to a hypertrophy stimulus.[98] Few studies have investigated the activation of mTOR in skeletal muscle of humans *in vivo*. However, recently Dreyer et al.[59] and Leger et al.[104] observed an increase in mTOR phosphorylation following an acute bout of resistance exercise and 8 weeks' long-term resistance training in humans, respectively, providing strong evidence for the role of mTOR in anabolic processes following resistance training.

p70 Ribosomal Protein S6 Kinase and Eukaryotic Initiation Factor 4E-Binding Protein

The most well defined effectors of Akt-mTOR signalling are the proteins implicated in translational control: ribosomal protein S6 kinase (S6K) and eIF4E-binding protein (4E-BP1).[122,128] Mammalian cells express two S6K isoforms (S6K1 and 2), and

the S6K1 isoform subsequently has duel cytosolic (p70 S6K) and nuclear (p85 S6K) complexes.[122] S6K appears to function downstream of mTOR-raptor, and rodent knockout models have revealed that of the two isoforms, S6K1 predominantly regulates cell size in skeletal muscle.[120,129] mTOR-raptor also regulates and suppresses 4E-BP1 via hyperphosphorylation to derepress 4E-BP1 inhibition of translation initiation cap binding protein eIF4E.[112,130]

S6K exerts its effect through multiple substrate targets, and has been implicated in orchestrating the regulation of numerous cellular functions (figure 4).[122] Numerous studies provide compelling support for the fundamental role of p70 S6K in skeletal muscle hypertrophy.[22,46,88,131,132] Early work by Baar and Esser[22] established a strong association between increased p70 S6K activity and skeletal muscle hypertrophy following 6 weeks of high-frequency electrical stimulation. Subsequently, work from Bodine and co-workers[88] used surgical ablation and pharmacological intervention to highlight the important role for p70 S6K in skeletal muscle hypertrophy processes. Results of other studies reveal that the exercise-induced p70 S6K response occurs with a resistance training-like stimulus, and that endurance exercise does not upregulate p70 S6K activity.[46,61,131,133] Indeed, recent work showing increased p70 S6K phosphorylation with stretch-activated mechanotransduction in skeletal muscle suggests that eccentric loading may be critical for S6K1 activation, and therefore hypertrophy.[17,134,135] Studies performed on humans support

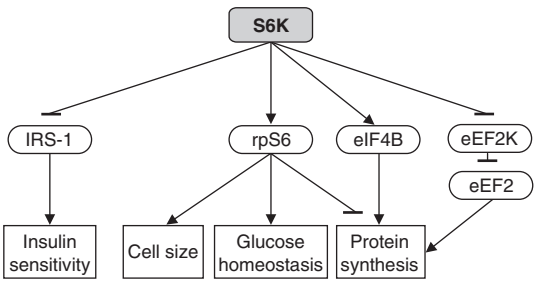

Fig. 4. Putative downstream targets and functions of ribosomal protein S6 kinase (S6K). Bars denote inhibition, arrows denote activation. **eEF2** = eukaryotic elongation factor 2; **eEF2K** = eukaryotic elongation factor 2 kinase; **eIF4B** = eukaryotic initiation factor 4B; **IRS-1** = insulin receptor substrate-1; **rpS6** = ribosomal protein S6.

the results of investigations undertaken on rodents in which upregulation of S6K1 and p70 S6K in skeletal muscle has been observed following an acute bout of resistance training.[59-61,105] The long-term regulation of hypertrophy and other cell processes by S6K1 is less clear, as this kinase may promote reciprocal effects on protein synthesis and repress IGF signalling via a negative feedback loop through insulin receptor substrate (IRS)-1 phosphorylation (figure 4).[122]

Given the well documented coregulation by mTOR-raptor, it is not surprising that 4E-BP1 phosphorylation in skeletal muscle emulates that of S6K1 to a large extent. Studies utilising surgical ablation and high-frequency electrical stimulation consistently show an increase in 4E-BP1 phosphorylation in skeletal muscle in rodents.[46,88,123] Furthermore, as translation initiation cap binding is prevented when dephosphorylated 4E-BP1 is bound to eIF4E, skeletal muscle overload has also been shown to produce a decrease in 4E-BP1-eIF4E binding.[88,133] Significant increases in phosphorylation of 4E-BP1 have also been observed following several resistance exercise models.[128,133] Conversely, an endurance-like stimulus has been shown to decrease 4E-BP1 phosphorylation, indicating a negative effect of endurance training on translational machinery and protein synthesis.[46] Interestingly, Koopman and colleagues[60] recently observed reduced 4E-BP1 phosphorylation (activation) immediately after and 2 hours after an acute bout of resistance training. Similarly, Dreyer and co-workers[59] also showed reduced 4E-BP1 phosphorylation following resistance exercise. Notably, these studies employed sedentary subjects and reported elevated AMPK activity, suggesting the training status of the subjects may have generated greater metabolic stress during intermittent high-intensity contractions. Increased AMPK activity in untrained subjects following resistance exercise may alter the early adaptive response of various kinases involved in protein synthesis.

Taken together, the results of the investigations discussed provide evidence for the resistance training-induced increase in protein synthesis via IGF signalling, but may also include other currently unknown kinases acting directly on mTOR-raptor or its downstream kinases. Furthermore, endurance

training promotes Akt-mediated glucose transport, but not hypertrophy signalling, and appears to have a significant negative effect on the translational machinery.

