Can AMPK mediated suppression of mTORC1 explain the concurrent training effect?

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Abstract

Endurance and resistance exercise are divergent modes of exercise training which each drive mode specific adaptive responses. Some of these adaptations are mutually exclusive, whilst others drive divergent effects on muscle contractile properties, mass and metabolic function. When both resistance and endurance exercise training are employed together, a process termed 'concurrent training', there appears to be a reduction in skeletal muscle adaptive potential. In real world terms this is evident in decathletes, in which personal bests represent approximately a 25% reduction compared to competitors from individual events. This review will detail the molecular pathways thought to drive the resistance and endurance training response and discuss recent evidence addressing the cross talk between these molecular pathways. Ultimately we will discuss why, in our opinion, the molecular events currently proposed to cause interference in skeletal muscle adaptation to concurrent training are an inadequate explanation for the repression on strength gains observed.

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Introduction

The title of "World's Greatest Athlete" is traditionally given to the gold medallist in the decathlon. No Olympic sport epitomises the ethos of the Olympic moto (faster, higher, stronger) more. However, when comparing decathlon bests to the world records for each individual event, it is obvious that it simply is not possible for a decathlete to be higher, faster or stronger compared to specialist competitors in each of the 10 decathlon events. Typically, when comparing world best's in each event, even the premier decathletes are between 7-25% worse. Thus, when training to excel in strength and endurance, skeletal muscle adaptation is compromised in the strength response, a process currently termed the concurrent training effect.

Obviously this is an over-simplified example as a decathlete's training pattern and body type are vastly different than the pure strength athlete's. These factors combined with differences in time spent on skill acquisition could explain the reduced performance in decathletes compared to purists. However, the concurrent training phenomenon was first tested experimentally by Robert C. Hickson in a landmark paper (Hickson, 1980) utilising cycling as the endurance component of a concurrent training program. Hickson showed that by combining endurance and strength training, strength gains plateaued and subsequently decline in the 10th week of the concurrent program (Hickson, 1980). These data (see figure1) demonstrated for the first time that endurance training was capable of interfering with the adaptive response to strength training as individuals on the strength alone program continued to make significant strength gains above the concurrent group. The scientific reasons behind this effect remain unclear, despite numerous experimental approaches. Interestingly, a recent meta-analysis of the concurrent training literature highlighted that when running is combined concurrently with resistance exercise there is a significant inhibition on muscle growth compared to when strength training is carried out alone (Wilson et al., 2012). Additionally, when the interference effect is assessed as a function of the volume of endurance type activity it would appear that the higher the volume the lower the growth and strength adaptations.

In this review we will explore the current understanding of the molecular control of strength and endurance training responses, highlighting points of cross talk that may be partly responsible for the concurrent training effect. Due to space constraints, we will focus primarily on growth inhibition mediated by concurrent training. To assess the impact of concurrent training on neuromuscular measures, readers are directed to Gustavo Nader's excellent review (Nader, 2006)

Mode specific adaptive responses to exercise

Although a gross over simplification, exercise is typically generalised into two modes; resistance and endurance exercise. Resistance exercise is comprised of movements carried out at high intensity (high force) and low volume (a small number of repetitions). Endurance training in contrast consists of low intensity (low force) and high volume movements (high repetitions). There are a number of mode specific adaptations that are critical to improving performance in the chosen events. In general terms resistance training leads to protein accretion, increased fibre cross-sectional area and higher force production whilst endurance training leads to an increase in mitochondrial

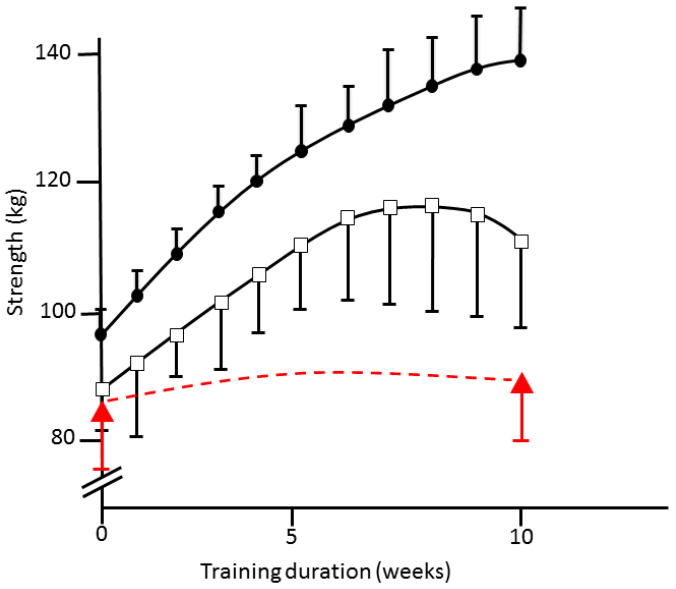

Figure 1. The strength response to concurrent exercise training. Subjects underwent 3 different 10 week training protocols involving 1) resistance training alone (30-40mins / day on 5 days / week), 2) endurance training alone (40mins / day on 6 days / week) and 3) concurrent training (30-40mins resistance training for 5 days / week in addition to 40 mins of endurance training on 6 days / week). Adapted from Hickson, 1980.

