European Journal of Applied Physiology (2019) 119:333–349
https://doi.org/10.1007/s00421-018-04061-x

INVITED REVIEW

The skeletal muscle fiber: a mechanically sensitive cell

Luke A. Olsen[1] · **Justin X. Nicoll**[2] · **Andrew C. Fry**[3]

Received: 4 October 2018 / Accepted: 21 December 2018 / Published online: 5 January 2019

Abstract
The plasticity of skeletal muscle, whether an increase in size, change in metabolism, or alteration in structural properties, is in a continuous state of flux largely dependent upon physical activity. Much of the past research has expounded upon these ever-changing aspects of the muscle fiber following exercise. Specifically, endocrine and paracrine signaling have been heavily investigated lending to much of the past literature comprised of such endocrinological dynamics following muscle activity. Mechanotransduction, the ability of a cell to convert a mechanical stimulus into an intracellular biochemical response, has garnered much less attention. Recent work, however, has demonstrated the physical continuity of the muscle fiber, specifically demonstrating a continuous physical link between the extracellular matrix (ECM), cytoskeleton, and nuclear matrix as a means to rapidly regulate gene expression following a mechanical stimulus. Similarly, research has shown mechanical stimuli to directly influence cytoplasmic signaling whether through oxidative adaptations, increased muscle size, or enhanced muscle integrity. Regrettably, minimal research has investigated the role that exercise may play within the mechanotransducing signaling cascades. This proposed line of study may prove paramount as muscle-related diseases greatly impact one's ability to lead an independent lifestyle along with contributing a substantial burden upon the economy. Thus, this review explores both biophysical and biochemical mechanotransduction, and how these signaling pathways may be influenced following exercise.

Keywords Mechanotransduction · Muscle · Exercise · mTOR · Hypertrophy · Integrin

Mechanotransduction: a brief history

Mechanotransduction is the ability of a cell to sense and respond to a mechanical stimulus and convert this stimulus into an intracellular biochemical response (Ingber 2006). Interest in this area has increased in recent years. However, investigations geared toward muscle biology, and exercise in particular, has largely been lacking in the mechanobiology field. Rather, much of the skeletal muscle changes following exercise have most notably been directed toward circulating growth factors, such as testosterone, insulin, and growth hormone, and their role upon the intracellular anabolic environment. Previous research has questioned the relative necessity of these endocrinological changes upon anabolism following exercise (West et al. 2010). In short, it has been proposed that the acute and chronic changes in muscle fiber characteristics are due to intrinsic mechanically sensitive properties of the muscle fiber with circulating growth factors playing an indispensable role. With this in mind, this review will cover the key mechanotransducing pathways within the muscle fiber and their likely role following a given mechanical stimulus such as exercise.

Albert Goldberg pioneered much of the seminal research exploring the possible intrinsic capacity of skeletal muscle to sense a mechanical stimulus and respond in lieu of many of the respected circulating growth factors. In the 1960s, Goldberg used hypophysectomized rats (those having

Communicated by Michael Lindinger.

✉ Andrew C. Fry
acfry@ku.edu

Luke A. Olsen
l794o991@kumc.edu

Justin X. Nicoll
justin.nicoll@csun.edu

[1] Biomedical Sciences, University of Kansas Medical Center, Kansas City, KS 66160, USA

[2] Department of Kinesiology, California State University, Northridge, CA 91330-8287, USA

[3] Department of Health, Sport, and Exercise Sciences, University of Kansas, Lawrence, KS 66045, USA

surgically removed pituitary glands as a means to reduce circulating pituitary-specific growth factors such as insulin) and then implemented a synergist ablation (SA) model (the removal of the gastrocnemius as to overload the plantaris and induce muscle growth) (Goldberg 1968). The results of Goldberg's work showed that, within 24 h, and reaching maximum at 5 days, the soleus of the hypophysectomized rats hypertrophied by ~40% which was similar to their non-hypophysectomized counterparts. These results, while not definitive, showed that skeletal muscle likely possesses intrinsic sensors (outside of circulating growth factors) to sense and convert mechanical stimuli into a functional intracellular response. Goldberg further demonstrated the ability of skeletal muscle to uniquely respond to the degree of mechanical tension placed on the muscle and subsequently hypertrophy dependent upon overload (Goldberg et al. 1975). This was found even in states of attempted muscle wasting (such as fasting). Moreover, cast immobilization studies, such as that of Booth (1977), found that immobilizing a muscle in a lengthened (stretched) position rather than a shortened (slack) position results in reduced atrophy and in some cases elevated hypertrophy. These early findings demonstrate a profound aptitude of the skeletal muscle to respond to a mechanical stimulus.

With this said, what is lacking within the literature is a comprehensive review concerning the exercise-induced biophysical and biochemical mechanosensors which regulate protein synthesis following acute and chronic exercise. Biophysical mechanotransduction denotes the direct force transmission through the cell to influence gene expression in a matter of seconds via intracellular structural reorientation. Biochemical mechanotransduction denotes the less rapid increase in cytosolic signaling proteins, such as the anabolic mechanistic target of rapamycin complex one (mTORC1), following mechanical stimulation as to influence gene expression. Thus, the goal of this review is to extensively summarize and question the ever-increasing field of mechanobiology and how this unique, and yet ever-prevalent, field may be the underlying signaling apparatus within the skeletal muscle fiber.

Muscle fiber protein synthesis

Much of intracellular metabolism can be partitioned into two metabolic processes, namely protein degradation termed catabolism and protein synthesis termed anabolism. There are two primary signaling proteins which lie at the center of both catabolism and anabolism signaling; specifically, AMP-Activated Protein Kinase (AMPK) and mTORC1, respectively, with AMPK both directly and indirectly inhibiting mTORC1 activity (Garcia et al. 2017). Concerning exercise, much is still being delineated between these signaling hubs, such as can both be elevated simultaneously? Can an increase in muscle mass occur with heightened levels of AMPK (Lundberg et al. 2014)? Is mTORC1 activity required for protein synthesis and subsequent hypertrophy? To answer these questions, the mechanisms behind their intracellular dynamics must first be understood and will briefly be discussed below.

Protein synthesis can be driven through a number of distinct intracellular signaling cascades, all of which uniquely influence protein synthesis. Many of these signals ultimately merge as to increase mTORC1 (Saxton et al. 2017). mTORC1 has been coined as the protein synthesis master regulator of the body. A myriad of upstream effectors have been identified to regulate its activity state such as an influx of amino acids, circulating growth factors, intracellular energy status (AMP/ATP ratio), and mechanical stimuli (Sabatini 2017; Saxton et al. 2017). Following one, or a combination of these inputs, mTORC1's activity state is increased, and elevated protein synthesis ensues.

mTORC1 can activate its anabolic effects through the phosphorylation of two primary mechanisms, phosphorylation of p70S6 kinase 1 (p70S6K) and the eIF4E-binding protein (4E-BP1) (Laplante et al. 2009) which result in increased activity of translation initiation (protein synthesis). P70S6K, upon direct phosphorylation from mTORC1, can phosphorylate eIF4B which is considered to be a positive regulator of the 5′-cap binding eIF4F complex (Saxton et al. 2017). The majority of proteins necessary for protein synthesis consist of 5′ TOP complex mRNA sequences thus necessitating p70S6K activity for efficient protein synthesis. Moreover, 4E-BP1 plays an important role in protein synthesis via inhibition of the eIF4F complex through its colocalization with eIF4E. Upon 4E-BP1 phosphorylation, 4E-BP1 disassociates from eIF4E permitting the initiation complex to form and translation of the mRNA to take place. Thus, an increase in mTORC1 activity is necessary for proper translation initiation and protein synthesis. Outside of driving translation initiation, mTORC1 has shown to influence ribosome biogenesis ultimately influencing translational capacity. However, this will not be described here and the reader is recommended to other reviews on the topic (Mayer et al. 2006; Jastrzebski et al. 2007).

Key mechanotransducing pathways

The skeletal muscle membrane is a mechanically sensitive structure that houses multiple mechanotransducing proteins and complexes; specifically, the G-coupled protein receptors (GPCRs), the dystrophin-associated glycoprotein complex (DAG), and the alpha7 beta1 (α7β1) integrin. These structures span the cellular membrane physically connecting the outside of the cell (extracellular matrix) to the inside of

the cell (cytoskeleton), allowing force transmission to take place in both an inside-out and outside-in manner (Qin et al. 2004). These protein complexes are preferentially localized at "protein islands" and costameres (Lillemeier et al. 2006). Protein islands are key hubs through which signals are transduced from the extracellular environment to the intracellular space allowing for rapid force transmission and signaling efficiency. The integrin has been characterized as a highly active transmitter of the above-mentioned forces and will be discussed below.

Integrins are a family of heterodimeric proteins consisting of 18 alpha and 8 beta subunits, dependent upon cell type, totaling 28 possible combinations (Legate et al. 2009). The mature skeletal muscle is primarily comprised of the α7β1 isoform. Within skeletal muscle, these proteins are positioned at the costamere, myotendinous junction, and neuromuscular junction. The transmembrane nature of the integrin allows it to physically connect the extracellular matrix (ECM) to the actin-cytoskeleton allowing for force transmission and intracellular biochemical signal regulation. In the integrin's resting state, such as during periods of minimal muscle activity, the extracellular head sits in a bent conformation blocking its interaction with extracellular ligands. Upon a stimulus such as exercise, the extracellular head swings straight, the two integrin subunits separate, and extracellular protein binding and cellular force propagation ensue (Schwartz 2010).