2.2.4 Cytokine Signalling

Cytokines are small polypeptides released at the site of inflammation in response to numerous factors, including cachexia, sepsis and exercise-induced muscle damage.[78,136] Several cytokines have been implicated in initiating protein degradation and suppression of protein synthesis following injury in skeletal muscle, most notably TNFα.

Tumour Necrosis Factor-α

Elevated TNFα concentration generates an increase in the activity of ubiquitin-conjugated protein degradation and inhibits insulin/IGF-mediated protein synthesis.[137-140] Furthermore, TNFα negatively affects anabolic processes by destabilising myogenic differentiation and altering transcriptional activity.[141,142] Suppression of the insulin/IGF signalling pathway by TNFα induces insulin resistance via impaired phosphorylation of IRS-1 and the Akt substrate AS160 kDa,[143-145] and suppresses protein synthesis through a decrease in IGF-1 and IGF binding protein gene expression, subsequently inhibiting elongation initiation and mRNA translational efficiency in skeletal muscle.[139,140] Early studies using intravenous administration of TNFα revealed a significant time-dependent increase in free ubiquitin and ubiquitin gene expression, highlighting the role of TNFα with regard to elevated muscle proteolysis.[138] This effect has subsequently been linked to additional intermediate steps stimulating ubiquitin ligase gene expression and muscle atrophy.[137,146-148]

Work by Sriwijitkamol and colleagues[149] revealed a 40% decrease in TNFα protein content in skeletal muscle in subjects following 8 weeks of cycle training, indicating a positive effect of sustained, low-intensity aerobic exercise on low-grade inflammation and metabolic status in this tissue. Conversely, strenuous exercise, particularly heavy eccentric contractions associated with resistance training, would be expected to generate an acute increase in local inflammation and TNFα concentration. Indeed, there is a significant increase in circulating systemic TNFα after muscle-damaging eccentric resistance training and marathon running.[150,151] Hamada and colleagues[152] observed an increase in TNFα mRNA abundance 3 days after a 45-minute bout of downhill running in muscle samples of healthy subjects, indicative of an acute inflammatory response associated with exercise-induced muscle damage. However, work from our laboratory indicates that the acute TNFα proinflammatory response appears to be unaltered by swimming exercise and ultimately attenuated with long-term resistance training (unpublished observations). Thus, it appears that exercise is capable of generating pro- and anti-inflammatory effects on skeletal muscle dependent on the interaction of training factors such as frequency, intensity and exercise mode, mediated at least in part via changes in TNFα activation. However, the chronic effects of repeated bouts of high-intensity exercise and the specific adaptive response with altered intensity, duration and frequency of contraction and mode of exercise on TNFα activity remain to be established.

Previous studies have predominantly utilised cell culture, pathological states or intravenous administration to identify the effect of TNFα. Hence, our knowledge of contraction-induced changes in TNFα and subsequent alterations within skeletal muscle is limited. Moreover, most investigations have focused on regulators and effectors of TNFα signalling, namely inhibitor of NFκB kinase (IKK), NFκB and p38 mitogen activated protein kinase.

Inhibitor of Nuclear Factor Kappa B Kinase and Nuclear Factor Kappa B

The binding of TNFα to its receptor at the cell membrane initiates a cascade of intracellular events. An important component of this cytokine-mediated pathway is the activation of a kinase that inhibits NFκB (IκB).[153,154] When IκB is bound to the nuclear transcription factor NFκB, IκB suppresses its role as a promoter of gene expression.[153,155] Phosphorylation of IκB by IKK targets it for subsequent degradation, releasing the NFκB complex (p50/p65) to initiate the expression of genes involved in multiple cell processes, including ubiquitin-mediated protein degradation.[155-158]

Recently, work by Cai and colleagues[159] established a mechanistic link between IKKβ/NFκB and expression of atrophy genes in skeletal muscle, confirming the findings of previous investigations that

identified a relationship between NFκB activation and muscle atrophy in models of disuse and muscular dystrophy.[160,161] Additional work in cell culture provides support for the proposed initiation of ubiquitin-proteasome transcriptional machinery in a NFκB-dependent manner.[162] Collectively, these results indicate that upregulation of the IKK/NFκB pathway exacerbates atrophy in skeletal muscle.

Given the capacity of contractile activity to induce local and systemic stress/inflammation and disturb cell homeostasis, exercise represents a stimulus capable of increasing NFκB activity in skeletal muscle. An acute bout of endurance exercise (60 minutes at ≈75% $\dot{V}O_{2max}$) decreases IκB content, and increases IKK and NFκB phosphorylation in rodent skeletal muscle.[163,164] In contrast, long-term cycling (8 weeks, 4 × per week for 45 minutes at 70% of peak oxygen uptake [$\dot{V}O_{2peak}$]) increased IκB and reduced TNFα protein content in skeletal muscle.[149] Durham and colleagues[165] also observed a decrease in NFκB activity following a bout of resistance training in humans. This latter finding is unexpected, given that a vigorous resistance training session with repeated eccentric contractions would typically be expected to result in muscle damage, inflammation and muscle remodelling. However, few exercise studies have investigated the effects of exercise on the IKK-NFκB-TNFα signalling pathway. Nonetheless, these findings may be interpreted as a protective effect of repeated bouts of exercise on the inflammatory response, decreasing local inflammation and cellular disturbance.

Altered transcriptional responses through signal transduction to NFκB with exercise-induced contraction may be an important process in skeletal muscle adaptation. Acute training bouts may increase NFκB activity for transient early adaptive events, while long-term training may reduce total NFκB activity and subsequent protein degradation, enabling net protein synthesis. Regardless, because of the innumerable functional outcomes of NFκB transcriptional control, much work remains to fully elucidate the cause-and-effect relationship between exercise and NFκB activity.