abundance and function, capillary density and greater fatigue resistance (Baar, 2009; Booth & Thomason, 1991).

Resistance Exercise

From a strength training perspective, the most visually obvious adaptation is an increase in muscle mass. Growth rates average at approximately 0.1% per day of training (Booth & Thomason, 1991). This growth is primarily mediated by increases in the contractile apparatus (Luthi et al., 1986) which increases skeletal muscle radiological density (Claassen et al., 1989) and radial diameter (Claassen et al., 1989; Luthi et al., 1986; Narici et al., 1996). Ultimately these changes amplify the capacity to produce force both at the whole muscle (Claassen et al., 1989; Luthi et al., 1986; Narici et al., 1996) and single fibre level (Malisoux et al., 2007). Each bout of resistance exercise when combined with the appropriate nutrition increases the rates of muscle protein synthesis (MPS) above breakdown for up to 48hrs (Phillips et al., 1997). It is presumed that such intermittent increases in protein synthesis in response to each bout of training are responsible for the gradual hypertrophy over a period of training (Atherton & Smith, 2012).

There are two potential mechanisms by which this increase in protein synthesis could occur, (i) increased overall mRNA expression, or (ii) increased mRNA translation. Following detailed investigation in both animal (Wong & Booth, 1990) and human (Chesley et al., 1992) models of resistance exercise, it is apparent that the translation step is a major rate limiting step in the control of the post exercise increase in protein synthesis (Atherton & Smith, 2012). Collectively this means that the increased protein synthesis seen in response to resistance exercise is due to increased mRNA activity and not increased mRNA production.

For these reasons the molecular control of muscle protein synthesis in response to resistance exercise and nutrition has been a hot topic of investigation for several decades. The major rate limiting step (in muscle at least) for protein synthesis is the initiation step (Gingras et al., 1999). Translation initiation is the process by which ribosomes are added to mRNA transcripts. On active mRNA transcripts ribosomes are normally stacked 80-100 nucleotides apart with the capacity to stack much closer. In response to an appropriate stimulus, ribosomes can stack up to 27-29 nucleotides apart (Wolin & Walter, 1988). Active mRNA transcripts can therefore increase their protein production by up to 3 fold. Not surprisingly, resistance exercise increases the amount of ribosomes bound to transcripts leading to shifted polysome profiles (Baar & Esser, 1999).

Molecular signals that regulate protein synthesis in response to resistance exercise

A range of animal studies have demonstrated that applying a strain to muscle independently of innervation can induce growth [reviewed (Hamilton et al., 2009)]. Therefore strain induced by contraction as opposed to contraction *per se* seems to be a key component for the hypertrophic response. In addition, recent work appears to suggest that the growth and protein synthesis responses to muscle loading is intrinsic to the muscle and apparently independent of local and circulating growth factors (Witkowski et al., 2010; Spangenburg et al., 2008; Hamilton et al., 2013; Goldberg et al., 1975; West et al., 2009; West et al., 2010; West et al., 2012; West & Phillips, 2012; Hornberger et al., 2004; Goodman et al., 2010; O'Neil et al., 2009).

Alternatively, progress has been made on the identification of non-hormonal pathways of muscle hypertrophy. For instance, Ca^{2+} entry through stretch activated calcium channels appear to be required for anabolic signalling processes (Spangenburg & McBride, 2006). In addition, mechanically sensitive Phospholipase D (PLD) is activated by resistance exercise and is required for anabolic signalling processes (Hornberger et al., 2006; O'Neil et al., 2009). Finally it is suggested that a mechanosensor exists somewhere in muscle (likely at a junction between the contractile apparatus and extracellular matrix) to couple strain to protein synthesis (Hamilton et al., 2009). However the identity of such mechanosensors are still unknown.

