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Review

mTOR and the health benefits of exercise

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ABSTRACT

Exercise is the greatest physiological stress that our bodies experience. For example, during maximal endurance exercise in elite athlete's cardiac output can increase up to 8-fold and the working muscles receive 21-times more blood each minute than at rest. Given the physiological stress associated with exercise and the adaptations that occur to handle this stress, it is not surprising that exercise training is known to prevent or effectively treat a multitude of degenerative conditions including cardiovascular disease, cancer, diabetes, depression, Alzheimer's disease, Parkinson's disease, and many others. Many of the health benefits of exercise are mediated by the mammalian/mechanistic target of rapamycin (mTOR), either in complex 1 or 2, not only within the working muscle, but also in distant tissues such as fat, liver, and brain. This review will discuss how exercise activates mTOR in diverse tissues and the ways that mTOR is important in the adaptive response that makes us bigger, stronger, and healthier as a result of exercise.

Contents

1. Introduction

Exercise is the most potent medicine known to man. For those who do not exercise, the outcome is clear. Low cardiovascular fitness accounts for 16% of all deaths in the United States [1]. That is higher than smoking, obesity, high cholesterol and diabetes combined. Furthermore, it is not just aerobic fitness that is important for health. The strongest third of the population is half as likely to die between the age of 40 and 60 as the weakest third [2]. If you consider only deaths from cancer, the strongest third of the population is one quarter as likely to die. When both cardiovascular fitness and strength training are combined, the effect is additive. In a 44 year study on 2000 Hawaiian men, those who made it to be centenarians were 2.5-times more likely to be in the strongest third of the population in midlife and were 13% more likely to participate in physical activity outside of work [3]. All of these data make it clear that, in humans, the truism "only the strong survive" is a literal truism.

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Unlike other interventions that increase longevity, such as caloric restriction, exercise increases the quality of life as well [4,5]. Chronic exercise has been proven to prevent or ameliorate cancer [6], cardiovascular disease [7], diabetes [8], muscle loss due to aging [sarcopenia; 9], osteoporosis [10], depression [11], Alzheimer's disease [12], memory loss [13], and a multitude of other health problems associated with increasing age. These effects are mediated not only by the changes that occur within the working muscle, but in other tissues such as fat, liver, and the brain as well.

Even though exercise can be a powerful medicine, it is not well prescribed because of its complexity. Exercise is not a single stimulus and the health effects change with the frequency, intensity and duration of training. Broadly, exercise can be grouped into three categories: (1) strength; (2) endurance; and (3) concurrent. Strength exercises are those activities that require an individual to work at a high percentage of their maximal capacity for a short period of time against a high load, such as when lifting a heavy weight. Endurance exercise requires an individual to work at a low percentage of their maximal capacity for a long period of time, such as when running on a flat surface. Concurrent exercise requires an individual to combine strength and endurance activities either in one event, such as rowing or cycling, or in separate sessions, such as training to be a heptathlete. The different physical demands of each type of exercise result in different adaptations and when the exercise is performed for a sufficient duration the result is distinct phenotypes. The most obvious phenotypic differences are that an individual who does predominantly strength exercise will have a large muscle mass, high maximal strength, and a high capacity for glycolytic metabolism, whereas an individual who habitually performs a strictly endurance exercise (such as running) is small and sinewy, has a higher VO_{2max}, more mitochondria and a greater capacity for aerobic energy production, and concurrent training results in an in-between phenotype combining a moderately large muscle mass with a high VO_{2max} and aerobic capacity. As will be described below, many of these phenotypic differences are the result of differential activation of the mammalian/mechanistic target of rapamycin (mTOR) within the working muscle.

2. mTOR and exercise in skeletal muscle

mTOR is a convergence point of growth signaling and nutritional status in the regulation of protein synthesis. Since skeletal muscle is the largest store of protein within the human body, it should not be surprising that mTOR is a central molecule in the determination of skeletal muscle phenotype. The amount of protein stored within muscle (the mass of a muscle) is the result of the acute regulation of myofibrillar protein balance: the arithmetic sum of myofibrillar protein synthesis and degradation [14]. Exercise results in an increase in both the rate of protein synthesis and degradation [15]. However, since protein synthesis can increase by 3-fold or more and protein degradation increases by as little as 30% [15], the net effect is an accumulation of more protein. The type of protein that accumulates is dependent of the type of exercise that was performed. When an individual performs a strength exercise, there is a large increase in the contractile (myofibrillar) proteins [16], whereas when endurance exercise is performed there is a rise in both myofibrillar and mitochondrial protein synthesis [17]. As will be discussed below, mTORC1 is required for the increase in myofibrillar protein synthesis, but appears to play a more limited role in mitochondrial protein synthesis (Fig. 1).