3. Genetic and Molecular Responses to Exercise

There is a paucity of evidence showing detailed continuity between specific signalling pathways, gene expression and subsequent protein synthesis. However, signalling proteins have been shown to activate numerous immediate early genes, transcription factors and molecular machinery responsible for promoting the rate of transcription of target gene mRNA.[159,166-169] The rate of mRNA synthesis versus degradation, the baseline abundance of each specific protein, and additional translational control mechanisms all contribute to net protein synthesis.[170] The following sections highlight important molecular and genetic adaptation responses with endurance and resistance exercise, and examine the effect of concurrent endurance and resistance training on the specificity of adaptation in skeletal muscle.

3.1 Endurance Exercise

Endurance training elicits both central and peripheral adaptations, alters neural recruitment patterns, and causes profound changes in muscle bioenergetics and enhanced morphological, metabolic substrate and acid-base status in skeletal muscle.[171] Briefly, endurance adaptation results in increased muscle glycogen stores and glycogen sparing at submaximal workloads via increased fat oxidation, enhanced lactate kinetics and morphological alterations, including greater type I fibre proportions per muscle area, and increased capillary and mitochondrial density. Moreover, repeated bouts of endurance exercise result in altered expression of a multiplicity of gene products, resulting in an altered muscle phenotype with improved resistance to fatigue.[172] Mitochondria are the main subcellular structures that determine the oxidative capacity and fatigue resistance to prolonged contractile activity in skeletal muscle.[173] Endurance training can increase steady-state mitochondrial protein content 50–100% within ≈6 weeks, but a protein turnover half-life of ≈1 week means a continuous training stimulus is required to maintain elevated mitochondrial content.[9] While enhanced oxygen kinetics, substrate transport and buffering capacity all contribute to enhanced endurance capability in skeletal muscle,

improved endurance is mostly associated with the increase in mitochondrial density and enzyme activity, termed 'mitochondrial biogenesis'.[8,172]

3.1.1 Mitochondrial Biogenesis

The expansion of the mitochondrial reticulum in skeletal muscle is a highly regulated and complex process that appears to require the coordinated expression of a large number of genes.[8,174] Mitochondrial biogenesis requires the co-expression of both the nuclear and mitochondrial genomes for assembly and expansion of the reticulum, and 95% of the genes necessary for biogenesis are encoded in the nucleus.[174] Thus, an important aspect of mitochondrial biogenesis is the import machinery regulating the transport of nuclear encoded precursor proteins into the organelle.[8] However, expression of genes promoting mitochondrial biogenesis is predominantly controlled by the global principles of gene regulation, that is, transcription initiation and interaction at the gene promoter.[174] Therefore, transcription factors and transcriptional co-activators represent critical regulators of mitochondrial biogenesis.

As noted, numerous transcription factors have been implicated in regulating expression of genes involved in mitochondrial biogenesis.[172] While no single transcription factor has been found to be responsible for the coordination of mitochondrial gene expression, several candidates appear to be important for mitochondrial biogenesis. These include the early growth response gene-1 (Egr-1) and nuclear respiratory factor-1 and -2 (NRF-1/2).[175] Egr-1 is associated with promoting transcription of the electron transport chain protein cytochrome C oxidase (COX)[176] while NRF-1 and NRF-2 are implicated in the transcriptional control of multiple mitochondrial genes including mitochondrial transcription factor A (Tfam) and recently identified mitochondrial transcription specificity factors.[177,178] Importantly, the Egr-1 and NRF transcription factors appear to increase in response to contractile activity[177,179,180] and short- and long-term endurance exercise.[181,182]

Peroxisome proliferator receptor-γ co-activator-1α (PGC-1α) has been established as an important regulator of mitochondrial content in skeletal muscle due to its apparent co-activation of multiple mitochondrial transcription factors.[175] Indeed, PGC-1α is the founding member of a family of transcriptional co-activators that has been proposed as a potential 'master regulator' of mitochondrial biogenesis.[172,183] In support of this contention, Lin and co-workers[184] over-expressed PGC-1α in mice skeletal muscle and observed increased proportions of type I fibres and increased endurance capacity. The biogenesis and maintenance of mitochondrial architecture is controlled by altered rates of mitochondrial protein fusion and fission,[185] a role for which mitofusin has been strongly implicated.[186,187] Recent evidence indicates that PGC-1α mediates a regulatory pathway involving mitofusin, and this pathway has been shown to be upregulated following a 10km cycling time trial.[188,189] This suggests that a PGC-1α-activated pathway promotes an increase in mitochondrial content in response to endurance exercise through enhanced mitochondrial protein fusion. Similarly, PGC-1α also mediates Tfam activation, a key component in mitochondrial DNA replication and transcription.[190,191] The NRF-1 transcription factor has been shown to activate Tfam, which enhances the capacity for assembly of protein complexes within the mitochondria.[183] Therefore, as a co-activator of NRF-1 transcription, PGC-1α is involved in regulating Tfam function.[192] Tfam activity also appears to increase in response to contractile activity and exercise, suggesting enhanced mitochondrial protein assembly with endurance training.[193,194]

PGC-1α is the co-activator of the peroxisome proliferator activated receptor (PPAR) family.[195,196] The three PPAR subtypes appear to regulate lipid homeostasis via expression of genes involved in mitochondrial fatty acid oxidation.[197,198] The physiological significance of increased PGC-1α-PPAR activated gene expression with endurance training is an enhanced capacity for fat utilisation during prolonged exercise, and may also be related to fast-to-slow fibre type conversion.[199,200] Indeed, this was highlighted by Wang and colleagues[200] who generated transgenic mice over-expressing PPARδ that resulted in a 2- to 3-fold increase in mitochondrial DNA content, significant type I fibre transformation, and a 90% increase in running performance. The small numbers of studies investigating PPAR activation following exercise

support these findings where both short-[42,201] and long-term[3,199,202] endurance exercise induces PPAR transcription.