One suggestion is that the mechanosensor/s may exist in the elements which link the skeletal muscle contractile apparatus to the sarcolemma and extracellular matrix (Philp et al., 2011). The contractile apparatus of skeletal muscle is intricately linked via membrane bound multi-subunit complexes known as costameres to the sarcolemmal membrane. Costameres are uniquely positioned to house a mechano-sensor. They are aligned to the z-discs of the peripheral myofibrils and through a series of complex protein-protein interactions couple force production by the sarcomeres through the sarcolemma to the extracellular matrix (Ervasti, 2003). An essential component of shaping tissue morphology and physiology is a cell's ability to alter the structural properties within and outwith itself to adapt to variations in the mechanical environment (Ingber, 1997). The concept of tensegrity predicts the existence of mechanisms that sense a variety of mechanical forces and transmit these cues into biochemical adaptive signals (Ingber, 1997). Based on the positioning of the costameres it is therefore no surprise that a number of signalling proteins have been described in or associated with costameres (Ervasti, 2003). Of interest to muscle hypertrophy is the Focal Adhesion Kinase (FAK). In response to increased mechanical deformation, FAK is recruited to focal adhesions where it controls molecules which regulate cell protein synthesis (Gan et al., 2006). Fluck and co-workers have previously demonstrated that chronic loading in chick muscle led to the increased expression and activation of FAK (Fluck et al., 1999). More recently Atherton and colleagues demonstrated that cyclic stretch in the rat derived L6 myotubes increased the phosphorylation of FAK (Atherton et al., 2009) and functional FAK is required for growth factor induced myotube growth and protein synthesis (Crossland et al., 2013).

Based on the linkage of FAK with costameres and its interaction with altered protein synthetic responses, FAK is a strong candidate as one, of likely many, skeletal muscle mechanosensors.

Although we still do not know the exact mechanosenosry mechanisms responsible for resistance exercise induced changes in muscle protein synthesis, research has shown that the protein kinase complex Mechanistic Target of Rapamycin (mTOR) acts as a major signalling hub to control translation initiation, ribosomal biogenesis and protein synthesis responses to resistance exercise (Drummond et al., 2009). mTOR exists as a complex with the protein raptor which defines it as mTOR complex 1 (mTORC1) (Zoncu et al., 2011). mTORC2 is defined by the existence of the adaptor protein rictor (Zoncu et al., 2011). Although mTORC1 has similarity to a lipid kinase it is in fact a protein kinase (transfers phosphate to protein targets). It acts as an important signalling hub that integrates signals from nutrition, hypoxia, energy stress, hormonal status and mechanical loading to regulate protein synthesis (Hamilton et al., 2009).

Mechanistic studies in cells have shown that mTORC1 has two well defined downstream targets 4EBP1 (eIF4E binding protein1) and rp70S6K1 (ribosomal protein S6 kinase of 70KDa) (Zoncu et al., 2011). Phosphorylation and activation of rp70S6K1 (S6K1) leads to an increase in the pioneer round of translation on new mRNA transcripts by phosphorylating the target S6K1 Aly/Ref like target (SKAR) (Ma et al., 2008). Additionally, through the regulation of S6K1, mTORC1 also controls the rate of elongation by relieving an inhibition of the elongation factor eEF2 through phosphorylation of eEF2 kinase (eEF2K) (Avruch et al., 2001). Finally mTORC1 also controls ribosomal biogenesis (Mayer & Grummt, 2006). A subset of mRNA transcripts known as 5'-TOP (5 prime teriminal oligopyrmidine tract) transcripts are selectively recruited to polysome fractions upon the activation of mTORC1 (Meyuhas & Dreazen, 2009). 5'TOP transcripts are enriched for growth factors and the enzymes that form the machinery required for building proteins such as ribosomal proteins and initiation/elongation factors. Therefore, induction of mTORC1 activity not only acutely increases global protein synthesis but it also selectively induces the synthesis of the protein synthesis machinery which helps maintain or increase protein synthesis capacity.

Support for the role of mTORC1 in skeletal muscle hypertrophy has arisen following studies utilizing the compound rapamycin. Rapamycin is a specific inhibitor of mTORC1 and use of this compound during chronic loading (Bodine et al., 2001) and acute resistance exercise in rodents (Kubica et al., 2008) or humans (Drummond et al., 2009) prevents increases in growth and muscle protein synthesis respectively. Whilst mTORC1 appears instrumental in mediating increased protein synthesis following acute resistance exercise (Drummond et al., 2009), few studies have examined the relevance of mTORC1 for long-term hypertrophy. Recently, Phillips et al, (2013) reported that individual's who responded the most to a period of resistance training displayed reduced mTORC1 activity, as indicated by down-regulation of mTORC1 transcriptional targets post-training (Phillips et al., 2013). This data clearly indicates that there is still considerable information unknown relating to the role of mTORC1 in the molecular regulation of the hypertrophy response. To further complicate matters, one of the key regulators of endurance adaptation AMPK (AMP dependant protein kinase; discussed in more detail in the next section) is also activated by resistance type exercise (Dreyer et al., 2006; Koopman et al., 2006) suggesting that signalling divergence is not clear cut in regulating the adaptive responses.