2.1. mTOR and strength exercise (myofibrillar protein synthesis)

Within skeletal muscle, the primary adaptation to strength exercise is an increase in muscle size and strength [18]. In 1999, we showed that the increase in muscle mass that occurs following repeated strength exercise was directly related to the load across the muscle and the activation of mTORC1 [19]. In this study, the increase in skeletal muscle mass following 6 weeks of strength training was directly correlated ($r = 0.998$) with the phosphorylation of the ribosomal S6 protein kinase (S6K1, a direct target for mTORC1) six hours after completion of a single bout of strength exercise (Fig. 2). This finding suggested that the ability to increase muscle mass as a result of strength exercise was related to the activation of mTORC1. This finding has been extended to show that mTORC1 activity after strength exercise in young people also correlates with the acute activation of myofibrillar protein synthesis [20], as well as the training-induced increase in muscle size and strength [21]. Furthermore, treating people with rapamycin (a highly specific mTORC1 inhibitor) before they perform strength exercise prevents the acute increase in mixed muscle protein synthesis [22] and chronic treatment of mice with rapamycin prevents load-induced skeletal muscle hypertrophy [23]. Interestingly, trained individuals increase muscle mass more slowly than

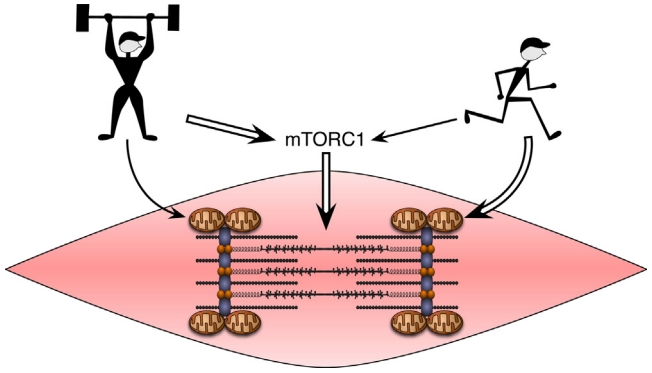

Fig. 1. Cartoon representing the fact that strength exercise activates mTORC1 and this results in an increase in myofibrillar protein synthesis and muscle mass. Endurance exercise primarily increases mitochondrial protein synthesis and this occurs independent of mTORC1.

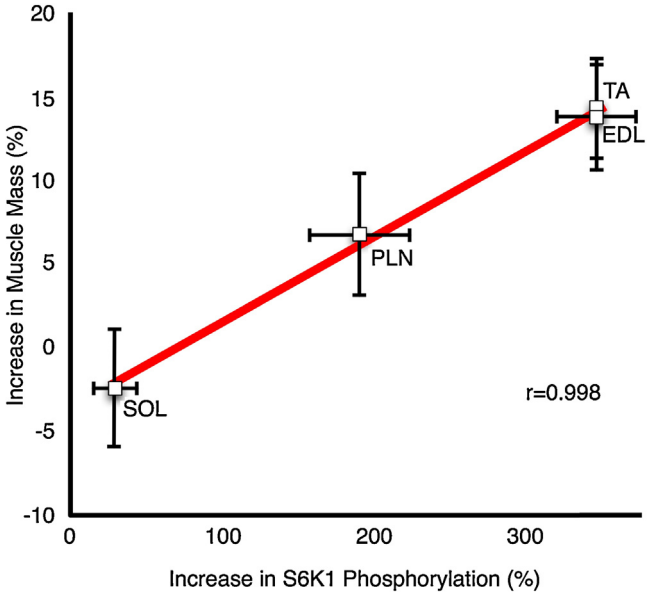

Fig. 2. Relationship between mTORC1 activation and the muscle hypertrophy. The phosphorylation of S6K1 six hours after a single bout of exercise is plotted against the increase in muscle mass that occurs with 6 weeks of training. There is a significant association between mTORC1 activity and the increase in muscle mass with a correlation of 0.998.
Adapted from Ref. [19].

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untrained and training is associated with a progressive decrease in mTORC1 activation [24]. The clearest demonstration that mTORC1 was required for muscle growth was performed by Troy Hornberger's group at the University of Wisconsin Madison using mice carrying a muscle-specific mutation in mTOR that makes the protein rapamycin resistant [25]. In this experiment, wild-type mice that underwent 14 days of increased loading showed a 43% increase in muscle fiber size and this increase was completely prevented by daily injections of 0.6 mg/kg rapamycin. However, in mice carrying the rapamycin-resistant mTOR, the muscle grew the same amount both in the presence and the absence of rapamycin [25]. These data show conclusively that mTORC1 increases myofibrillar protein synthesis after strength exercise and that this increase in mTORC1 activity is required for muscle to grow bigger in response to training.