Increased PGC-1α-PPAR-mediated transcription is an important endurance adaptation, and is imperative for establishing an endurance phenotype. Collectively, the results from the studies reviewed here not only implicate PGC-1α in the regulation of aerobic metabolism, but also mitochondrial architecture and fast-to-slow fibre type transformation. Endurance exercise has been routinely shown as a potent stimulator of PGC-1α gene and protein expression.[6,41,182,203-205] As might be expected, we[61,203] and others[46] have observed little effect of resistance training stimuli on PGC-1α mRNA and protein expression. Accordingly, exercise-induced upregulation of PGC-1α represents an essential molecular response in mitochondrial biogenesis and exercise-specific adaptation to endurance but not resistance training in skeletal muscle.

3.1.2 Metabolic Gene Expression

In addition to mitochondrial biogenesis, increased gene expression of metabolic proteins following endurance exercise contributes to promoting an enhanced endurance phenotype.[3] These include genes encoding enzymes and transporters involved in carbohydrate and fat metabolism such as hexokinase, lipoprotein lipase and carnitine palmitoyltransferase.[6,206] Endurance exercise has been shown to increase the mRNA abundance and transcription of a variety of metabolic genes in the post-exercise recovery period.[5,6,206-208] This upregulation of metabolic genes following exercise appears to peak in the initial hours of recovery and generally returns to resting levels within 24 hours.[5,207] It has been postulated that the cumulative effect of this transient upregulation with repeated bouts of exercise may be an underlying mechanism for exercise-induced adaptation with endurance training.[6] However, in contrast to PGC-1α activity, resistance training may also alter the expression of a number of metabolic genes (e.g. PDK4), an effect that may be restricted to those proteins involved in carbohydrate metabolism.[5]

3.2 Resistance Exercise

Increased muscle cross-sectional area and altered neural recruitment patterns represent the principal adaptations to repeated bouts of heavy resistance exercise.[12] Increased cross-sectional area (i.e. hypertrophy) following resistance training occurs when the rate of protein synthesis is greater than protein degradation.[209,210] Fundamentally, the hypertrophy response to overload is qualitatively and quantitatively controlled via the production of cellular proteins and new muscle cells. Adaptation to resistance training includes increased protein synthesis via regulatory changes in transcriptional and translational mechanisms, and in the production of muscle cells that are added to existing myofibres or combine and form new contractile filaments, each providing additional contractile machinery with which to generate force.[11,128] In addition, while a degree of protein degradation is required for muscle remodelling, resistance training may also decrease long-term activation of atrophy pathways, resulting in supplementary net protein synthesis.[211]

3.2.1 Hypertrophy

Compensatory hypertrophy in skeletal muscle following resistance training involves an increase in ribosomal protein synthesis.[128] Regulation of ribosomal protein synthesis is controlled by phosphorylation events altering mRNA translation initiation, elongation and termination, and the cellular ribosome content, which determines the synthesis of protein per mRNA.[130,212-214] Modulation of translation initiation is a particularly important regulatory site for global protein synthesis in response to a resistance exercise stimulus, and is the rate limiting step and most frequent target for translational control.[130] Given its ability to ultimately enhance protein synthesis through translation initiation, IGF-1 and IGF-binding protein gene expression following an exercise stimulus has been the focus of extensive investigation.

Over-expression and localised infusion of IGF-1 have both been shown to induce significant skeletal muscle hypertrophy.[215-217] IGF-1-mediated protein synthesis primarily involves PI3K-Akt-mTOR signalling.[218,219] Importantly, studies show IGF-1-mediated p70 S6K and 4E-BP1 phosphorylation and eIF4E-eIF4G association, indicating IGF-1 activa-

tion of kinases proximal to the translational machinery. IGF-1 has also been shown to enhance satellite cell recruitment, proliferative potential and life span.[83,220,221] Thus, IGF-1 appears capable of inducing hypertrophy via an enhanced programme of gene expression, increased ribosomal-mediated translation and satellite cell activation. This strongly implicates IGF-1 as a potent multifactorial regulator of hypertrophy.

Skeletal muscle IGF-1 and IGF-binding protein mRNA and protein content increase in response to contractile activity in a variety of overload models.[222-226] However, the effect of resistance exercise on IGF-1 *in vivo* in humans is equivocal, as IGF-1 mRNA has been reported to increase,[225,227,228] decrease[4,229] and remain unchanged[224,230] in response to these stimuli. Differences in exercise mode, individual variability and the unknown time-course of expression for the IGF-1 response may provide some explanation for these discordant findings. Nonetheless, the IGF-1 genotype appears to enhance the strength response to resistance exercise in humans, as the IGF-1 promoter polymorphism has been associated with greater strength gains following 10 weeks of resistance training.[231] Therefore, despite only partial clarity of *in vivo* human data, the available evidence implicates IGF-1 gene expression in exercise-induced muscle hypertrophy in response to resistance training.