Endurance Exercise

Endurance exercise leads to a cluster of local skeletal muscle adaptations culminating in improved fatigue resistance (Booth & Thomason, 1991). These include, but are not limited to, increased angiogenesis (increased capillaries), mitochondrial biogenesis (increased number of mitochondria) and fibre type switching (muscle fibres switching from a fast to slow phenotype) (Lira et al., 2010). Unlike the adaptive responses to resistance exercise, much of what we know relating to the adaptive response to endurance training seems to be controlled primarily at the level of transcription (Egan & Zierath, 2013).

Transcription is dependent upon the activity of transcription factors, which bind to and enhance the expression of specific subsets of target genes. Transcription factors are themselves tightly regulated, controlled by transcriptional co-activators and co-repressors in addition to numerous forms of post-translational modification. The most characterised skeletal muscle co-activator is the peroxisome proliferator activated receptor-γ co-activator 1α (PGC-1α) (Puigserver et al., 1998). PGC-1α loss and gain of function models have indicated that PGC-1α regulates aspects of mitochondrial gene transcription and angiogenesis in response to exercise (Geng et al., 2010), with muscle-specific overexpression of PGC-1α resulting in mitochondrial biogenesis, improved skeletal muscle fatigue resistance and increased aerobic capacity (Calvo et al., 2008). It should also be noted however that both whole body (Leick et al., 2008) and muscle-specific PGC-1α knockout mice respond to endurance training (Rowe et al., 2012). Human studies have also questioned the pivotal role of PGC-1α for endurance training adaptation (Keller et al., 2011). Collectively this data would therefore suggest that PGC-1α is part of a co-ordinated program initiating a transcriptional response to endurance training, however, as with any fine-tuned process, high levels of redundancy appear to exist with multiple signalling pathways converging to increased gene transcription post-exercise (Lira et al., 2010; Egan & Zierath, 2013).

Whilst co-activators such as PGC-1α might mediate some of the adaptive response to exercise, the initial signals stemming from muscle contraction are important drivers of adaptation. Collectively, it is thought that this alteration in the cellular milieu is pivotal in mediating the adaptive response to exercise (White & Schenk, 2012; Philp et al., 2012). Muscle contraction alters intracellular Ca^{2+} homeostasis (Tavi & Westerblad, 2011), decreases glycogen content (Bergstrom & Hultman, 1966) disturbs the AMP/ATP ratio (Hancock et al., 2006) and NAD^+/NADH ratios (White & Schenk, 2012). Sensitive to this metabolic flux are a group of energy sensing proteins that translate altered cellular energy status to gene and protein modification (Egan & Zierath, 2013). Research over the last decade has identified specific signalling cascades sensitive to metabolic intermediates, such as Calcium-Calmodulin (CaM) kinases, NAD^+ dependent Sirtuins (SIRT1-7), the cAMP sensitive PKA/CREB proteins and the AMP dependent protein kinase AMPK (Egan & Zierath, 2013).

Whilst each of these proteins plays important roles in skeletal muscle adaptation, the remainder of this review will focus on AMPK. As its name would suggest, AMPK responds to changes in AMP levels, more specifically the ratio between ATP and AMP in that an increase in AMP activates the kinase (Hardie & Hawley, 2001). In addition, AMPK has a glycogen binding domain in its β-subunit, allowing it to sense glycogen content and it is activated by CaMKK in response to changes in calcium (McBride et al., 2009; Fogarty et al., 2010; Jensen et al., 2007a; Jensen et al., 2007b). Alterations in the NAD^+/NADH ratio lead to activation of the NAD^+ sensitive de-acetylase SIRT1 which also indirectly activates AMPK (Lan et al., 2008). AMPK has

been hypothesised to have evolved as an ancient energy stress sensor (Hardie et al., 2006) which is highly exercise responsive (Winder & Hardie, 1996) with a number of studies implicating AMPK in the post-exercise adaptive response (Rockl et al., 2007; O'Neill et al., 2011).