2.2. Activation of mTORC1 by strength exercise

The data above show that mTORC1 is activated by strength exercise and that this activation is required for the phenotypic adaptations that occur with training. However, they do not describe how the load across a muscle is converted to an increase in mTORC1 activity. The first indication that strength exercise could activate mTORC1 in a non-canonical manner was when Hornberger stretched muscles *in vitro* in the presence or absence of the 3-phosphoinositide-dependent protein kinase (PI3K) specific inhibitor wortmannin. In canonical growth factor signaling, a growth factor binds to a membrane receptor and activates PI3K and Akt/PKB and both PI3K and Akt are required for mTORC1 activation [26]. In the presence of 500 nM wortmannin, a concentration that completely inhibits insulin-stimulated activation of PI3K, Akt, and mTORC1 (ribosomal protein S6 kinase 1 (S6K1) phosphorylation), S6K1 was phosphorylated normally following mechanical loading [27]. Furthermore, when muscles lacking Akt1/PKBα were stretched, mTORC1 was activated normally, suggesting that the activation of mTORC1 following loading was not due to PI3K/Akt signaling [27]. These *in vitro* experiments were followed by an elegant *in vivo* experiment using mice expressing a dominant negative form of the insulin-like growth factor (IGF)1 receptor in their muscles [28]. As expected, neither insulin nor IGF1 could activate mTORC1 in the muscles of these mice. However, when these mice were loaded, both the activation of mTORC1 and the growth of the muscle were completely normal [28]. We then performed a series of experiments to determine whether PI3K was activated physiologically by strength exercise in the same way that it is by growth factors. First, we demonstrated that whereas insulin increases the phosphorylation of the IGF1 receptor, this does not occur following resistance exercise [29], suggesting that receptor tyrosine kinases, including the IGF1 receptor are not activated by resistance exercise. Further, even though insulin increased the association of PI3K with the insulin receptor substrates (IRS) 1/2, following a bout of strength exercise this association never increased. In fact, there was decrease in the association of IRS1/2 with PI3K from 3 to 6 h after strength training, consistent with feedback inhibition of insulin signaling [29]. Lastly, when we deleted the inhibitor of PI3K signaling, PTEN (phosphatase and tensin homolog), specifically in striated muscle there was no more load-induced muscle growth than seen in wild type animals. In an elegant series of experiments by Dr. Daniel West, the limited role for growth factors in the activation of mTORC1 in muscle and subsequent hypertrophy has also been shown in humans. In these experiments, subjects performed resistance exercise on one arm by itself, whereas the other arm was worked on a separate day together with the legs. The result was a 10-fold greater level of growth hormone, twice the IGF1, and a 3-fold greater testosterone [30] in the circulation on the day that the legs were trained. In spite of the greater hormonal levels, mTORC1 activation [30], protein synthesis [30], and hypertrophy were the same in both arms [31]. Taken together, these data suggest that mTORC1 is not activated in the classical growth factor/PI3K/Akt manner following resistance exercise.

Following loading, mTORC1 is likely activated by the growth factor-independent movement of proteins to and from the lysosome. After strength exercise, there is increased phosphorylation of the mTORC1 repressor TSC2 (tuberous sclerosis complex 2) within an RxRxxS*/T* motif [32]. Jacobs and her colleagues used ultrathin muscle sections to first demonstrate that the phosphorylation of TSC2 was associated with its removal from the lysosome where it acts as a GTPase activating protein toward the small G-protein Rheb (Ras homologue enriched in brain). This means that TSC2, by activating the intrinsic enzymatic activity of Rheb, increases the amount of Rheb in the GDP-bound state [33]. The GTP-bound form of Rheb is required for the subsequent activation of mTORC1. Therefore, removing TSC2 from the lysosome promotes mTORC1 activation by increasing the proportion of Rheb in the GTP-bound state [32]. The kinase that phosphorylates TSC2 at the RxRxxS*/T* sites following strength exercise remains unknown, but as this is a classic Akt substrate motif, it is likely that an AGC (protein kinase A/G/C family) kinase is involved. Due to the ability of this kinase to be activated by mechanical loading, it is likely that the kinase lies downstream of a mechanoreceptor, an individual protein or more likely a protein complex, that senses the load across the muscle. A number of different proteins/protein complexes have been proposed as the mechanoreceptor (Fig. 3) including: (1) integrins and focal adhesion kinase [34–37]; (2) β-dystroglycan and the dystroglycan-associated glycoprotein complex [38–40]; and (3) a stretch activated channel [41]. However, whether one or more of these pathways are associated with the phosphorylation of the RxRxxS*/T* motif of TSC2 has yet to be determined.

Beyond the mechanical activation of an RxRxxS*/T* kinase, stretch increases the production of phosphatidic acid (PA). PA is known to play an important role in the activation of mTORC1 following treatment with mitogens [42] by binding to the FKBP12-rapamycin binding (FRB) domain of mTOR [43]. Using 1-butanol to inhibit phospholipase D (PLD), Hornberger and colleagues were able to prevent the stretch activation of mTORC1 [44]. However, further work in this area with more physiological models showed that stretch did not increase the activity of PLD and blocking PLD activity did not prevent stretch-induced activation of mTORC1 [45], suggesting that PLD was not the enzyme that increased PA in response to stretch. In a series of elegant experiments, You and colleagues then showed that diacylglycerol kinase (DGK) activity increased biphasically with stretch, DGKζ could increase mTORC1 activation by serum, and that muscles from DGKζ knockout mice did not show as great an increase in PA in response to stretch [45]. Consistent with the ability of DGKζ to increase mTORC1 activity and the role of mTORC1 in muscle growth, electroporating DGKζ into muscle resulted in skeletal muscle hypertrophy, whereas the kinase dead DGKζ did not [45]. These data suggest that DGKζ is involved in the activation of mTORC1 in skeletal muscle in response to stretch. However, whether DGKζ is required for the mechanical activation of mTORC1 has yet to be determined. In fact, the absolute level of S6K1 phosphorylation in DGKζ knockout muscles following stretch is the same as the wild type controls [45], suggesting that even though DGKζ can modulate mTORC1 activity, it is not required to maximize the effect of loading on skeletal muscle mTORC1 activity.