The Boppart Lab has conducted much of the research concerning α7β1 integrin dynamics following exercise. Most notably, their group has shown that following a bout of eccentric exercise, mice overexpressing the α7β1 integrin have significantly greater anabolic signaling, such as mTORC1, compared to their wild-type counterparts (Lueders et al. 2011). Moreover, Burkin investigated muscle integrity and regenerative properties in mice which overexpressed the α7β1 integrin and, similar to that mentioned above, they observed elevated hypertrophic signaling with a concomitant increase in satellite cell content and improved muscle membrane integrity (Boppart et al. 2006).

Due to its sensitivity to mechanical perturbation, it has been proposed that high levels of mechanical tension are required for the integrin to become active. However, we have preliminary data to suggest otherwise. We found integrin phosphorylation to increase to a similar degree in a fatigued arm (aerobic exercise preceding resistance exercise) which produced a marked decrease in power when compared to the non-fatigued arm (resistance exercise only). Interestingly though, the integrin was not recruited following a low-intensity stimulus (aerobic exercise) which suggests a certain exercise-intensity threshold for integrin recruitment. Taken together, while power output was decreased in the experimental arm, it would appear that maximal muscle activity is not required for an increase in integrin phosphorylation. This is an important finding as a number of populations, such as in-season athletes, do not frequently take part in high-intensity weight-room training sessions in which maximal muscle activity is performed. Collectively, here we propose that similar muscle fiber structural adaptations can be achieved even with a sharp decrease in total muscle output. Further research is necessary to expand upon these findings.

Phosphatidic acid

As mentioned above, transmembrane proteins such as the α7β1 integrin are comprised of a number of signaling characteristics which are enhanced through both increased phosphorylation and total quantity following mechanical stimulation. However, the prevalence of integrin signaling on protein synthesis, compared to its role as a force transmitter, has been scrutinized. While past investigations utilizing the mouse model reported a correlation between integrin activity and intracellular anabolism (Zou et al. 2011), recent work within our lab did not find anabolic signaling to increase in parallel with integrin phosphorylation. While differences in exercise interventions between the two studies may partly explain these discrepancies, it is speculated here that, at least within humans, there are likely other factors with greater prevalence concerning anabolic mechanotransducing mechanisms within the skeletal muscle; one such mechanism being the dynamic signaling molecule phosphatidic acid.

Phosphatidic acid (PA) is a lipid second messenger which is found within a number of cellular locations. PA plays a direct role in the activation of mTORC1, most notably through its binding to the rapamycin-sensitive FKBP12–rapamycin-binding (FRB) domain located upon mTORC1 (Joy et al. 2014). Increased phospholipase D1 (PLD1), the enzyme which catalyzes the conversion of phosphatidylcholine to PA, increases mTORC1 activity (Hornberger et al. 2006). In skeletal muscle, PLD1 is found to reside upon the z-disc of the sarcomere, rendering it susceptible to muscle activity. However, more recent investigations within the Hornberger Lab have shed doubt on the absolute necessity of PLD1 on PA signaling. You et al. (2014) found that the enzyme diacylglycerol kinase zeta (DGKζ) is the primary activator of PA increasing mTORC1. This was proposed due to DGKζ's interaction with the late-endosomal lysosome (LEL). mTORC1 is also found to reside at the LEL. Thus, following an increase in muscle activity, the enzymatic activity of DGKζ to form PA is in close proximity to mTORC1 increasing likelihood for interaction and anabolism.

Thus, how might exercise influence DGKζ activity as to increase PA production and subsequent protein synthesis? A study by Thalacker-Mercer et al. (2013) investigated the pre-training levels of the skeletal muscle transcriptome.

In short, the transcriptome is the genome-wide expression and activity of transcription factors—proteins which regulate gene expression. Interestingly, this study found that individuals who responded the most to heavy resistance exercise, categorized as "extreme responders", had the greatest pre-training levels of DGKζ. This denotes the likelihood of these subjects being primed and ready to increase PA levels following muscle activity. Moreover, this study implemented what would be considered a high-intensity resistance exercise protocol (~ 75% 1RM) (Bamman et al. 2007). It may then be reasoned that a large mechanical stimulus is necessary for increased DGKζ activity compared to low-intensity exercise. While this does not give a cause-and-effect relationship, it does further promote the likelihood of DGKζ working as an anabolic signaling factor following exercise.

Last, and what may be the least investigated area concerning PA, is the effect that increased localization of PA at the outer-membrane of the mitochondria has on mitochondrial dynamics. It has been suggested that mitochondria are stagnant organelles, though it is now well accepted that mitochondria are highly dynamic and break apart or come together through a process called fission or fusion, respectively. Following exercise, mitochondrial fusion has been demonstrated to take place (Fealy et al. 2014). However, the process through which mitochondrial fusion and fission occur remains unclear. Adachi et al. (2016) demonstrated that an increase in mitochondrial-PLD, and thus PA, increased mitochondrial fusion through sequestration of the mitochondrial fission protein dynamin-related protein 1 (Drp1). PLD can be localized at the outer mitochondrial membrane and may be one of the primary mechanisms through which PA is increased at the mitochondria subsequently initiating mitochondrial fusion. As mentioned above, PLD is also found at the z-disc of the sarcomere lending it susceptible to mechanical activity and PA production. It is thus likely that, upon exercise which stimulates the z-disc and subsequent activity of PLD, PA is produced and translocates to the mitochondria initiating mitochondrial fusion and improved mitochondrial function.

How then might the style of exercise, specifically low-intensity and high-intensity exercise, differentially influence DGKζ dynamics ultimately altering the PA–mTORC1 relationship? Similarly, how might the PA enzymatically catalyzed by PLD regulate mitochondrial fusion as to influence intracellular oxidative adaptations? It may be reasoned from the Thalacker-Mercer findings that relatively heavy resistance exercise is necessary for PA–mTORC1 signaling axis to take place; however, endurance exercise has also been demonstrated to drive mTORC1 signaling (Kazior et al. 2016). It is clear that phosphatidic acid dynamics is a field requiring further research.

MAPK's

Mitogen-activated protein kinases (MAPK) are a group of protein signaling molecules that respond to diverse extracellular stimuli. Of the numerous proteins studied in the MAPK pathway, the three most studied proteins are extracellular signal-regulated kinases 1 and 2 (ERK1/2), c-jun N-terminal kinase (JNK) and p38-MAPK (p38) (Long et al. 2004). All three kinases respond to circulating growth factors, and mechanical (contraction) and metabolic stresses. ERK1/2 is typically involved in regulating cell growth and proliferation (Wu et al. 2000; Haddad and Adams 2004). JNK is highly mechanosensitive and increases its activity in response to increasing mechanical load and regulates proliferation, hypertrophy, and cellular death (apoptosis) (Martineau and Gardiner 2001; Tan et al. 2009; Lessard et al. 2018). p38 is involved in satellite cell activity, improving the metabolic properties, and related to muscle phenotype of muscle tissue (Khurana and Dey 2002; Hawley et al. 2014; Nicoll et al. 2017). Together, MAPKs integrate exercise-related stimuli into biochemical transcriptional responses. This concept is evident considering evidence showing the overexpression of ERK and p38 signaling is involved in promoting a slow oxidative phenotype in skeletal muscle (reviewed by Schiaffino et al. 2007). However, it does appear that the nature of fiber-type transition is contingent of the ligand or upstream extracellular stressor. For example, Murgia and colleagues (2000) reported that continuatively active Ras (upstream of ERK) increases the expression of a slow muscle phenotype. However, Shi et al. (2008) reported that activation of ERK2 signaling promoted an upregulation of a fast-twitch fiber phenotype in mouse soleus. Thus, considering these conflicting results, MAPK are involved in modulating muscle fiber phenotype but the specific gene program (fast or slow) may not just depend on the individual MAPK activated, (ERK or p38) but also the upstream ligands and kinases that activate it.

To date, much of the literature has focused on the role that the mTOR pathway contributes to hypertrophy and exercise adaption (Spiering et al. 2008; Hawley et al. 2014). However, increasing evidence points to the integration of MAPK and mTOR signaling converging at several points during transduction to coordinate transcriptional responses (Martin et al. 2014; West et al. 2016). Resistance exercise is a potent stimulator of MAPK; however, it appears a minimum threshold of volume or intensity is necessary to activate ERK1/2 and p38 (Burd et al. 2010; Holm et al. 2010). JNK is the most mechanosensitive MAPK and activation of this protein increases with increasing eccentric resistance exercise loads, even with equalized time under tension (Gehlert et al. 2015). Recent

evidence suggests JNK is the "molecular switch" that regulates muscle fiber hypertrophy or atrophy in response to resistance exercise or endurance exercise, respectively (Lessard et al. 2018). This corroborates evidence showing JNK's integration on mTOR and p70S6K signaling responses to contraction in humans (Gehlert et al. 2015) and growth factors in murine models (Martin et al. 2014). The activation of ERK may play a supporting role in resistance exercise muscle adaptions by supporting the maintenance of muscle mass via insulin-like growth-factor I (IGF-1)-mediated mechanisms and increases in ribosome biogenesis (Haddad and Adams 2004; Figueiredo et al. 2015). Short-term resistance training can increase the total expression of ERK, while highly-trained, elite powerlifters and weightlifters have a lower total ERK expression compared to untrained controls (Galpin et al. 2016). Stressful resistance exercise with insufficient recovery may shift skeletal muscle to an inflammatory/apoptotic state at rest (Nicoll et al. 2016). The activation of ERK and p38 appears to depend on the exercise stimulus as high-volume, moderate-load resistance exercise causes differential activation of ERK1/2 and p38 compared to high-load, low-volume exercise (Burd et al. 2010; Holm et al. 2010; Hulmi et al. 2012). There is a paucity of data that directly investigate the role MAPK contributes to chronic exercise adaptations in humans. Despite their known role in regulating mechanotransductive signals, more research is warranted to fully elucidate their role in resistance exercise-induced adaptations in human skeletal muscle.