Almost two decades of research across a number of labs have revealed that both AMPK activity and phosphorylation are highly responsive to numerous modes of endurance type exercise (Winder et al., 2006). In vitro studies have suggested that AMPK regulates PGC-1α gene expression (Irrcher et al., 2008) in addition to regulating transcriptional activity via phosphorylation at Thr^{177} and Ser^{538} (Jager et al., 2007). Additionally, exercise induced mitochondrial translocation of PGC-1α has recently been suggested to require functional AMPK (Smith et al., 2013). Beyond PGC-1α, AMPK has been linked to the transcriptional regulation of glucose transport, following the observation that AMPK phosphorylates and inactivates HDAC5, leading to increased GLUT4 expression (McGee et al., 2008b). Loss of AMPKα2 activity also impairs exercise induced fibre type shifts (Rockl et al., 2007), whilst blunting total AMPK activity, via disruption of two of the AMPK regulatory subunits β1/β2 leads to reduced exercise capacity and impaired mitochondrial function (O'Neill et al., 2011). However, it should also be re-iterated that signalling specificity to endurance exercise has also not been proven. For instance a number of endurance exercise models have demonstrated an increase in read outs of mTORC1 activity (a key regulator of resistance training adaptations) (Benziane et al., 2008; Wilkinson et al., 2008; Mascher et al., 2011).

Molecular pathway Crosstalk – the limiter on divergent muscle adaptation?

Given the central role that mTORC1 and AMPK play in resistance and endurance exercise adaptation respectively; a key question is whether convergence between these pathways may account for the concurrent training effect. As an energy sensor, one of the key roles of AMPK is to rapidly switch off energy consuming pathways and switch on energy producing pathways in response to an energy stress (Hardie et al., 2006). Protein synthesis requires a high-energy demand (approximately 4 high energy phosphate bonds per peptide bond formed) and so under times of energy stress when AMPK is active, protein synthesis is suppressed via crosstalk at several points in the mTORC1 pathway (see figure 2 for a summary) (Inoki et al., 2003; Gwinn et al., 2008).

The first evidence that AMPK activation can inhibit mTORC1 activity in response to energy stress was reported by Kun-Liang Guan's group (Inoki et al., 2003). The mechanism was dependent upon the phosphorylation and activation of the negative regulator of mTORC1, TSC2 (Tuberous Sclerosis Complex 2) (Inoki et al., 2003). TSC2 acts as an important "switch" in the control of mTORC1 activity. TSC2 is phosphorylated and inhibited by p90RSK (Roux et al., 2004) and by PKB (Dan et al., 2002; Potter et al., 2003) in response to mitogenic stimulation leading to increased mTORC1 activity. Whereas, phosphorylation by AMPK at Ser^{1345} leads to increased TSC2 activity and subsequent repression of mTORC1 (Inoki et al., 2003).

A second mechanism of AMPK repression was recently identified by Ruben Shaw's group (Gwinn et al., 2008). Their data identified that Raptor, which controls docking of mTORC1 substrates into the mTORC1 complex (Schalm et al., 2005) is phosphorylated by AMPK at Ser^{792} (Gwinn et al., 2008). This phosphorylation event leads to the binding of Raptor to 14-3-3 which prevents Raptor from docking with mTORC1 substrates and an inhibition of mTORC1 function (Gwinn et al., 2008).

Thus, *in vitro*, AMPK clearly can regulate the activity of mTORC1. However, whether endogenous AMPK can mediate the same suppressive effect on mTORC1 in skeletal muscle *in vivo* is less clear. Genetic support for the role of AMPK in regulating skeletal muscle mass has been provided following a series of elegant studies utilizing conditional, muscle specific AMPK knockout mice (Mounier et al., 2011; Lantier et al., 2010; Mounier et al., 2009). Further, AMPKα1 is specifically activated by chronic muscle loading in mice (McGee et al., 2008a) which presumably acts to regulate mTORC1 activity, as deletion of AMPKα1 enhances mTORC1 signalling and muscle growth in response to loading (Mounier et al., 2009). These data, albeit in mouse models of hypertrophy, indicate that the AMPK-mTORC1 interaction may play a role in regulating skeletal muscle mass.

AMPK activation with the compound activator AICAR can impair the activation of mTORC1 signalling following acute resistance exercise in rodents (Thomson et al., 2008). However, this approach has not been used to study the role of AMPK on load-induced hypertrophy in either rodent or human models

Do interference signals always impair adaptation?