Concomitant with the removal of TSC2 from the lysosome following strength exercise, mTOR (the enzymatic component of mTORC1) itself moves to the lysosome [32]. It is likely that the movement of mTOR to the lysosome is the result of the acute increase in amino acids within the muscle after exercise [46]. As with other tissues, muscle is extremely sensitive to changes in intracellular amino acids. When strength exercise is performed in a

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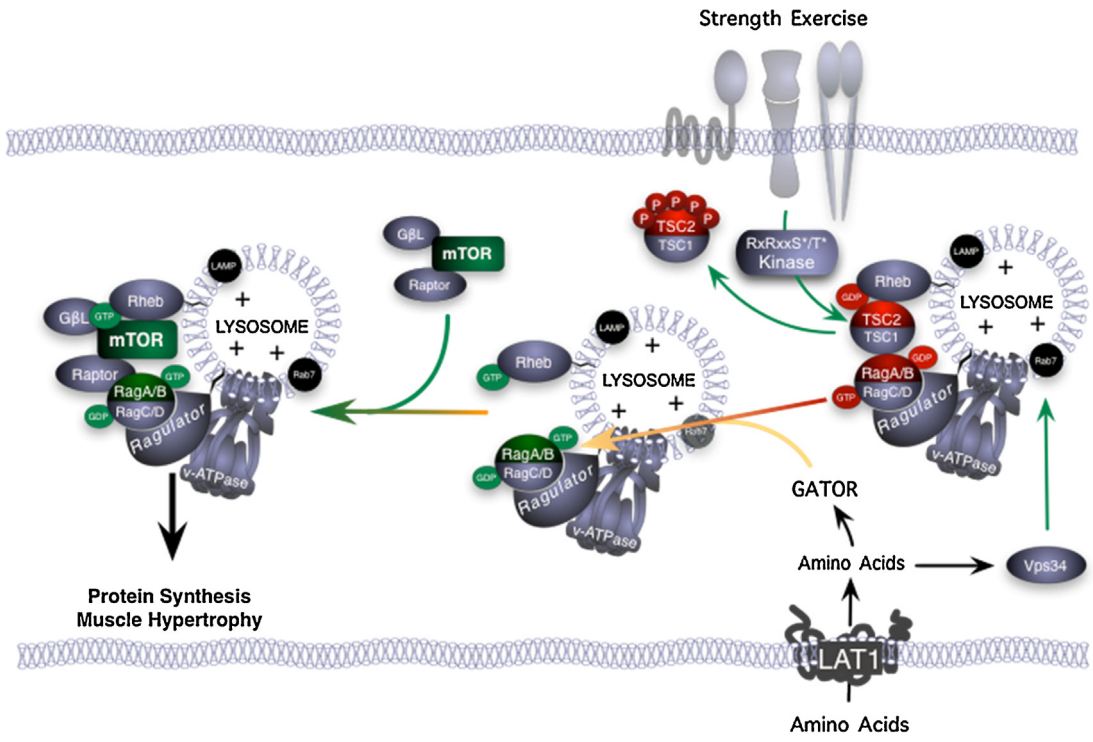

Fig. 3. Representation of the activation of mTORC1 following resistance exercise. Lifting a heavy weight to failure stimulates a mechanoreceptor that in turn activates an RxRxxS*/T* kinase that phosphorylates and moves the tuberosclerosis complex away from the lysosome allowing Rheb to remain in the GTP bound state. Simultaneously, amino acid uptake and intracellular amino acid levels increase. The extra amino acids stimulate either the LRS or folliculin to act as a GAP toward RagC/D and GATOR and the Ragulator to GTP load RagA/B and activate the complex. The active Rag complex then binds to raptor and positions mTOR beside its activator GTP bound Rheb. The resulting elevation of mTORC1 activity drives myofibrillar protein synthesis and eventually leads to an increase in muscle mass and strength.

fasted state, both protein synthesis and degradation increase [14]. Providing either all 20 amino acids, or only the essential amino acids results in a further increase in the rate of protein synthesis. This suggests that exercise is not enough to maximally activate mTORC1 and protein synthesis in the absence of amino acids. Interestingly, only a high amount of the essential amino acids can decrease the rate of protein degradation following the exercise bout [14]. This suggests that the increase in protein degradation in the fasted state is partially needed to supply the essential amino acids for *de novo* protein synthesis. Even though all of the amino acids are required for the increase in protein synthesis, the amino acid leucine appears to be the primary amino acid needed to stimulate mTORC1. Animals who receive an oral gavage of increasing amounts of leucine show a linear increase in mTORC1 activity in their skeletal muscle [47]. Similarly, the ability of a meal to stimulate mTORC1 activation and protein synthesis in people is directly related to the rate, and extent, of the increase of leucine within the blood [48]. Furthermore, adding leucine to a sub-optimal protein load is enough to increase mTORC1 activity and protein synthesis back to optimal levels [49], whereas omitting leucine from a protein meal results in less mTORC1 activation following exercise [50]. Together, these data suggest that mTORC1 activity following strength exercise is dependent on the presence of high levels of intracellular amino acids and that leucine specifically acts as a trigger for activating mTORC1. Therefore, the synergistic effects of exercise and amino acids on mTORC1 and protein synthesis are discussed below.