Stretch-activated channels

While the muscle fiber membrane houses structural proteins such as the α7β1 integrin, it also contains ion channels which become active following mechanical stimulation. These channels, termed stretch-activated channels (SAC), span the membrane and alter their conformation upon muscle contraction. This change in conformation decreases the membrane resting potential allowing for an influx of calcium. Spangenburg and McBride (2006) found that, upon myofiber SAC inhibition and mechanical stimulation, downstream anabolic signaling proteins, such as p70s6k, were decreased. Moreover, McBride et al. (2000) showed that the inhibition of SACs decreased total muscle growth. These studies demonstrate SAC as a mechanotransducer and its necessity in the anabolic response following exercise. However, an area poorly understood is the manner through which the SAC communicates to drive this anabolic signaling cascade.

There are three primary pathways through which SACs have been proposed to drive their anabolic effect, namely cytoskeletal remodeling, calmodulin/calcineurin interaction, and elevated heat shock protein 70 (HSP70) (Stiber et al. 2009; Stary and Hogan 2016). The first two have been reviewed at length and thus this section will focus on the SAC–HSP70 connection. HSP70 is part of a family of heat shock proteins which are termed chaperones due to their role in protein shuttling and folding (Senf et al. 2013). Heat shock proteins are often thought to require a rise in temperature, termed heat stress, to increase their activity. However, Stary et al. (2008) demonstrated the ability of heat shock proteins, specifically HSP70, to respond to mechanical stimulation in lieu of any change of temperature or circulating growth compounds, rendering HSP70 as a mechanosensor. Elevated HSP70 following muscle activity is largely influenced by the transient cytosolic calcium concentrations (Stary and Hogan 2016), much of which may be attributed to the myofiber SAC lending a likely link between the SAC and HSP70.

Similarly, HSP72 (a homologue of HSP70) was shown to positively correlate with intracellular anabolism (Locke 2008). Here, Locke used a synergist ablation model to induce an increase in muscle size and analyzed the tissue at various time-points following surgery to determine HSP72 content. Interestingly, there was a steady increase in HSP72 which paralleled muscle growth throughout all time-points. However, the HSP72-regulating transcription factor, heat shock factor (HSF), was found only to increase on days one, two, and three, with no expression found at later time-points. It is speculated here that this HSF-independent increase of HSP72 works through elevated cytosolic calcium signaling via increased SAC activity and this increased HSP72 content then activates NF-*K*B which is necessary for muscle growth (Locke 2008). Thus, while calcium is often discussed primarily in its ability to allow muscle contraction to take place through its interaction with the cross-bridge cycle, here we describe the absolute necessity of adequate SAC function on subsequent calcium influx in the overall anabolic signaling cascade brought about, in part, by mechanical stimuli (Fig. 1).

Cellular microenvironment

Much of the literature concerning intracellular dynamics has focused around that which occurs inside the cell. However, it has been shown that the cellular microenvironment, such as the extracellular matrix (ECM), greatly influences the cell phenotype. Indeed, Discher and Engler (2006) elegantly demonstrated this through changing the relative microenvironment stiffness [as measured by change in kilopascals (kPa)] upon which stem cells were plated, subsequently influencing the lineage that these undifferentiated cells differentiated toward. For example, when these cells were plated on substrates comprised of 1 kPa stiffness, the cells took on the characteristics of neurons. When the

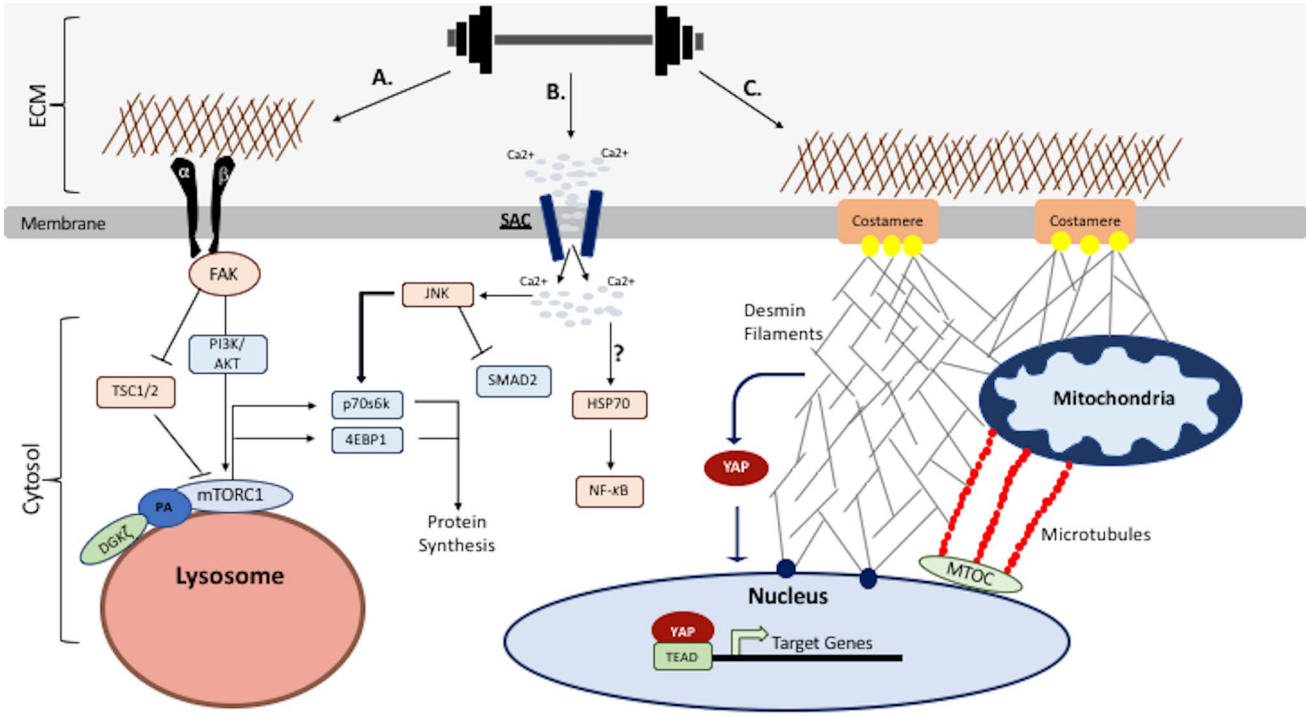

Fig. 1 Three prominent mechanotransducing pathways proposed to increase following exercise. **a** Following resistance exercise, the muscle-specific α7β1 integrin binds to the extracellular matrix, recruiting focal adhesion kinase (FAK) to its cytoplasmic tail, inhibiting tuberous sclerosis complexes 1 and 2 (TSC1/2) and activating PI3K/AKT, both of which indirectly increase mTORC1. Also shown is the DGKζ on the lysosome increasing PA activity which directly activates mTORC1. mTORC1 can then phosphorylate both 4E-BP1 and p70s6k which then increases protein synthesis. **b** Increased intracellular calcium content via conformation change of SAC's following exercise leading to increased HSP70 and NF-*K*B. Elevated calcium content increases JNK which inhibits SMAD2 and phosphorylating p70s6k. **c** Rapid force transmission through the ECM through costameric proteins, along the cytoskeleton, ultimately influencing the organelles with which it interacts—here showing the mitochondria and nucleus. Upon increased cytoskeletal tension, YAP translocates to the nucleus, binds with TEAD transcription factors, ultimately increasing ribosome biogenesis mRNA transcripts. Also shown are microtubule cytoskeletal structures initiating from the microtubule organizing center (MTOC) influencing the mitochondria (You et al. 2014; Goodman et al. 2015; Pasqualini et al. 2016)

stiffness was increased to 8–17 kPa, a similar stiffness to the microenvironment of skeletal muscle, the stem cells took on the characteristics of a myocyte. When the stem cells were plated on substrates of even greater stiffness (25–40 kPa), they took on an osteogenic lineage. Thus, the influence that the microenvironment has upon cellular dynamics cannot be understated. How then might exercise influence the muscle fibers' microenvironment ultimately altering their phenotype?

The ECM is comprised of a conglomerate of proteins of both structural and signaling characteristics alike. It primarily consists of type I, III, and IV collagen proteins, the latter of which is predominantly found within the basement membrane of the muscle fiber. The ECM also consists of proteoglycans, hyaluronan, fibronectin, elastin, and laminin (Kjaer 2004). The ECM is found to house a number of cell types such as fibroblasts, growth factors, cytokines, and the muscle-specific stem cell called satellite cells, the latter of which being found to reside between the muscle fiber sarcolemma and the basal lamina (Gattazzo et al. 2014). The degradation and synthesis of properties within the ECM are driven by the matrix metalloproteinases (MMP) and tissue inhibitors of metalloproteinases (TIMP), respectively (Kjaer 2004).