As we have discussed, loss of AMPK activity promotes muscle growth in rodent models (Mounier et al., 2009) and preceding resistance exercise with AMPK activation, either pharmacologically (Thomson et al., 2008) or via endurance exercise (Coffey et al., 2009) impairs the mTORC1 response. However when resistance exercise is preceded by a single bout of endurance exercise (90mins of continuous cycling) the anabolic response as measured by protein synthesis is not supressed by prior endurance exercise (Carrithers et al., 2007). When the concurrent literature is analysed it becomes apparent that most of the signalling data is derived from cycling based exercise. A recent meta-analysis on the concurrent training effect has strongly confirmed that endurance training in itself is hypertrophic (Wilson et al., 2012) and cycling exercise (1hr of 1 legged cycling 65-70% maximal oxygen uptake) increases both mTORC1 and protein synthesis (Mascher et al., 2011). Additionally, although there is a trend, the effect size for hypertrophy is not significantly different for concurrent training with cycling as the mode when compared to strength training alone (Wilson et al., 2012).

In fact it seems that a wide range of loading and contraction paradigms are capable of inducing substantial skeletal muscle hypertrophy in healthy, untrained individuals (Burd et al., 2012; Mitchell et al., 2012). Short term (Lundberg et al., 2013) and prolonged (21weeks) moderate volume concurrent cycling training in untrained (Mikkola et al., 2012) is as effective at achieving hypertrophy as strength training alone. Additionally, acute concurrent exercise in sedentary individuals provides a hypertrophic stimulus (Carrithers et al., 2007). With this in mind it appears that substantial synergy exists between moderate/high intensity cycling and resistance exercise in inducing muscle hypertrophy in healthy, untrained individuals.

In contrast, when running is employed as the mode of endurance exercise, there appears to be a significant interference effect on hypertrophy (Wilson et al., 2012). As to why the mode of endurance exercise (running vs. cycling) has such a differential effect on mTORC1 related signalling is currently unclear. One explanation could be due to the increased proportion of active muscle recruitment in running exercise, which in turn results in greater metabolic disturbance. Alternatively, it could be related to contraction type i.e. concentric contractions occurring with cycling vs. an eccentric component, which occurs with running. It may also be that circulatory factors might differ between running and cycling