Even though muscle is a primary storage site for amino acids within our bodies, little is known about how amino acids drive mTORC1 activation and protein synthesis in this tissue. From an elegant series of experiments in cell culture, we know that the movement of mTOR to the lysosome following the addition of amino acids is dependent on the Rag family of small G-proteins [51,52]. The Rag proteins are a family of four homologous proteins that form a heterodimeric complex with either RagA or RagB forming one half of the complex and Rag C or RagD forming the other half (Fig. 3). In the absence of amino acids, RagA/B is held in the inactive GDP bound state by the GAP activity of the GATOR1 complex [53], whereas RagC/D is in the inactive GTP bound state. When amino acids are high, the GATOR2 complex inhibits the GATOR1 complex and removes the GAP activity toward RagA/B [53]. The Ragulator complex then acts as a GEF toward RagA/B activating this half of the heterodimer [54]. Meanwhile, either the tumor suppressor folliculin or the leucyl tRNA synthase (LRS) acts as a GAP toward RagC/D [55,56]. The LRS is attractive in this role as it would provide the leucine-sensitivity that we see in muscle following strength exercise. However, there is some question as to whether the LRS can perform this role *in vivo* [53]. Regardless, once RagA/B is GTP bound and RagC/D is GDP bound, the Rag complex binds to the rapamycin sensitive companion of mTOR (raptor) and through its interaction with the Ragulator on the lysosomal membrane recruits mTOR to the lysosome [57] where the active mTOR complex 1 can be completed by the association with GTP bound Rheb [33].

None of this detail of amino acid signaling is known to occur in muscle following exercise. However, we do know that intracellular amino acid levels (leucine in particular) increase acutely after strength exercise [46], possibly due to an increase in amino acid transporters, including the primary leucine transporter in muscle LAT1 [58]. Furthermore, the amino acid sensitive regulator of membrane vesicle trafficking, VPS (vesicular trafficking protein) 34 is known to be increased following strength exercise [46]. Together, these data suggest a model (Fig. 3) whereby strength exercise, through a mechanoreceptor, activates an RxRxxS*/T* kinase that phosphorylates and moves the TSC2 complex away from the lysosome allowing Rheb to remain in the GTP bound state. Simultaneously, exercise increases amino acid uptake and intracellular amino acid levels. The extra amino acids stimulate either the LRS

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or folliculin to act as a GAP toward RagC/D and GATOR2 to move GATOR1 away from the lysosome allowing the Ragulator complex to GTP load RagA/B and activate the complex. The active Rag complex then binds to raptor and positions mTOR beside its activator; GTP bound Rheb. The resulting elevation of mTORC1 activity drives myofibrillar protein synthesis and eventually leads to an increase in muscle mass and strength.

2.3. mTORC1 and endurance exercise (mitochondrial protein synthesis)

Protein synthesis is an energy costly process. Between 20 and 50% of resting metabolic rate goes toward protein turnover [59]. Therefore, it is not surprising that the activity of mTORC1 can alter the rate of metabolism in cells [60]. In fact, rapamycin has been shown to decrease the master regulator of mitochondria, the peroxisome proliferator activator receptor gamma co-activator (PGC-1α), and mitochondrial proteins in muscle cells [60]. Since acute endurance exercise increases PGC-1α activity within the working skeletal muscle [61] and performing endurance exercise 5 times a week for 12 weeks can double mitochondrial protein [62], it is only natural to assume that endurance exercise increases mitochondrial protein synthesis through mTOR. However, this does not appear to be the case. Carter and Hood [63] stimulated C2C12 myotubes to contract 3 h a day for 4 days and showed a 1.5–2.5-fold increase in mitochondrial proteins. Surprisingly, when they added rapamycin to the media the mitochondria proteins increased normally following the 4-day treatment period. In fact, mitochondrial transcription factor A went up more in the presence of rapamycin [63]. This suggests that mitochondrial protein synthesis in muscle cells is not dependent on the rapamycin-sensitive aspects of mTORC1. In support of this hypothesis, we have shown that whereas myofibrillar protein synthesis after endurance exercise is increased following the ingestion of protein, the rate of mitochondrial protein synthesis is not [64]. Further, rapamycin has no effect on the rate of mitochondrial protein synthesis in mice after a 1 h run on a treadmill, even though it completely blocks the increase in myofibrillar protein synthesis [65]. These data suggest that when cells are in exponential growth mTORC1 may be necessary to maintain normal metabolism. However, in terminally differentiated muscle cells and muscles *in vivo* the rapamycin-sensitive activity of mTORC1 does not seem to be involved in mitochondrial protein synthesis. It should be noted however that some functions of mTORC1 are less sensitive to rapamycin [66]. For example, Choo et al. [66] have demonstrated that rapamycin has a more potent inhibitory effect on S6K1 than another mTORC1 target eukaryotic initiation factor 4E binding protein (4E-BP1). This is important since Morita and colleagues have suggested that in exponentially growing cells 4E-BP1 controls mitochondrial protein synthesis and biogenesis [67], suggesting that further experiments are needed to determine the role of mTORC1 in mitochondrial protein synthesis in skeletal muscle. Whereas the role of mTORC1 in regulating mitochondrial protein synthesis after endurance exercise is uncertain, mTORC1 is necessary for the endurance exercise-induced increase in myofibrillar protein synthesis, likely through the mechanism described above for resistance exercise.