Activation and differentiation of non-specialised satellite cells into new muscle cells is an additional mechanism that contributes to compensatory hypertrophy. Eccentric contraction during resistance exercise is capable of inducing substantial damage to contractile and structural components of skeletal muscle.[232,233] Satellite cells located at the basal lamina that surrounds a myofibre are activated for the repair and maintenance of the muscle milieu and addition of myonuclei, both important components for muscle regeneration and hypertrophy.[227,234] Primary regulators of satellite cell activation include the myogenic regulatory factor (MRF) family of transcription factors and cell cycle kinases, which provide molecular landmarks for the transition from satellite cell quiescence to activation, proliferation and differentiation.[234] The best characterised of the MRFs are the myogenic differentiation (MyoD) and myogenin (MyoG) transcription factors.

Satellite cell gene expression from functionally overloaded skeletal muscle reveals that both MyoD and MyoG are expressed during the hypertrophy process, and activated satellite cells can significantly contribute to activity-dependent muscle growth.[227,235,236] A single bout of contractile activity is sufficient to increase cell cycle kinases and MyoD and MyoG mRNA abundance in skeletal muscle of both rodents and humans.[4,5,222,237,238] Moreover, this response does not appear to be attenuated with long-term resistance training (3 days per week for 16 weeks), which induced MyoD and MyoG mRNA responses equal to a single resistance training bout.[239] This implicates the MRFs in contributing to the myogenic programme and resultant compensatory hypertrophy response with resistance training. However, increased MyoD and MyoG expression has also been observed following low-frequency electrical stimulation and endurance exercise.[203,238,240,241] Endurance cycling/swimming is unlikely to induce muscle damage and subsequent satellite cell activation; hence, the MyoD/MyoG response to an endurance exercise stimulus has been postulated to regulate a pathway for exercise-induced changes in mitochondrial enzymes and/or muscle fibre type transformation.[238,241] While there is an established role for MRFs in satellite cell activation and subsequent increases in myonuclei number and myofibre size, it appears that these transcription factors have additional and as yet undefined roles in skeletal muscle adaptation to endurance exercise.

3.2.2 Atrophy

Skeletal muscle atrophy is characterised by a decrease in structural and contractile protein content and fibre diameter.[136] Moreover, while hypertrophy pathways may suppress the activity of some mediators of protein breakdown, atrophy is not simply the reversal of hypertrophy, but comprises unique mechanisms in a series of pathways regulating proteolysis.[78] Atrophy occurs when protein degradation exceeds protein resynthesis, and is often prevalent in conditions such as inactivity, aging and disease.[136,242]

Current understanding of skeletal muscle atrophy implicates at least three systems in the regulation of proteolysis. The calcium-dependent protease cal-

pain family and proteolytic caspase class of proteins have been proposed to mediate skeletal muscle myofibrillar disassembly and cleavage of actomyosin protein, respectively.[243,244] Similarly, cathepsin, a proteolytic enzyme involved in lysosomal proteolysis, has been implicated in the degradation of membrane proteins such as receptors, channels and transporters.[136] While the initial fragmentation of structural and contractile protein via calpain, caspase or lysosomal pathways is required to enable degradation, the destruction of the protein fragments appears to be coordinated by a common system.[245,246]

The destruction of myofibrillar protein is primarily carried out by the ATP-dependent ubiquitin proteasome pathway, a process involving the interaction of multiple enzymes regulating 'ubiquitin-tagging' of proteins for destruction by the proteasome.[247] The ubiquitin ligase class of enzymes that couple ubiquitin to myofibrillar protein substrates prior to proteasome degradation may also degrade MyoD and inhibit subsequent satellite cell activation.[239,248] Work by Bodine et al.[246] and Gomes et al.[249] has identified important ubiquitin ligase proteins that are upregulated during skeletal muscle atrophy: the muscle-specific atrophy F box (MAFBx, also known as atrogin-1) and muscle ring finger (MuRF) proteins. The evidence supporting their proposed role in muscle atrophy is compelling, as the increase in gene expression of these ubiquitin proteins has been systematically induced with fasting, cachexia, diabetes mellitus, uraemia, denervation, glucocorticoid release and disuse atrophy models.[151,211,245,246] The results from these studies suggest that the MAFBx and MuRF proteins are valid and reliable markers of skeletal muscle atrophy. However, the molecular proteins that initiate MAFBx and MuRF gene expression are still largely unknown. Principal candidates implicated in MAFBx and MuRF activation include the forkhead (FoxO) transcription factors and TNFα via p38 MAPK and NFκB.[78]

Myostatin (or growth and differentiation factor 8) is a transforming growth factor-β family member that may not be classified as an atrophy-inducing factor *per se*, but functions as an inhibitor of muscle hypertrophy.[250,251] The role of myostatin as a negative regulator of hypertrophy is highlighted by the extraordinary increase in muscle mass of myostatin-deficient animals and humans.[252,253] Furthermore, transgenic over-expression of myostatin has been shown to reduce muscle mass, fibre size and myonuclei number, suggesting that increased myostatin expression may have the capacity to exacerbate atrophy.[254] Myostatin appears to exert its regulatory effect on muscle mass via inhibition of satellite cell proliferation, differentiation and self-renewal.[255,256] Therefore, downregulation of myostatin gene expression can result in hypertrophy following skeletal muscle regeneration.[257]