Interestingly, while MMPs and TIMPs work in a manner to alter the ECM tension state through regulating protein content, they also influence growth factor signaling through mechanotransduction. Specifically, mechanical stimulation at the cellular membrane, such as that found with exercise, can drive nitric oxide signaling. This in turn can activate MMPs which untether hepatocyte growth factors (HGF) from the ECM. HGF can then increase satellite cell activity (Yamada et al. 2006). It is readily agreed upon that satellite cells are required, or in the least beneficial, for hypertrophy and is thus one mechanism by which MMP's work to influence anabolism.

Mackey and colleagues (2004) have shown that an acute maximal eccentric stimulus of the knee extensors led to a significant ECM remodeling through a short-term increase in TIMPs and MMPs along with a subsequent increase in

collagen IV. Moreover, Koskinen (2002) utilized an animal model in which rats ran downhill as to stimulate an eccentric muscle action. These rats showed a unique temporal regulation of ECM factors such as an increase in MMP-2 mRNA both 4 and 7 days following the acute exercise, increased TIMP-1 as early as 6 h following the exercise, and increased collagen IV 7 days following the training intervention but only in the fast twitch muscle fibers.

Taken collectively, the underlying question is how might cells sense this change in their microenvironment? This question is fundamental to the field of mechanobiology as any external mechanical stimulus, such as that brought about by exercise, must first be transmitted through the ECM, into the muscle fiber, ultimately influencing gene expression. The elderly are often found to have a fibrotic ECM comprised of increased collagen deposition with minimal MMP activity leading to an over-abundance of collagen content (Garg et al. 2016). Due to direct interaction of transmembrane proteins with the ECM, such as the α7β1 integrin, intracellular signaling cascades can be directly altered through ECM protein turnover such as that brought about by aging or exercise. This directly relates to the necessity of proper tissue quality as to improve muscle force transmission and signaling. If an individual is continuously exposing a given muscle to a certain stressor, such as high-intensity exercise with minimal recovery, it is likely that the ECM protein content will take on a fibrotic-like environment. This will likely culminate into altered intracellular signaling along with negatively influencing muscle force transmission.

The skeletal muscle microenvironment has also been shown to be a key factor influencing satellite cell dynamics (Murach et al. 2018). The satellite cell is the skeletal muscle-designated stem cell which is often found to reside in its quiescent state (inactive) between the sarcolemma and basal lamina. Following muscle activity, the satellite cell can leave its quiescent state, proliferate (create more satellite cells), differentiate (change phenotype), and insert itself into the muscle fiber as to provide a means to increase transcriptional dynamics via greater nuclear number. Interestingly, recent research has shown mechanically sensitive properties of the satellite cell (Gattazo et al. 2014). Moreover, Eftestol (2016) showed the necessity of high load, compared to a low-load stimulus, to induce myonuclear accretion. Regrettably, much of the past literature in satellite cell mechanotransduction has been focused on the effect that circulating compounds, such as those secreted from the fibroblast or skeletal muscle fiber, have on satellite cell dynamics. Thus, an area of much-needed investigation is biophysical mechanosensation of the satellite cell and how exercise, both low and high intensity, may be propagated to its intracellular space as to regulate gene expression. Specifically, similar to the skeletal muscle fiber, might the satellite cell be able to transmit force from transmembrane proteins, through the cytoskeleton, directly to the nucleus as to modulate its activity in a matter of seconds? Much is to be discovered in this fascinating area of research.

While the state of the ECM is clearly important concerning its ability to influence both biochemical and biophysical mechanotransduction, this altered ECM environment must first be sensed and transmitted intracellularly. This largely takes place though "bridges" connecting the ECM to the actin-cytoskeleton, termed costameres. Costameres are muscle-specific focal adhesion complexes found at the muscle membrane which are aligned in parallel with the sarcomeric z-disc (Ervasti 2003). While these protein complexes work dually as both chemical and mechanical integrators, its role as a lateral force transmitter has been most intensely studied.

Upon muscle contraction and cross-bridge movement within the sarcomere, the force generated must be transmitted to the tendon as to initiate movement. This transmission of force can take place in both lateral and longitudinal directions (Hughes et al. 2015). Longitudinal force transmission runs the length of the muscle fiber from z-disc to z-disc and to the tendon via the myotendinous junction to initiate movement. Lateral force transmission runs the width of the muscle fiber, in a central to peripheral manner, working from the z-disc to the cytoskeleton, through the costamere, and out to the ECM. It has been demonstrated that ~ 80% of the force generated within a muscle fiber is transmitted laterally (Ramaswamy et al. 2011). This finding raises a number of questions, specifically, how might different modes of contraction, such as eccentric and concentric muscle actions, regulate and possibly improve the efficiency of lateral force transmission? This specific question will be discussed further in following sections.

The cytoskeleton

Similar to the ECM, the cellular cytoskeleton is a dynamic macrostructure analogous to a scaffolding system, consisting of continuous protein flux largely influenced by internal and external mechanical stimuli (Ingber 2006). Indeed, upon muscle activity, cytoskeletal microtubules buckle and break, intermediate and microfilaments shorten and lengthen, all of which activate or deactivate a number of signaling cascades which are freely moving within the cytosol or immobilized upon the cytoskeleton (Chicurel et al. 1998).

The cytoskeletal's effect upon cellular function can readily be seen with the intermediate filament desmin. Desmin is the most abundant intermediate filament within the skeletal muscle physically connecting a number of organelles such as the mitochondria, nucleus, and lysosome, along with the costamere to the force-generating sarcomere (Milner et al. 2000; Shah et al. 2004). This being so, force transmitted from the ECM, through the costamere, along the protein

desmin, ultimately influences the structures/organelles through which it interacts. While the nucleus will be of specific focus, cytoskeletal regulation of mitochondrial function has been demonstrated through controlling mitochondrial morphology. A comprehensive review can be found here (Pasqualini et al. 2016).

Concerning the nucleus, it has been well appreciated since the 1980s that there is a direct physical connection from the muscle fiber membrane to the nucleus through the integrin–cytoskeleton–nuclear matrix link (Ingber 2006). This continuous link allows for force to propagate intracellularly upon transmembrane protein stimulation, leading to cytoskeletal tension, deformation of nuclear transmembrane proteins, and ultimately influencing gene expression through chromatin deformation. The ability of the force to propagate from the cellular membrane to the nucleus has been wonderfully demonstrated by Tajik et al. (2016). Here they physically pulled on the transmembrane integrin with magnetic tweezers and observed an increase in gene expression, all of which took place within ~ 15 s. Moreover, the same group showed that, upon pulling on the integrin, the protein Src was phosphorylated on the opposite side of the cell within 300 ms (far faster than growth factor-induced signaling taking ~ 5–15 min) (Na et al. 2008).

Tajik's demonstration of rapid force transmission leads to a number of questions which may be applied to the field of exercise science. First, how do intracellular structural proteins, specifically those of the cytoskeleton, change in quantity and/or spatial positioning following both acute and chronic periods of training? If changes do occur, how does this influence the degree by which force is transmitted through the muscle fiber to the nucleus? Interestingly, Barash et al. (2002) demonstrated a significant decrease in desmin following eccentric muscle activity. Here they showed that desmin content was sharply decreased followed by a threefold supercompensatory increase 5–7 days following the eccentric stimulus. Thus, how might this threefold increase in the cytoskeletal protein desmin influence force transmission to the mitochondria, nucleus, or lysosome? Might this improved cytoskeletal network decrease mechanical perturbation of the mitochondria which may positively influence oxidative capabilities through a decrease in reactive oxygen species? Much is to be better understood concerning the effect of cytoskeletal flux upon intracellular organelle activity (Fig. 2).

The nuclear matrix

An area of much interest in the mechanobiology field is the mechanically sensitive properties which make up the nucleus. The nucleus is the DNA-housing center which regulates gene expression following the integration of a myriad of signals. An interesting aspect of the mechanically sensitive nucleus is the continuity of the intranuclear space and the cytoskeleton through the LINC (linker of nucleoskeleton and cytoskeleton) complex (Fruleux et al. 2016). More than 20 years ago, the Ingber Lab investigated this physical coupling of the nucleus and cytoskeleton (Maniotis et al. 1997). They demonstrated that, upon physical perturbation of the transmembrane integrin, force was transmitted toward the nucleus resulting in nuclear deformation and change in gene expression. As mentioned above, it was demonstrated that this propagation of mechanical tension could produce an increase in gene expression in less than 15 s. However, the mechanism(s) underlying this rapid increase in gene expression are still under investigation. Interestingly, Tajik et al. (2016) did show that the specific gene which increased expression was shown to stretch upon initiation of the mechanical stimulus. This stretch, termed "chromatin stretching", likely revealed binding sites for the transcriptional machinery and subsequent upregulation of transcription. Moreover, it has elegantly been demonstrated that the nuclear actin physically moves specific DNA sequences toward gene regulating sites such as the nuclear pore complex (NPC) and nuclear speckle regions (D'Angelo 2018; Vera et al. 2014). The NPC comprises the primary mechanism which allows for nucleo-cytoplasmic shuttling of proteins/mRNA while speckle regions house many of the transcriptional hardware and thus genes in close proximity to either of these areas are often increased in their expression.