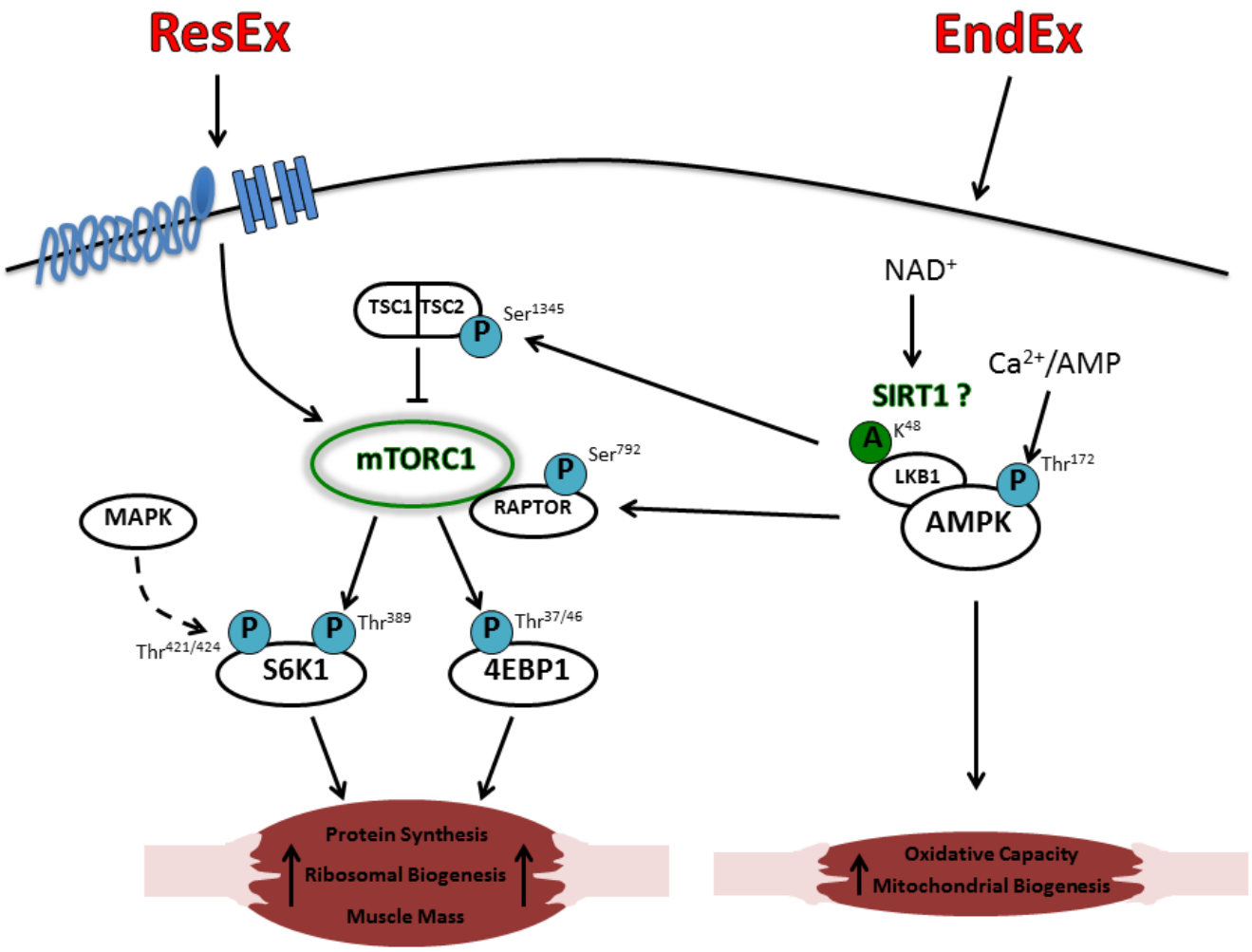

Figure 2. Cross talk between the AMPK and mTORC1 pathways. This figure highlights points of cross talk between these two divergent pathways.

exercise, which in turn might supress mTORC1 activity. Unfortunately, there is a paucity of data addressing the acute interference effects of running type exercise on hypertrophic stimuli making conclusions impossible at this time. In order to dissect out the true molecular nature of the interference effect, study designs that incorporate truly divergent signalling paradigms are needed (Atherton et al., 2005) to overcome the clear molecular 'noise' that occurs during resistance and cycling exercise studies.

To date the evidence pertaining to the molecular control of the concurrent training effect is somewhat unsatisfactory and seems unlikely to be fully explained by a simple interference between AMPK and mTORC1. The original work from Hickson demonstrated that it takes 10 weeks of concurrent training to see the interference effect. This therefore indicates that (1) concurrent exercise studies to date are asking the wrong question by addressing acute metabolic and signalling responses, (2) there is a pressing need for long term concurrent training studies allowing molecular analysis of the concurrent effect *in situ*, and (3) the concurrent effect appears to influence a secondary period of growth, rather than the initial growth response, as both the response to an acute bout of exercise and the initial hypertrophic gains are not altered by signalling divergence.

To understand the concurrent training effect, it would seem important to determine how the adaptive response to resistance training evolves during the course of a training program. Clearly endurance exercise is not always inhibitory for mTORC1 related signalling (Apro et al., 2013) or myofibrillar protein synthesis post acute exercise in young healthy individuals (Carrithers et al., 2007), however the fact remains that prolonged exposure to endurance training blunts the resistance exercise adaptive response (Hickson, 1980). Therefore, what is the adaptive response that is important for improvements in muscle mass that normally would occur between 6-12 weeks of resistance training that are independent of acute changes in protein synthesis?

One possibility is that chronic endurance training might gradually blunt the rate of protein translation, so that over time there is a compromise in protein accretion which eventually impairs force development and mass gains. A change that may be undetectable after a single bout of exercise. Alternatively, the enhanced efficiency of protein synthesis that resistance training imparts on skeletal muscle in response to further exercise bouts (Kim et al., 2005) could be blunted. If endurance exercise were to blunt this improved efficiency it may not be detected as a change in muscle protein synthesis but instead as a change in synthesis in specific muscle fractions.

A second alternative to AMPK-mTORC interference is that rather than a gradual blunting of the adaptive response,