The capacity of exercise to repress, reverse or exacerbate various atrophy-signalling pathways and catabolic states is still unclear. Early work by Sandri et al.[258] showed that ubiquitin protein expression in mice increased following one night of voluntary wheel running. Their findings were later corroborated by other studies incorporating repeated bouts of resistance training that also induced a post-exercise increase in skeletal muscle ubiquitin protein content.[259,260] Indeed, Yang et al.[261] observed an increase in MAFBx and MuRF mRNA abundance following a single bout of resistance exercise. Conversely, resistance training has also been shown to reduce MuRF and MAFBx gene expression and restore muscle mass and strength following 2–6 weeks' disuse atrophy, decreasing ubiquitin ligase mRNA abundance by a minimum of ≈40%.[211,262] Myostatin gene expression also appears to be reduced following resistance exercise in humans,[225,263,264] although a single study has reported an increase in myostatin mRNA abundance after 12 weeks of resistance training.[265] Moreover, Matsakas and co-workers[266] observed a decrease in myostatin mRNA in rodents following 1 and 3 days (2 × 60 minutes per day) of swim training, and attributed this to the need for skeletal muscle remodelling with repeated concentric contractile activity.[266]

Training history may alter the response of atrophic gene expression, where acute bouts of resistance exercise in untrained muscle may induce an atrophy programme due to muscle damage, but may also be required for regeneration remodelling. Indeed, long-term resistance training may ultimately produce a decrease in atrophy gene expression, thereby enhancing the capacity for compensatory hypertrophy. Collectively, these findings suggest that exercise-

induced skeletal muscle contraction is capable of altering regulators of skeletal muscle atrophy, including pathways regulating ubiquitin ligase and satellite cell activation. However, the interaction of mode of contraction, duration and intensity of exercise likely modifies the specific response of atrophy and/or hypertrophy pathways.

3.3 Concurrent Training

The concomitant integration of endurance and resistance training in a regular training plan is termed concurrent training. To date, few studies have attempted to elucidate mechanisms of adaptation in skeletal muscle with concomitant aerobic and hypertrophic stimuli. Furthermore, the results of studies investigating adaptation and performance changes in humans undertaking concurrent strength and endurance training have been equivocal.[267] Accordingly, since the classic investigative work of Hickson,[268] subsequent studies have reported a variety of adaptive consequences when combining resistance and endurance training.

The conundrum of variable results arising from concurrent training research is not surprising, given the complexity of signalling and gene expression that accompanies endurance and resistance training. Indeed, it is reasonable to suggest that the specific adaptations to the divergent exercise modes appear to be incompatible, at least at the cellular/molecular level. Heavy resistance training does not lead to mitochondrial biogenesis, and the larger myofibril cross-sectional area increases diffusion distances for oxygen and substrates.[269] Therefore, with respect to alterations in the muscle milieu, this does not induce a favourable adaptation for endurance capacity. Likewise, long-term endurance training does not have a marked effect on myofibril size, and the muscles altered [AMP/Ca^{2+}] and subsequent residual fatigue may have a negative effect on muscle protein synthesis and the ability to generate force.[269] Consequently, this does not produce an adaptation conducive for increased muscular size and strength.

The majority of research aimed at elucidating the adaptive responses to concurrent training has been confined to 'end-state' measures such as maximum strength/power or maximal aerobic capacity. Consequently, it is not possible to deduce the timing and identity of the regulatory events that orchestrated the observed 'endpoint' adaptations. As a result, there has been little or no elucidation of the mechanisms underlying the specificity of training adaptation or interference to these pathways during concurrent training. Early work by Riedy and colleagues[270] examined whether enlarged rodent skeletal muscle following 30 days of surgical ablation responded to endurance training in a similar manner to control muscle. They observed comparable increases in succinate dehydrogenase activity in enlarged versus normal muscle and concluded that the response to endurance training was unaltered in hypertrophied muscle. Conversely, Stone and co-workers[271] assessed the effect of 6 weeks' concurrent surgical overload and endurance training on citrate synthase, and observed compromised oxidative enzyme content with concomitant hypertrophy. Putman and colleagues[272] reported reduced strength development with concurrent compared with strength training alone, greater fast-to-slow fibre-type transition, and attenuated hypertrophy of type I fibres following concurrent training. These inconclusive findings provide little mechanistic insight regarding the possible interference and/or incompatibility of adaptation with concurrent strength and endurance training. Work from our laboratory[61,203] has shown that highly adapted and specialised phenotypes retain a capacity to induce a molecular adaptation response at opposite ends of the strength-endurance adaptation continuum. Our findings suggest that the apparent interference effect during concurrent training is not simply the result of the incompatibility between strength and endurance phenotypes, but involves the interaction of acute molecular adaptive events when repeatedly alternating between exercise modes. Indeed, emerging evidence provides a number of possible mechanisms that may, in part, offer a rationale for adaptation specificity and an 'interference' phenomenon with concurrent training.