An interesting line of investigation with no apparent current research is the structural characteristics of the nuclear pore complex (NPC) in regulating gene expression and hypertrophy following exercise. In short, it has been demonstrated that the myocyte enhancer factor 2c (Mef2c), a protein which regulates muscle hypertrophy, can be recruited by nucleoporin 210 (Nup210) through its interaction with the protein Trip6. This Mef2c/Trip6/Nup210 complex can then colocalize with a number of muscle growth genes physically connecting them to the NPC (D'Angelo 2018). As previously mentioned, genes close to the NPC often have increased expression. Moreover, it has been speculated that some of the possible regulators of this Mef2c recruitment and Nup210 immobilization work in part through the LIM-domain protein Trip6, which are found to be localized at focal adhesion complexes (such as the costamere) rendering this protein to be highly mechanically regulated. Moreover, movement of specific genes within the nucleus following an external stimulus has been found to regulate gene expression. Vera (2014) found this to be the case with the heat shock protein gene. Upon periods of heat stress, heat shock protein genes were found to physically move to speckle regions of which house a high number of transcription-regulating factors. While this study utilized heat stress as the stimulus, HSP70, as mentioned above, is mechanically

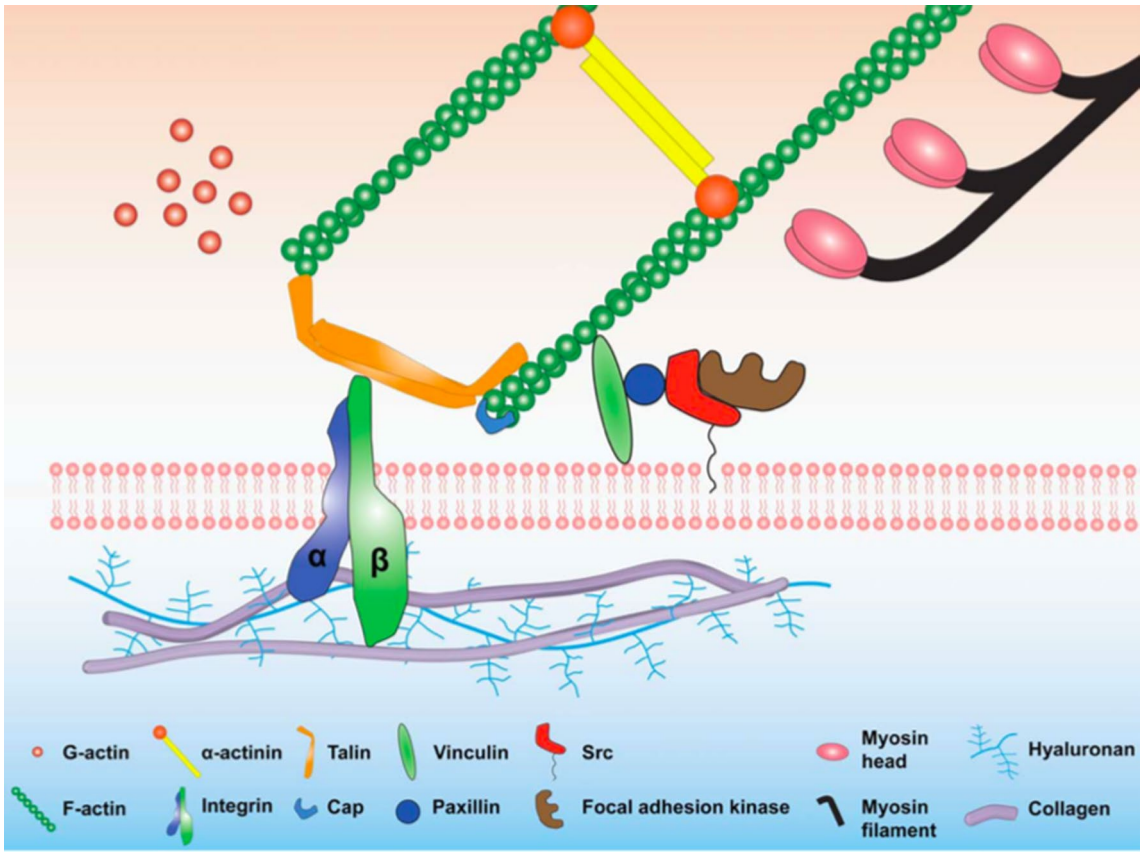

Fig. 2 Physical continuity between the extracellular matrix, integrin, and cytoskeleton. Following muscle activity, the integrin becomes active, binds to the extracellular matrix, and recruits signaling proteins to its cytoplasmic tail such as the focal adhesion kinase. Structural proteins are also recruited allowing physical interaction with the actin-cytoskeleton allowing for force propagation throughout the intracellular space. Used with permission (Ye et al. 2014)

sensitive and thus it is proposed that direct force transmission to the nucleus may influence the DNA movement and subsequent increase in HSP70 expression.

An area of great interest concerning nuclear mechanotransduction is the effect that exercise, whether high or low intensity, has on cytoskeletal protein kinetics. Specifically, does exercise influence the overall quantity or quality of the cytoskeleton? This is a key question as research conducted in 2002 found that the level of cytoskeletal pre-stress, which correlates with cytoskeletal filament content, influences force transmission to the nucleus ultimately regulating gene expression (Wang et al. 2002). Indeed, Asparuhova et al. (2009) likened the cytoskeleton to a 'memory device' whereby previous mechanical activity which rearrange cytoskeletal filaments subsequently influence the cytoskeletal pre-stress. This change in pre-stress from a prior stimulus will then regulate force transmission and gene expression during a following bout of mechanical activity. Moreover, skeletal muscle is likely a key system through which pre-stress regulates inter-nuclear communication as its nuclei are found at the periphery of the cell (Roman et al. 2018). Thus, how might dissimilar modes of exercise, such as high or low intensity, influence cytoskeletal pre-stress and subsequent degree to which the nucleus senses the mechanical stimulus? If these two styles of exercise do influence cytoskeleton flux in a unique manner, it can then be reasoned that this will alter cytoskeletal-nuclear force transmission and subsequent gene expression. This is an interesting field of investigation with no current lines of inquiry lending it ripe for future research.

As the last three sections have attempted to bring to light, there is a direct physical connection between the cellular microenvironment, the cytoskeleton, and the nuclear matrix, demonstrating the intrinsic biophysical mechanotransducing communication system through which mechanical stimuli, such as that found with exercise, can lead to rapid gene expression in lieu, and in conjunction, with biochemical signal-transduction. An underlying question of this physical continuity is the applicability of the information on the overall training regimen of athletes and the general population alike. The following section will attempt to do so (Fig. 3).

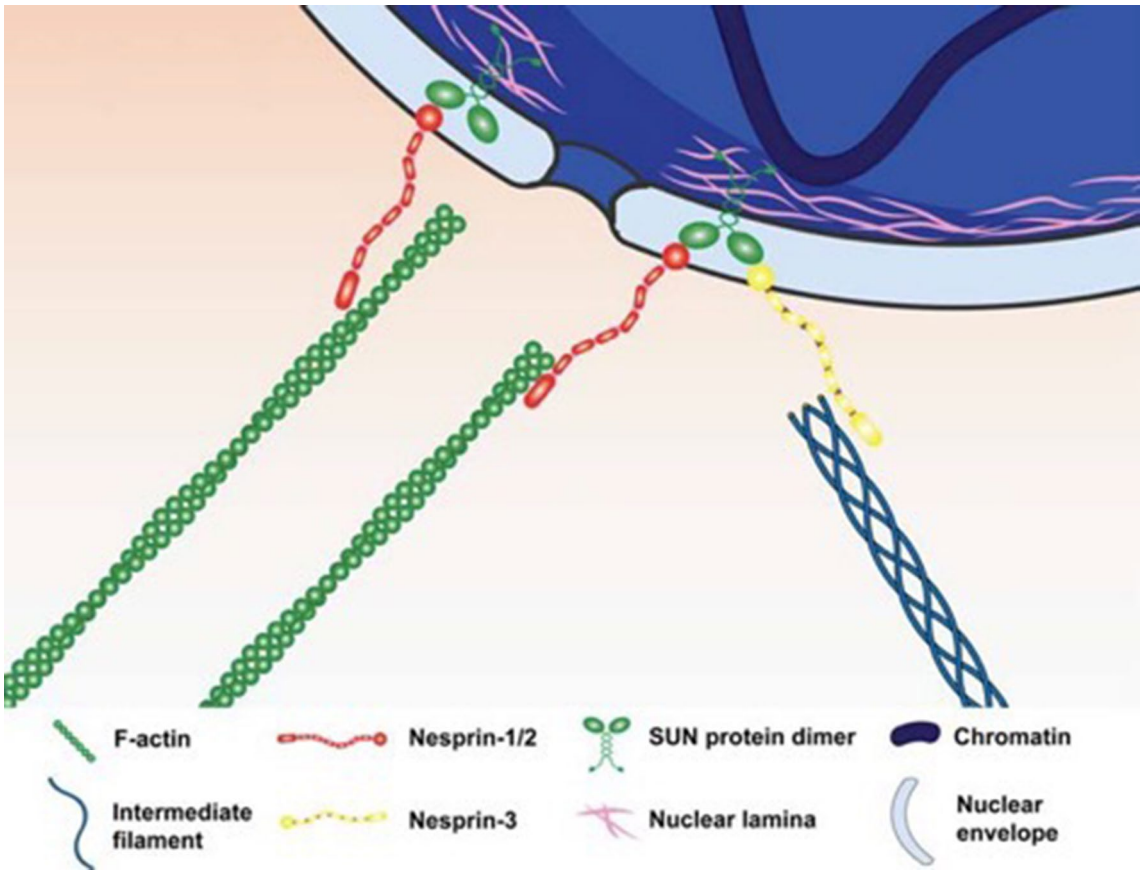

Fig. 3 Physical link between the cytoskeleton and the nucleus. Upon muscle activity, force is transmitted along the cytoskeletal intermediate filaments, through the nuclear transmembrane proteins comprised of the LINC complex, into the nuclear matrix. How exercise influences nuclear rearrangement through biophysical mechanotransduction is yet unknown. Used with permission (Ye et al. 2014)

Intensity-dependent mechanotransduction

Exercise intensity lies upon a continuum with low- and high-intensity exercise on opposing ends. Low intensity is often thought to consist of an aerobic style of exercise with high intensity consisting of an anaerobic style of exercise, such as resistance exercise. As previously mentioned, much of the past literature has speculated that mechanically sensitive proteins and their respective pathways are largely activated following exercise which creates high levels of mechanical tension within the muscle, such as that found with resistance training. However, recent evidence within our lab demonstrates that, rather than the simplistic viewpoint of an "off" or "on" switch, a number of mechanically sensitive proteins alter their function dependent upon the degree to which the mechanical stimulus is acting upon the protein. One protein which demonstrates this unique degree of regulation following divergent modes of stimulation is the protein focal adhesion kinase (FAK).