2.4. mTORC1 and concurrent exercise (limiting muscle growth)

Far from increasing mTORC1 activity, during running, the high amounts of metabolic stress induced by endurance exercise can decrease mTORC1 activity [68]. This decrease in mTORC1 activity following running may be the result of the activation of the 5′-adenosine monophosphate activated protein kinase (AMPK). In people unaccustomed to endurance exercise, at the beginning of an exercise bout, or when you increase the intensity of exercise, the rate of energy consumption outpaces the rate of energy production resulting in the rapid breakdown of ATP and the production of AMP [69]. The increase in the AMP/ATP ratio activates AMPK within the exercising muscle [70] and AMPK is thought to be important for the increase in mitochondrial protein that results from endurance exercise training [71]. However, AMPK is also known to negatively regulate mTORC1 [72]. Activation of AMPK by the AMP analog AICAR (5-amino-1-β-D-ribofuranosyl-imidazole-4-carboxamide) is known to decrease mTORC1 activation following acute strength exercise in rodents [73]. Further, when the α1 isoform of AMPK is knocked out in mouse muscle, chronic loading results in greater muscle hypertrophy [74], suggesting that AMPK could physiologically decrease mTORC1 activity and function during concurrent exercise. However, this is still controversial. Some report that AMPK has no effect on mTORC1 activity after exercise [75]. However, when people perform high intensity sprints, that activate AMPK, prior to strength exercise there is a decrease in mTORC1 activity [76], whereas when they perform low intensity exercise, that does not activate AMPK, there is no change in mTORC1 activity [77]. These data suggest that unaccustomed or high intensity endurance exercise can decrease mTORC1 activity. In fact, in people who take part in a training program that either uses strength exercises alone or combines high intensity resistance and endurance exercise the increase in muscle size and strength is less in the concurrent training group [78,79]. Further, a meta-analysis of these studies suggests that performing strength exercises alone results in 33% more hypertrophy and 25% more strength than when concurrent strength and endurance are performed [80]. This suggests that concurrent training results in lower mTORC1 activation, protein synthesis, and muscle hypertrophy.

3. mTOR and exercise in the heart

Endurance exercise not only affects the working skeletal muscles, but also has a dramatic affect on the phenotype of the heart. Unlike skeletal muscle where the primary adaptation to endurance exercise is an increase in mitochondrial mass, in the heart endurance exercise results in volume overload, eccentric, or physiological hypertrophy [81]. The endurance athlete's heart is characterized by an increase in the volume of the ventricles and improved contractility [82,83]. The result is that the ejection fraction remains the same for the bigger ventricle resulting in a significant increase in cardiac output. Strength exercise also results in cardiac hypertrophy, however strength athletes undergo concentric hypertrophy where the thickness of the wall and not the volume of the chamber increases [84]. Athletes performing concurrent training get a mixture of the two phenotypes, increased volume and wall thickness resulting in improved cardiac output and heart function [82,84]. The cardiac adaptations that occur as a result of exercise underlie the long recognized protective effect of exercise on mortality due to cardiovascular disease [7].

Over the last 10 years, it has become clear that mTORC1 signaling underlies physiological cardiac hypertrophy as a result of endurance exercise. Interestingly, unlike skeletal muscle where the activation of mTORC1 occurs independent of Akt [27], in the heart PI3K and Akt are required for physiological hypertrophy [85,86]. This suggests that the stimulus or the initial mechanical sensor is different between the two types of muscle. Through a series of elegant genetic studies in mice, the costamere has been identified as the likely mechanoreceptor that leads from an increase in the stretch of the heart to the activation of mTORC1 (Fig. 4). The costamere is a repeating structure within a muscle that connects the extracellular matrix to the intermediate filaments within the

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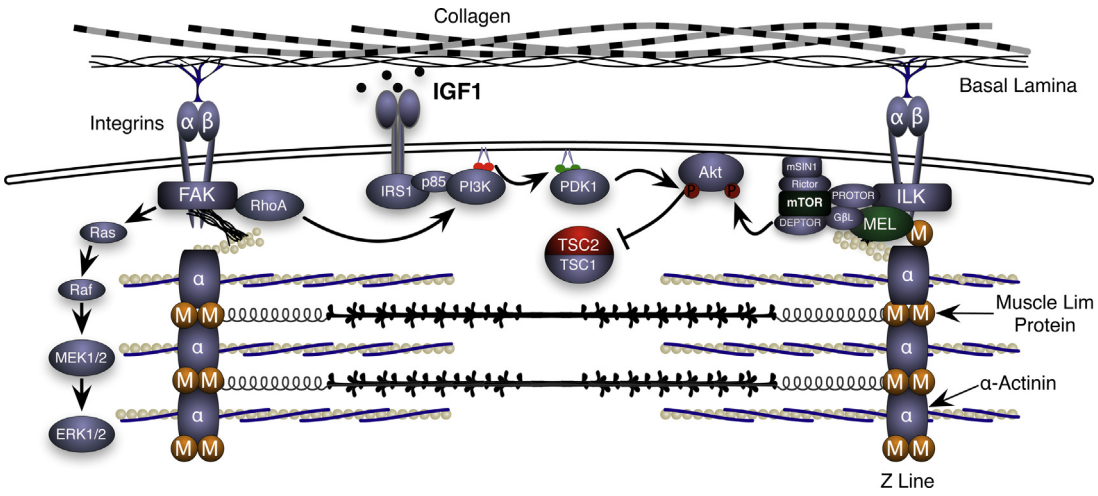