In the first instance, a possible mechanism regulating training specificity involves the elongation phase of translation mediated by eukaryotic elongation factors, which represent a rate-limiting step in protein synthesis.[1] A key component of this translational machinery is eukaryotic elongation factor 2 (eEF2), which mediates translocation of the ribosome along the mRNA. eEF2 is phosphorylated and

inactivated by eEF2K in response to stimuli that increase energy demand or reduce energy supply.[273] Moreover, the activation of eEF2K appears to be regulated upstream via calmodulin and AMPK-mediated signalling, which are kinases activated in response to endurance exercise.[274,275] Indeed, Rose and colleagues[276] provide strong evidence for the phosphorylation and inactivation of eEF2 in a calcium-calmodulin-dependent manner in response to 90 minutes of submaximal cycling (≈67% $\dot{V}O_{2peak}$). Likewise, Atherton and co-workers[46] observed an increase in eEF2 phosphorylation immediately after, and 3 hours following an endurance-like stimulus. This suggests that inhibition of eEF2 activity by endurance exercise results in a decrease in translation elongation and protein synthesis (figure 5). Conversely, IGF-1 signalling has been implicated in the phosphorylation and inhibition of eEF2K and subsequent activation of eEF2.[273] Data exist showing that phosphorylation by p70 S6K inactivates eEF2K, while mTOR has also been shown to phosphorylate eEF2K decreasing kinase activity.[212,277] Increased mTOR and p70 S6K activity following resistance training would be expected to promote hypertrophy in part via increased eEF2 activity (figure 5). In support of this contention, a resistance-like stimulus has been demonstrated to decrease eEF2 phosphorylation, likely enhancing elongation and protein synthesis.[46] Nonetheless, contrasting regulation of eEF2-mediated elongation by endurance and resistance training may represent a point of divergence for control of protein synthesis.

Additionally, the FoxO transcription factor has been implicated in promoting mRNA abundance of genes involved in processes as varied as mitochondrial biogenesis and myofibrillar protein degradation.[78,175] FoxO functions on the promoter regions and initiates transcription of a number of genes, including PGC-1α and MAFBx, and the activity and nuclear abundance of FoxO is regulated by Akt.[86,169,278] When Akt phosphorylates FoxO, it translocates from the nucleus to the cytosol and is prevented from promoting transcription, and may also be subject to cytosolic proteasomal degradation.[279] Akt activation following resistance exercise would likely result in phosphorylation of FoxO and subsequent inhibition of ubiquitin ligase gene expression (figure 6). While these events would be expected to promote hypertrophy, work by Southgate and co-workers[280] suggests that this results in the concomitant downregulation of PGC-1α gene

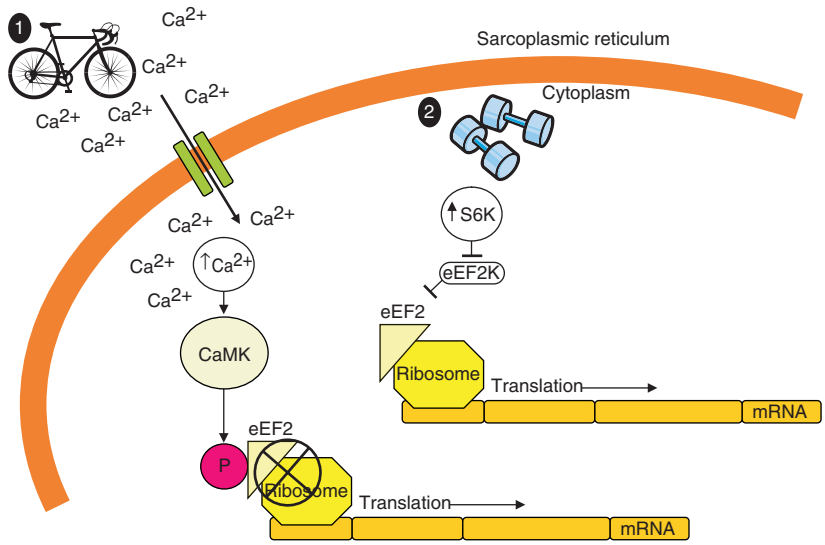

Fig. 5. Putative divergent regulation of eukaryotic elongation factor 2 (eEF2) by (**1**) endurance and (**2**) resistance exercise. Bars denote inhibition and arrows denote activation.[46,212,276] In (**1**), the association of eEF2 and ribosome is inhibited by eEF2 phosphorylation (P). **Ca**$^{2+}$ = calcium; **CaMK** = calmodulin-dependent kinase; **eEF2K** = eukaryotic elongation factor 2 kinase; **mRNA** = messenger RNA; **S6K** = ribosomal protein S6 kinase; ↑ indicates increase.

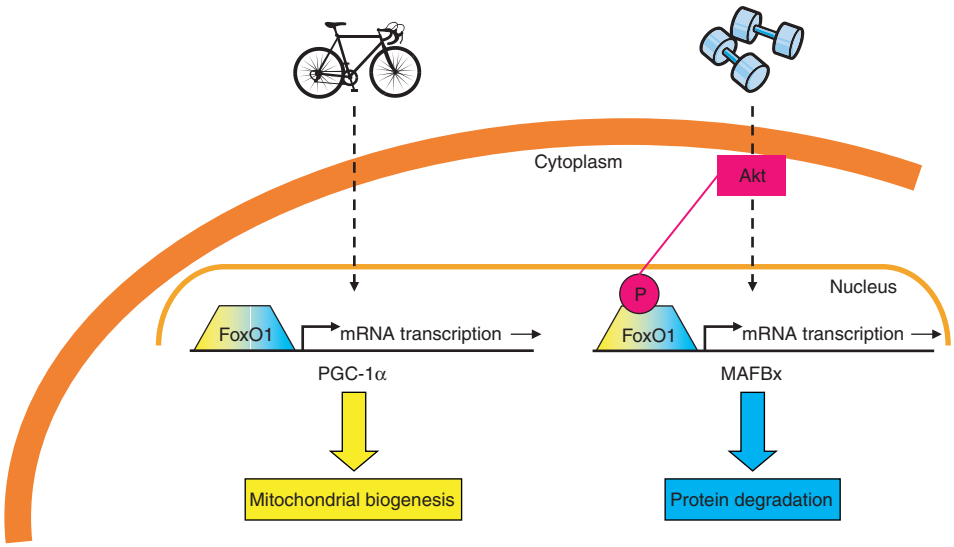

Fig. 6. Proposed effects of acute endurance and resistance training on forkhead box O1 (FoxO1) mediated transcription activation.[280,281] **PGC-1**α = peroxisome proliferator activated receptor γ co-activator-1α; **MAFBx** = muscle atrophy F box protein; **mRNA** = messenger RNA.