FAK is spatially found to bind to the sarcomeric myosin protein while in its resting state (Fonseca et al. 2005). Following high levels of mechanical tension, FAK can become active and translocate to the beta1 integrin tail leading to auto-phosphorylation and subsequent anabolic signaling (Klossner et al. 2009). Interestingly, following an aerobic stimulus, FAK was shown to act as an epigenetic factor through chromatin remodeling along with acting as a transcription factor to the muscle regulatory gene myogenin (Mei et al. 2010). The latter was found following the introduction of a hypoxic stimulus driving FAK interaction with the methyl-CpG binding domain 2 (MBD2), reducing MBD2's interaction with histone deacytalase 1 (HDAC1), and ultimately decreasing methylation of the myogenin promotor. DNA methylation at the promotor has been widely demonstrated to reduce gene expression. Thus, the inhibition of methyl binding at this site is paramount for enhanced gene expression.

Moreover, low-intensity resistance exercise in conjunction with blood flow restriction (BFR) has been shown to increase a number of morphological adaptations such as an increase in muscle fiber size, oxidative adaptations, and power output capabilities, all while using a relatively low

external load comprising 20–30% of one's 1RM (Loenneke et al. 2012a). While the key drivers behind this phenomenon have yet to be solidified, it is proposed that a "cell swelling" effect is likely at play and may be an influential mechanism through which BFR drives its anabolic effect (Loenneke et al. 2012b). As evident in its name, BFR restricts, or occludes, venous blood flow leading to a pooling effect increasing muscle cell volume. BFR has been speculated to drive this cell swelling effect through altering the intracellular and extracellular pressure gradient subsequently leading to an increase in cellular fluid uptake. This increase of cellular fluid uptake may then influence mechanotransduction in two specific mechanisms—increased integrin activity and/or driving cytoskeletal reorganization. Indeed, it has been demonstrated that integrins may be a key mediator in the cell swelling effect (Low et al. 1998). Moreover, the deformation of the cellular membrane following an increase in cellular volume would likely influence cytoskeleton dynamics. How this would occur has yet to be investigated and is an area requiring further research.

Nakada et al. (2016) reported that the degree of mechanical overload via varying degrees of synergist ablation resulted in ever-increasing levels of ribosome biogenesis markers. Specifically, as the external stimulus increased, the 18S and 28S ribosomal RNA (rRNA) increased in parallel. In contrast, Romero et al. (2017) demonstrated a marked increase in ribosome biogenesis following endurance exercise which likely poses minimal mechanical overload. Fyfe et al. (2018) similarly found enhanced ribosome biogenesis following the combination of endurance and resistance exercise compared to resistance exercise alone. These investigations clearly utilized divergent modes of exercise with differing levels of mechanical overload yet rendering a similar elevation in ribosome activity; interestingly, much of which took place in an mTORC1-independent manner. A proposed mechanism underlying this observation is the mechanosensor yes-associated protein (YAP). YAP is regulated in part by the cytoskeleton whereby increased cytoskeletal tension leads to YAP dephosphorylation, nuclear translocation, and subsequent enhanced transcription of ribosome biogenesis mRNA transcripts such as c-Myc (Halder et al. 2012; Goodman et al. 2015). Goodman et al. (2015) demonstrated that this YAP-induced increase in ribosome biogenesis can take place through an mTORC1-independent mechanism. Similar to that previously mentioned, while endurance exercise may pose a reduced mechanical overload, the possible cell-swelling effect brought on by elevated intracellular metabolites may ultimately regulate cytoskeletal dynamics and subsequently influence YAP activity.

Taken collectively, the premise that mechanotransduction is only at play following high levels of mechanical tension leaves much to be desired. Rather, mechanically sensitive proteins and pathways should be viewed to lie on a continuum with their activity state not necessarily being increased or decreased dependent upon the degree of mechanical tension, but rather the protein taking on a different role which is dictated by the position of the stimulus on the mechanical tension spectrum.

Muscle action-specific mechanotransduction

It has been well documented that not only does the muscle fiber respond uniquely to divergent metabolic stimuli, it can also respond uniquely to the mode of muscle action such as eccentric, concentric, or isometric muscle actions (Franchi et al. 2017). The intrinsic response to these diverse modes of muscle activity has been shown in part to be driven through differentially regulated mechanically sensitive pathways ultimately culminating into specific signaling cascades and gene expression (Rindom et al. 2016).

Rindom's premise (2016) is that the specific muscle action dictates the relative activity of specific intracellular macromolecular structures; such that during eccentric muscle actions, transmembrane receptors are preferentially recruited, whereas concentric muscle actions largely recruit sarcomeric proteins. While this may be a rather simplistic viewpoint, it does render some interesting questions. Specifically, does one mode of exercise give rise to greater muscular adaptations, due in part to the mechanotransduction pathway initiated, compared to other modes? As an example, one may wish to develop the ability of a given fiber type such as a fast twitch fiber, or the muscle as a whole, to transmit force. With the above-proposed platform as a means to differentiate between the cellular properties recruited dependent upon mode of muscle action, this individual may benefit from implementing eccentric muscle actions to improve their muscle force transmission. This is recommended because, as previously mentioned, up to 80% of force is transmitted in a lateral direction (Ramaswamy et al. 2011). The key structures which allow for this lateral transmission of force are the integrin, cytoskeleton, and extracellular matrix. These structures, as Rindom described in their excellent review (Rindom et al. 2016), are highly recruited during eccentric muscle actions.

While important muscle fiber structural adaptations are required for adequate muscle force transmission, other sought-after goals may be of preference such as an increase in muscle size. This, too, can be categorized in a muscle action-specific manner through differential regulation of cellular signaling. Eliasson et al. (2006) investigated this through the implementation of either maximal concentric or maximal eccentric muscle actions and subsequent analysis of anabolic signaling proteins such as p70s6k, mTOR, AKT, and ribosomal protein S6 (rpS6). Here they found that eccentric muscle actions led to a fourfold increase in p70s6k

phosphorylation at residues Ser424/Thr421 and a twofold increase in phosphorylation at residue Thr389 while the concentric muscle action did not show any noticeable increase in p70s6k activity. Moreover, there were noticeable differences in the phosphorylation of rpS6 in favor of eccentric activity compared to concentric.

Hornberger and colleagues directly investigated this differential effect of signaling kinetics following the type of muscle activity and found that the implementation of multiaxial and uniaxial muscle actions, mimicking eccentric and concentric muscle actions, respectively, uniquely regulated muscle fiber signaling (Hornberger et al. 2005). Specifically, multiaxial stress resulted in a significantly greater phosphorylation of p70s6k along with ERK. This increase in phosphorylation, specifically that of p70s6k, was found to be decreased following pharmacological inhibition of the cytoskeleton, whereas no such decrease was found with uniaxial muscle activity. This demonstrates the ability of the cytoskeleton to sense different muscle actions subsequently altering protein phospho-kinetics. As previously mentioned, the cytoskeleton is in a continuous state of flux and has been proposed to be at the center of muscle fiber mechanosensation. Moreover, with the cytoskeleton sensitive to the specific mode of muscle action, how might eccentric or concentric exercise regulate cytoskeletal pre-stress and nuclear mechanotransduction? This exciting line of inquiry will undoubtedly provide great insight into what is currently a poorly understood means of muscle fiber communication.

It must be noted that the above does not imply preference from one mode of muscle action over another. Rather, the utilization of a broad spectrum of muscle actions is recommended as to regulate cellular anabolism, structural protein adaptations, and metabolic changes, as is necessary for often sought-after training goals. A number of specific populations require a greater prioritization of one mode of muscle action over another; whether this be a given sporting endeavor or one's health. For example, the sport of American Football requires a number of abrupt change-of-directions resulting in large eccentric forces working upon the muscles of the lower body. These athletes may then warrant a greater emphasis upon exercise implementing an eccentric overload. Thus, dependent upon the population, the use of one mode of muscle activity over another will inevitably vary.