Fig. 4. The activation of mTORC1 in cardiac muscle during endurance exercise. Endurance exercise results in an increase in blood returned to the heart resulting in a stretch on the myocardium that is detected at the costamere by integrin linked kinase and focal adhesion kinase. FAK through the small G-protein Rho recruits PI3K to the membrane resulting in an increase in PIP_3 and the phosphorylation of Akt at Thr308. At the same time, ILK together with melusin recruits mTORC2 to the costamere resulting in the phosphorylation of Akt at Ser473 and activation of the protein. Active Akt then phosphorylates and dissociates TSC2 from the lysosome and resulting in the subsequent activation of mTORC1 and physiological hypertrophy (see Fig. 3).

muscle [87]. In the heart, these structures line up over the *z*-lines at the end of each sarcomere resulting in a repeating striation of costameres along the length of the fiber [87]. At the core of the costamere are the integrins, heterodimeric proteins that connect fibronectin and the extracellular matrix to the cytoskeleton [88]. The cytoplasmic tails of the α and β integrins form a nucleation point for a wide range of signaling molecules including integrin linked kinase (ILK) and focal adhesion kinase (FAK) [88]. ILK is actually a pseudokinase that acts more as a scaffolding protein, bringing important signaling molecules together at the costamere [89,90]. Central to its role in signaling in the heart, ILK associates with melusin, a muscle-specific protein that binds to the cytoplasmic tail of β1 integrins [91], and the rapamycin-insensitive companion of mTOR [rictor; 92]. Together, melusin and mTORC2 modulate the phosphorylation of Akt, and by extension mTORC1 activity, in cardiac muscle [92,93]. The importance of these costameric proteins in the activation of mTORC1 and subsequent physiological hypertrophy of the heart is seen when they are overexpressed or knocked out. Knockout of the integrins [94,95], ILK [96], or melusin [91] results in a pathological hypertrophy whereas overexpression studies show a physiological hypertrophy and resistance to pathological growth similar to endurance exercise [93].

FAK also plays a role in the activation of mTORC1 in cardiac muscle through its ability to recruit PI3K to the costamere [97]. FAK is able to associate with PI3K through its interaction with RhoA, a small G-protein that is involved in cytoskeletal reorganization [98]. By recruiting PI3K to the membranes surrounding the costamere, FAK indirectly controls the production of phosphoinositide (3,4,5) trisphosphate (PIP_3) and thereby Akt/mTORC1 activity [98]. FAK has a further role in activating the Ras/Raf/MEK/ERK pathway [99], which is important in the development of concentric hypertrophy [100].

Lastly, exercise is presumed to increase IGF1 signaling within the heart [101]. This presumption is based on the fact that increasing the amount of the IGF1 receptor in the heart results in greater cardiac hypertrophy following swim training but not aortic banding [101]. This finding suggests that IGF1 is produced in an autocrine manner during exercise, but not during pathological hypertrophy, and that this leads to an increase in PI3K/Akt/mTORC1 signaling. However, football players who performed 25 min of high intensity endurance exercise showed no increase in plasma IGF1 levels [102], suggesting that systemic IGF1 does not increase significantly during exercise. This does not mean that local levels of IGF1 are not increased by exercise since it is possible to increase IGF1 levels 47-fold in skeletal muscle without observing an increase in circulating IGF1 [103].

Together, these data suggest the following model for how exercise results in a physiological hypertrophy of the heart (Fig. 4). (1) Exercise results in an increase in blood returned to the heart resulting in a progressive increase in cardiac output up to 40% of VO_{2max} [104]. This extra volume results in a stretch on the myocardium that is detected at the costamere by ILK and FAK. (2) FAK through the small G-protein Rho recruits PI3K to the membrane resulting in an increase in PIP_3 and the phosphorylation of Akt at Thr308. (3) ILK together with melusin recruits mTORC2 to the costamere resulting in the phosphorylation of Akt at Ser473 and activation of the protein. (4) Active Akt can then phosphorylate and dissociate TSC2 from the lysosome and this results in the subsequent activation of mTORC1 and physiological hypertrophy [105].

4. mTOR and exercise in non-muscle tissue

4.1. Exercise and the brain

Exercise has significant effects on the body well outside of muscle. The brain in particular appears to be sensitive to the effects of exercise. Exercise in rodent models is known to drive neurogenesis within the dentate gyrus and hippocampus resulting in an improvement in learning and memory [106,107]. This effect of exercise is also likely to occur in humans and appears to be directly related to aerobic fitness. In cross-sectional and MRI studies, the greater the fitness level, the greater the hippocampal volume and the better the memory at any age [108–110]. The result is that in a large cohort of young people, aerobic fitness correlates with intelligence [111]. Much of the effect of exercise on the brain is thought to be mediated by the brain-derived neuropeptide (BDNF). Seven nights of access to a running wheel (rodents will cover 4–10 km a night when given free access to a running wheel) is sufficient to dramatically increase the expression of BDNF in the hippocampus [112]. Increases in BDNF occur concomitant with an increase in S6K1 phosphorylation in the soleus muscle 14 days after a concurrent exercise model which led to improved learning [113]. Most