expression (figure 6). Equally, endurance exercise is associated with increased PGC-1α gene expression and mitochondrial biogenesis, promoting an oxidative phenotype.[8] However, the nuclear location of FoxO with endurance exercise may suppress net protein synthesis due to increased activity of ubiquitin gene expression and subsequent protein degradation. Therefore, altered regulation of FoxO activity with contrasting modes of exercise may generate contradictory gene expression profiles, ultimately reducing the specificity of adaptation.

Finally, the most compelling mechanism proposed to mediate the specificity of training and subsequent interference effect with concurrent training may be the AMPK-Akt 'master-switch' hypothesis of Atherton and colleagues (figure 7).[46] In a rodent model in which muscle fibres were electrically stimulated for prolonged periods at low frequency (to mimic endurance training) or for short periods with high frequency (to mimic resistance training), they observed a reciprocal relationship in the activation of AMPK and Akt pathways in response to these extreme divergent stimuli. Specifically, after low-frequency stimulation they observed increased AMPK-TSC2 activity, PGC-1α gene expression, and an inhibition of mTOR-mediated translation initiation. Conversely, after high-frequency stimulation there was increased Akt-mediated hypertrophy signalling concomitant with a decrease in AMPK and suppression of TSC2 activity. Based on these findings they proposed that the AMPK and Akt signalling may represent divergent pathways that, when activated, direct skeletal muscle adaptation to either an aerobic or hypertrophic phenotype (figure 7).

The current literature provides a number of possible mechanisms to explain the specificity of training adaptation in response to strength and endurance exercise. Indeed, it appears that divergent adaptive phenotypes are induced via the complex manipulation of numerous common signalling and gene expression pathways, highlighting the intricacy of adaptation to exercise stimuli. Regardless, alternating exercise modes during concurrent training likely reduces the capacity for the simultaneous acquisition of hypertrophy and/or mitochondrial training-induced adaptation responses compared with single-mode training.

4. Conclusions

The aim of training is to provide an overload stimulus that generates specific molecular responses to enhance the adaptive phenotype. In this regard, key regulators of skeletal muscle adaptation are

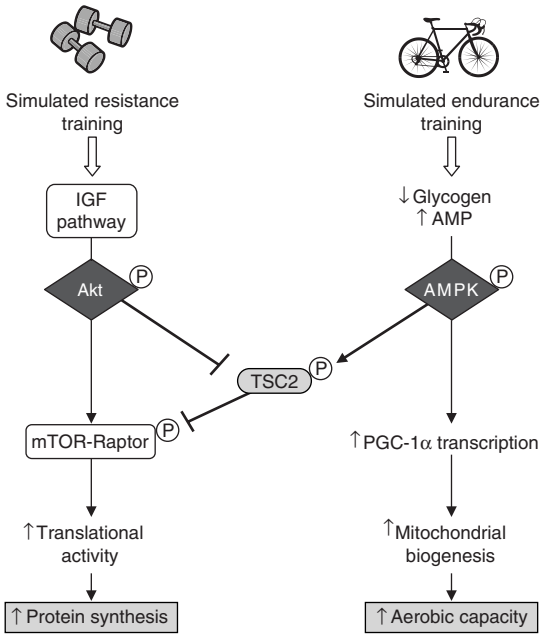

Fig. 7. Putative adaptive pathways in response to endurance- and resistance-like stimuli. Bars denote inhibition and arrows denote activation. **AMP** = adenosine monophosphate; **AMPK** = adenosine monophosphate kinase; **IGF** = insulin-like growth factor; **mTOR** = mammalian target of rapamycin; **P** = phosphorylation; **PGC-1**α = peroxisome proliferator activated receptor γ co-activator-1α; **TSC2** = tuberous sclerosis complex 2; ↑ indicates increase; ↓ indicates decrease.

emerging that are likely to significantly contribute to promoting the specificity of training responses, driving the muscle phenotype to either ends of an adaptation continuum. Thus, endurance training should activate pathways to promote adaptation toward enhanced oxidative capacity and resistance to fatigue during prolonged contractile activity. Conversely, resistance training should upregulate translational machinery and satellite cell activity, increasing protein synthesis and muscle cross-sectional area.

The adaptation continuum provides a framework with which to assess the molecular bases of training adaptation. However, this simplistic approach of characterising the adaptation to endurance and resistance training does not address the multifaceted nature of training specificity. This is undoubtedly complicated by the addition of other training modes, nutritional interventions and recovery modalities. Nonetheless, continued discovery of mechanisms involved in regulating the adaptive response will enhance our understanding of the specificity of training adaptation. Greater knowledge regarding exercise-induced adaptation in skeletal muscle requires the application of innovative training interventions to promote and extend our current understanding of adaptive events that may ultimately translate to novel training practices for athletic endeavour. Understanding the specificity of training adaptation is not only important for sport and exercise scientists, but may also provide therapeutic targets for the treatment of acute and chronic skeletal muscle diseases.

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