Integration of diverse signals

While the majority of this review has been geared toward mechanically sensitive properties of the muscle fiber, it must be understood that the biochemical milieu induced by autocrine, paracrine, and endocrine factors alike intertwine with mechanotransducing signaling events as to culminate into a functional response. In 1995, Plopper and colleagues (1995) brilliantly described this phenomenon. As stated by Plopper, "growth factors and ECM must work hand-in-hand to produce the full cellular response". Furthermore, Takada and colleagues (2017) recently demonstrated the ternary complex formed by the anabolic insulin-like growth factor 1 (IGF-1), integrin, and the IGF-1 receptor axis. This functional complex formation is formed in such a manner that upon IGF-1 binding to its designated receptor (IGF1R), the integrin is subsequently recruited and forms a ternary complex. Inhibition of the specific residues upon the integrin which allow for IGF1-IGF1R binding to take place reduces cellular proliferation through inhibition of several anabolic downstream pathways. While this area has yet to be investigated in skeletal muscle, it would appear a promising line of study.

Furthermore, post-transcriptional modification of the IGF-1 pre-mRNA has shown to be influenced via mechanical activity leading to alternative splicing and subsequent synthesis of the IGF-1Ec splice variant, also known as mechano-growth factor (MGF) (Matheny et al. 2010). Hill (2003) observed the proliferative effect of MGF on quiescent satellite cells. In fact, much of literature concerning MGF's muscle promoting function has largely been geared toward its role upon satellite cell proliferation. However, the absolute necessity of functional satellite cells upon muscle growth has been questioned (McCarthy et al. 2011), lending doubt to MGF's primary anabolic effect working through these muscle progenitor cells (Barton 2006). Rather, it is likely that other muscle growth-promoting characteristics of MGF take precedence. Most notably, it was shown that the injection of a plasmid containing the MGF vector into rat muscle led to a dramatic 25% increase in muscle mass within 3 weeks (Goldspink et al. 2001). However, how MGF influences muscle growth is an ongoing area of debate. It has been proposed that these proliferative effects work through the MAPK signaling pathway (Matheny et al. 2010). Recent scrutiny, however, has questioned this mode of MGF signaling leaving the anabolic effects of MGF to remain elusive (Fornaro et al. 2014). Indeed, it may be that MGF plays a permissive role in muscle growth following exercise compared to supraphysiological doses administered in cell culture and animal models. Interestingly, work by Bamman et al. (2007) showed that the degree of MGF activity following exercise differs between those considered "high" or "low" responders. Thus, these discrepancies make it clear that further research of MGF signaling following exercise is greatly needed.

Growth hormone, similar to IGF-1, has come under immense scrutiny concerning its role upon muscle growth, namely it has been proposed that growth hormone does not play a significant role in intracellular anabolic signaling. This, in our opinion, is dogmatic, lacking context of the dynamic and integrating nature of the muscle fiber. Past

and current investigations have demonstrated the positive role GH has upon collagen activity (Doessing et al. 2010). This is often not considered when investigating hypertrophy and protein synthetic machinery but is nevertheless important due to many of the factors mentioned above, namely adequate ECM–cytoskeletal force transmission which can be improved via increased collagen synthesis. Specifically, improved extracellular collagen content influences the above-mentioned lateral force transmission subsequently influencing both biophysical and biochemical mechanotransduction.

Thus, while it may seem tempting to compartmentalize mechanotransduction and growth factor-stimulating pathways, it should not be seen as such. Rather, the harmonious integration of a diverse array of signaling cascades, from both mechanical and hormonal stimuli alike, should be viewed as, while different pieces to the muscle remodeling puzzle, they ultimately culminate to form a functional response driving cellular adaptation (Fig. 4).

Future perspectives

While much has been described concerning the muscle fiber mechanotransducing network and how it may be influenced by exercise, this field of study is only in its infancy. Indeed, while the past two decades have largely focused on the mechanically sensitive skeletal muscle membrane, minimal research has been directed toward the relationship between extracellular matrix dynamics and the resultant

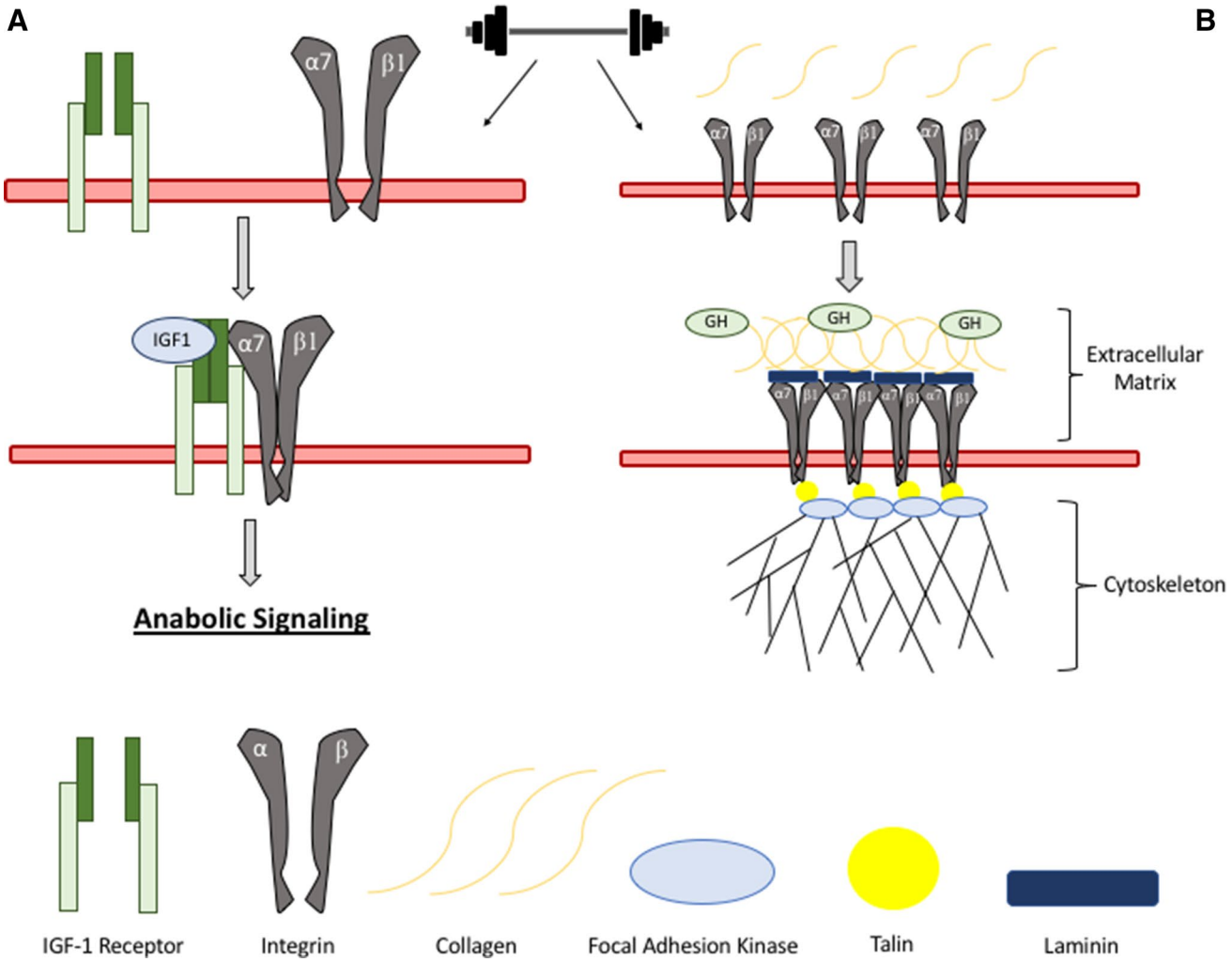

Fig. 4 Integrative signaling of commonly accepted growth factor signaling and mechanically sensitive intracellular and extracellular properties. **a** Following exercise, a proposed ternary complex is formed between the insulin-like growth factor-1 receptor, insulin-like growth factor, and the α7β1 integrin receptor ultimately inducing anabolic downstream signaling (Takada et al. 2017). **b** Following exercise (dependent on intensity), growth hormone secretion increases with a resultant increase in collagen. This is proposed to improve intracellular force transmission through the integrin, cytoskeleton, and subsequently to the nucleus (Doessing et al. 2010)

effect upon intracellular mechano-signaling. Moreover, the mechanically sensitive properties of the satellite cell and muscle fiber nuclei remain poorly understood. These areas of mechanobiology will prove important as the role of the ever-changing extracellular matrix tension state on gene expression has been readily identified (Engler et al. 2006). The field of mechanobiology, and specifically biophysical mechanotransduction, will require techniques which are not frequently used within exercise physiology; for example, the use of three-dimensional magnetic twisting cytometry as a means to impose a physical stress on the muscle membrane and identify rapid rearrangement of the cytoskeleton/nuclear matrix (Tajik et al. 2016). Of specific interest, this could be used with primary muscle cells from trained and untrained test-subjects and the resultant speed at which force is transmitted to the nucleus can be measured along with real-time imaging of rapid transcription and translation (protein synthesis) (Chao et al. 2012). A following "omics" approach, such as proteomics, could then be utilized to gain widespread cellular information (Ohlendieck 2011). These areas and strategies will require increasing levels of expertise and thus collaboration will continue to be important to further the field of mechanobiology and exercise science.

Author contributions All authors listed have made substantial, either direct or intellectual, contribution to the work. All authors approved the manuscript for publication.