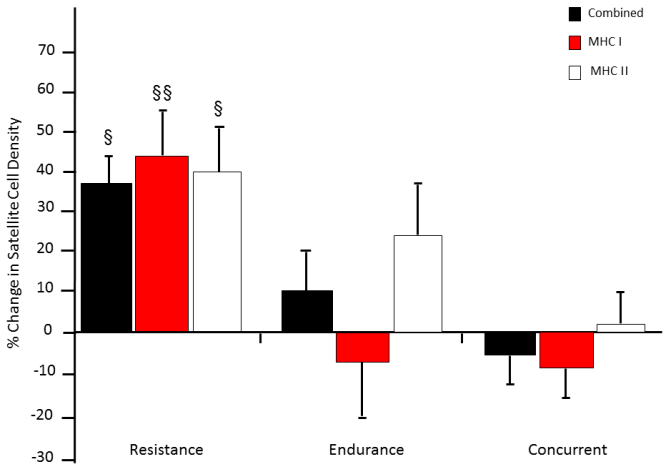

Figure 3. The impact of concurrent training on satellite cell activation 4 days post exercise. Subjects underwent unilateral resistance exercise (this leg served as the resistance exercise alone condition) with biopsies pre and 4 days post exercise followed by a 6 day wash out. After the wash out period they underwent another bout of unilateral resistance exercise (this leg served as the concurrent leg) followed by bi-lateral endurance exercise (the non-resistance exercised leg served as the endurance exercise alone leg) (90mins cycling at 60% W_{max}). Again biopsies were taken before and 4 days after exercise in both legs. Satellite cells were then stained and counted. Adapted from Babcock *et al*, 2012.

endurance training affects a secondary adaptation that is required to support the hypertrophic response beyond initial increases in muscle mass and neuromuscular improvements. Indeed the importance of translational capacity in the maintenance of skeletal muscle mass has been reviewed recently (Van der Meer et al., 2011). Translational capacity is regulated in part by the amount of nuclear DNA, and so it has been proposed that the number of muscle nuclei (myonuclei) per fibre regulates skeletal muscle translational capacity (Van der Meer et al., 2011). The basis of this concept is that myonuclei regulate distinct cytosolic regions within cells (Cheek, 1971), and so post-development, for a muscle to increase in size, as would occur during hypertrophy, generation of additional myonuclei is needed to support the translational capacity of the increased cross-sectional area of the muscle fibre (Van der Meer et al., 2011). Skeletal muscle is capable of increasing myonuclei number due to a pool of muscle-derived stem cells commonly referred to as satellite cells (Relaix & Zammit, 2012). Satellite cells reside in the basal lamina and have been shown to incorporate into muscle fibres to initiate repair and regeneration (Relaix & Zammit, 2012). A role for satellite cells in load-induced hypertrophy has been hotly contested for many years (O'Connor & Pavlath, 2007; McCarthy & Esser, 2007). Genetic mouse models in which satellite cells have been ablated demonstrate that load-induced hypertrophy can occur in the absence of a functional satellite cell pool (McCarthy et al., 2011), whereas regeneration does not, suggesting an obligatory role in this process (Relaix & Zammit, 2012). It therefore seems likely that satellite cells form part of a co-ordinated response in skeletal muscle to maintain or increase myonuclear number in a host of physiological and pathophysiological scenarios (Relaix & Zammit, 2012).

Babcock and colleagues recently reported that concurrent training led to impaired satellite cell activation in response to resistance exercise, compared to resistance exercise alone (Babcock et al., 2012). Interestingly, satellite cell density increased by 38% four days following the exercise bout in the resistance exercise group, whereas the concurrent group displayed a 6% reduction in satellite cell density compared to basal conditions, resulting in a 44% difference between the two groups post exercise (see Figure 3). In addition, this response seemed to occur predominantly in slow muscle fibres, as MHC1 muscle fibre satellite cell density displayed a greater increase following resistance exercise (46% increase) compared with aerobic and concurrent exercise (-7 and 8%) respectively (Babcock et al., 2012). This study is important for two reasons, first the study design should be commended as it assesses the concurrent response beyond the initial exercise period (24h) and examines adaptation 4 days post-exercise. Secondly, it is the first study addressing the role of concurrent training on satellite cell activation, thus potentially highlighting an important adaptive response that has to date been over-looked. It will be interesting to see whether further longitudinal training studies are performed to assess the role of satellite cells and by extension the myonuclear domain in adaptation interference to concurrent exercise training.

Conclusions

Since the initial observations by Hickson (1980) that endurance exercise interferes with strength and mass gains following resistance exercise, scientists have searched for a mechanistic explanation to these findings. Progress in the last decade has meant that AMPK and mTORC1 have emerged as logical molecular correlates of skeletal muscle adaptation to training (see Figure 2), and as such serve as a good place to start when searching for a molecular basis to concurrent training. However, whilst both these proteins are involved in phenotypic responses to exercise, the complexities of exercise adaption and redundancy in higher organisms mean that concurrent training is unlikely to be explained purely by outputs from two pathways. We believe that by characterising the precise molecular control of exercise adaptations, and extending this analysis beyond the initial exercise adaptive 'window' will shed more light on the concurrent training phenomena. It is hoped that this understanding will then allow the effective design of exercise and nutritional strategies to maximise adaptive responses, which will ultimately translate to allowing individuals to become faster, higher and stronger.

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