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importantly, the increase in BDNF was correlated with the phosphorylation of S6K1 in the soleus with an *R* value of 0.92 [113], suggesting that mTORC1 activation in skeletal muscle (possibly as an indicator of the intensity of exercise) might be important in the exercise-induced increase in hippocampal BDNF and neurogenesis. In young men, short periods of acute cycling resulted in a doubling of serum BDNF levels and an improvement in cognitive function [114]. However, it is unlikely that serum BDNF would cross the blood brain barrier. Therefore, the exercise-induced changes in brain derived BDNF are likely the result of a local signal in the brain (for an excellent review see [115]). In animals, five days of forced treadmill running induces a 70% increase in BDNF protein within the brain, which is associated with increased BDNF receptor activation and subsequent mTORC1 signaling in the hippocampus [116]. Chen and Russo-Neustadt have traced the effects of exercise from the increase in BDNF protein, to the phosphorylation of the BDNF receptor (tropomyosin-related-kinase; Trk), to the activation of PI3K/Akt [117]. This suggests that BDNF can activate the canonical PI3K/Akt/mTORC1 pathway downstream of the Trk receptor following exercise. The activation of mTORC1 in turn leads to an increase in protein synthesis in neuronal dendrites [118] and this likely underlies the fact that mTORC1 activity in the brain is required for synaptic plasticity and long-term potentiation [119]. Therefore, the ability of exercise to increase mTORC1 activity in the brain may underlie the beneficial effects of exercise on brain function.

Another way that mTORC1 may be activated in the brain as a result of exercise is through the upregulation of reelin, a large secreted glycoprotein important in synaptic plasticity and brain development. In developing brains, exercise increases the production of reelin [120] and reelin is thought to signal through the ApoE receptor to PI3K/Akt/mTOR [121]. However, while reelin increases in developing brains with exercise, in healthy adults there is no increase in reelin with exercise [120,122] even though mTORC1 activity and BDNF go up [116], suggesting that BDNF is likely the dominant pathway leading to activation of mTORC1 in the brain following exercise.

4.2. Exercise and metabolic stress and the regulation of mTORC1 in other tissues

As discussed above, exercise results in a significant metabolic stress throughout the body. Since metabolic stress activates AMPK and this can result in the inhibition of mTORC1, it follows that exercise could lead to inhibition of mTOR in tissues such as liver, fat, and tumors [123]. Since mTORC1 plays a role in lipid biosynthesis [124], inhibiting mTORC1 through AMPK might decrease adiposity in liver and fat tissues [123]. In fact, activating AMPK with AICAR results in decreased mTORC1 activity and protein synthesis in the liver [125]. Since endurance exercise increases AMPK activity within the liver and fat [123], this suggests that endurance exercise may transiently block mTORC1 activity throughout the body. Since blocking mTORC1 with rapamycin can improve longevity [126], this might underlie some of the health benefits of habitual exercise. However, this overly simplistic and somewhat contradictory view on the control of phenotype by a single molecule needs to be tempered with the statement that signaling molecules are highly dynamic both in their on/off time course and in their cellular localization. Furthermore, they have differential effects depending upon what tissues they are active in. The importance of mTORC1 function for skeletal muscle health is unequivocal, however we believe that some of the effects of rapamycin on longevity may be mediated in part through mTORC1 inhibition in tissues other than muscle and we would suggest that rapamycin improves longevity in rodents in spite of its negative effects on muscle.

5. Conclusions

Exercise is a potent treatment for many diseases that reduce lifespan and quality of life. Many of the effects of exercise on quality of life likely reflect the ability of exercise to alter mTORC1 activity within diverse tissues. In some cases, such as skeletal and cardiac muscle size, the effect of exercise on mTORC1 and the resulting change in tissue phenotype is clear. In other tissues, such as the brain, liver, and fat, the relationship between exercise, mTORC1 activation, and tissue phenotype and function has yet to be delineated. Over the next few decades, the importance of exercise in modulating mTORC1 and the resulting impact on health will become clear. From the existing data, exercise and mTORC1 will be shown to be central to improving not only longevity but also quality of life.

6. Remaining questions

1. What is the mechanoreceptor that transduces load into a signal that directly activates mTORC1 in skeletal muscle?
2. What is the RxRxxS*/T* kinase that is upstream of TSC2 and drives the movement of the TSC complex away from the lysosome?
3. Does the GATOR/Rag/Ragulator complex control the movement of mTORC1 to the lysosome and activation following strength exercise?
4. Does the leucyl tRNA synthase underlie the central role of leucine as the trigger for the activation of mTORC1 and the increase in protein synthesis?
5. Does mTORC1 play a role in mitochondrial biogenesis after endurance exercise in skeletal muscle through phosphorylation of 4EBP?
6. Does melusin play a role in skeletal muscle hypertrophy?
7. Is IGF1 protein increased locally following endurance exercise and is this necessary for physiological hypertrophy of the heart?
8. How is BDNF increased in the brain after exercise and does mTORC1 play a role?
9. Does BDNF expression directly activate mTORC1 in the brain and is this required for the learning and memory benefits of exercise?
10. What is the metabolic consequence of mTORC1 inhibition in liver and fat as a result of exercise?

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