References

Adachi Y, Itoh K, Yamada T, Cerveny KL, Suzuki TL, Macdonald P, Frohman MA, Ramachandran R, Iijima M, … Sesaki H (2016) Coincident phosphatidic acid interaction restrains Drp1 in mitochondrial division. Mol Cell 63(6):1034–1043

Asparuhova MB, Gelman L, Chiquet M (2009) Role of the actin cytoskeleton in tuning cellular responses to external mechanical stress. Scand J Med Sci Sports 19(4):490–499

Bamman MM, Petrella JK, Kim JS, Mayhew DL, Cross JM (2007) Cluster analysis tests the importance of myogenic gene expression during myofiber hypertrophy in humans. J Appl Physiol 102:2232–2239

Barash IA, Peters D, Friden J, Lutz GJ, Lieber RL (2002) Desmin cytoskeletal modifications after a bout of eccentric exercise in the rat. Am J Physiol Regul Integr Comp Physiol 283:958–963

Barton ER (2006) Viral expression of insulin-like growth factor-I isoforms promotes different responses in skeletal muscle. J Appl Physiol 100:1778–1784

Booth FW (1977) Time course of muscular atrophy during immobilization of hindlimbs in rats. J Appl Physiol 43:656–661

Boppart MD, Burkin DJ, Kaufman SJ (2006) Alpha7beta1-integrin regulates mechanotransduction and prevents skeletal muscle injury. Am J Physiol Cell Physiol 290:C1660–C1665

Burd NA, Holwerda AM, Selby KC, West DWD, Staples AW, Cain NE, Cashaback JGA, Potvin JR, Baker SK, Phillips SM (2010) Resistance exercise volume affects myofibrillar protein synthesis and anabolic signaling molecule phosphorylation in young men. J Physiol 588(16):3119–3130

Chao JA, Yoon YJ, Singer RH (2012) Imaging translation in single cells using fluorescent microscopy. Cold Spring Harb Perspect Biol 4(11):a012310

Chicurel ME, Singer RH, Meyer CJ, Ingber DE (1998) Integrin binding and mechanical tension induce movement of mRNA and ribosomes to focal adhesions. Nature 392:730–733

D'Angelo MA (2018) Nuclear pore complexes as hubs for gene regulation. Nucleus 9(1):142–148

Doessing S, Heinemeier KM, Holm L, Mackey AL, Schjerling P, Rennie M, Kjaer M (2010) Growth hormone stimulates the collagen synthesis in human tendon and skeletal muscle without affecting myofibrillar protein synthesis. J Physiol 588(Pt 2):341–351

Eftestøl E, Egner IM, Lunde IG, Ellefsen S, Andersen T, Sjåland C et al (2016) Increased hypertrophic response with increased mechanical load in skeletal muscles receiving identical activity patterns. Am J Physiol Cell Physiol 311:C616–C629

Eliasson J, Elfegoun T, Nilsson J, Köhnke R, Ekblom B, Blomstrand E (2006) Maximal lengthening contractions increase p70 S6 kinase phosphorylation in human skeletal muscle in the absence of nutritional supply. Am J Physiol Endocrinol Metab 291:E1197–E1205

Engler AJ, Sen S, Sweeney HL, Discher DE (2006) Matrix elasticity directs stem cell lineage specification. Cell 126:677–689

Ervasti JM (2003) Costameres: the Achilles' heel of Herculean muscle. J Biol Chem 278:13591–13594

Fealy CE, Mulya A, Lai N, Kirwan JP (2014) Exercise training decreases activation of the mitochondrial fission protein dynamin-related protein-1 in insulin-resistant human skeletal muscle. J Appl Physiol 117:239–245

Figueiredo VC, Caldow MK, Massie V, Markworth JF, Cameron-Smith D, Blazevich AJ (2015) Ribosome biogenesis adaptation in resistance training-induced human skeletal muscle hypertrophy. Am J Physiol Endocrinol Metab 309(1):E72–E83

Fonseca PM, Inoue RY, Kobarg CB, Crosara-Alberto DP, Kobarg J, Franchini KG (2005) Targeting to C-terminal myosin heavy chain may explain mechanotransduction involving focal adhesion kinase in cardiac myocytes. Circ Res 96:73–81

Fornaro M, Hinken AC, Needle S, Hu E, Trendelenburg AU, Mayer A, Rosenstiel A, Chang C, Meier V, Billin AN et al (2014) Mechano-growth factor peptide, the COOH terminus of unprocessed insulin-like growth factor 1, has no apparent effect on myoblasts or primary muscle stem cells. Am J Physiol Endocrinol Metab 306:E150–E156

Franchi MV, Reeves ND, Narici MV (2017) Skeletal muscle remodeling in response to eccentric vs. concentric loading: morphological, molecular, and metabolic adaptations. Front Physiol 8:447. https://doi.org/10.3389/fphys.2017.00447

Fruleux A, Hawkins RJ (2016) Physical role for the nucleus in cell migration. J Phys Condens Matter 28:363002

Fyfe JJ, Bishop DJ, Bartlett JD, Hanson ED, Anderson MJ, Garnham AP, Stepto NK (2018) Enhanced skeletal muscle ribosome biogenesis, yet attenuated mTORC1 and ribosome biogenesis-related signalling, following short-term concurrent versus single-mode resistance training. Sci Rep 8(1):560

Galpin AJ, Fry AC, Nicoll JX, Moore CA, Schilling BK, Thomason DB (2016) Resting extracellular signal-regulated protein kinase 1/2 expression following a continuum of chronic resistance exercise training paradigms. Res Sports Med 24(3):298–303

Garcia D, Shaw RJ (2017) AMPK: mechanisms of cellular energy sensing and restoration of metabolic balance. Mol Cell 66:789–800

Garg K, Boppart MD (2016) Influence of exercise and aging on extracellular matrix composition in the skeletal muscle stem cell niche. J Appl Physiol (1985) 121:1053–1058

Gattazzo F, Urciuolo A, Bonaldo P (2014) Extracellular matrix: a dynamic microenvironment for stem cell niche. Biochim Biophys Acta 1840:2506–2519

Gehlert S, Suhr F, Gutsche K, Willkomm L, Kern J, Jacko D, Knicker A, Schiffer T, Wackerhage H, Bloch W (2015) High force development augments skeletal muscle signalling in resistance exercise modes equalized for time under tension. Pflugers Arch 467(6):1343–1356

Goldberg AL (1968) Protein synthesis during work-induced growth of skeletal muscle. J Cell Biol 36(3):653–658

Goldberg AL, Etlinger JD, Goldspink DF, Jablecki C (1975) Mechanism of work-induced hypertrophy of skeletal muscle. Med Sport Sci 7:185–198

Goldspink G, Yang SY (2001) Method of treating muscular disorders. United States patent. Patent no US 6,221,842 B1

Goodman CA, Dietz JM, Jacobs BL, McNally RM, You JS, Hornberger TA (2015) Yes-associated protein is up-regulated by mechanical overload and is sufficient to induce skeletal muscle hypertrophy. FEBS Lett 589(13):1491–1497

Haddad F, Adams GR (2004) Inhibition of MAPK/ERK kinase prevents IGF-1-induced hypertrophy in rat muscles. J Appl Physiol 96:203–210

Halder G, Dupont S, Piccolo S (2012) Transduction of mechanical and cytoskeletal cues by YAP and TAZ. Nat Rev Mol Cell Biol 13:591–600

Hawley JA, Hargreaves M, Joyner MJ, Zierath JR (2014) Integrative biology of exercise. Cell 159:738–774

Hill M, Wernig A, Goldspink G (2003) Muscle satellite (stem) cell activation during local tissue injury and repair. J Anat 203(1):89–99

Holm L, van Hall G, Rose JA, Miller BF, Doessing S, Richter EA, Kjaer M (2010) Contraction intensity and feeding affect collagen and myofibrillar protein synthesis rates differently in human skeletal muscle. Am J Physiol Endocrinol Metab 298:E257–E268

Hornberger TA, Armstrong DD, Koh TJ, Burkholder TJ, Esser KA (2005) Intracellular signaling specificity in response to uniaxial vs. multiaxial stretch: implications for mechanotransduction. Am J Physiol Cell Physiol 288:C185–C194

Hornberger TA, Chu WK, Mak YW, Hsiung JW, Huang SA, Chien S (2006) The role of phospholipase D and phosphatidic acid in the mechanical activation of mTOR signaling in skeletal muscle. Proc Natl Acad Sci USA 103:4741–4746

Hughes DC, Wallace MA, Baar K (2015) Effects of aging, exercise, and disease on force transfer in skeletal muscle. Am J Physiol Endocrinol Metab 309(1):E1–E10

Hulmi JJ, Walker S, Ahtiainen JP, Nyman K, Kraemer WJ, Häkkinen K (2012) Molecular signaling in muscle is affected by the specificity of resistance exercise protocol. Scand J Med Sci Sports 22(2):240–248

Ingber DE (2006) Cellular mechanotransduction: putting all the pieces together again. Faseb J 20:811–827

Jastrzebski K, Hannan KM, Tchoubrieva EB, Hannan RD, Pearson RB (2007) Coordinate regulation of ribosome biogenesis and function by the ribosomal protein S6 kinase, a key mediator of mTOR function. Growth Factors (Chur, Switz). 25(4):209–226

Joy JM, Gundermann DM, Lowery RP, Jäger R, McCleary SA, Purpura M, Wilson JM (2014) Phosphatidic acid enhances mTOR signaling and resistance exercise induced hypertrophy. Nutr Metab 11:29

Kazior Z, Willis SJ, Moberg M, Apró W, Calbet JAL, Holmberg H-C, Blomstrand E (2016) Endurance exercise enhances the effect of strength training on muscle fiber size and protein expression of Akt and mTOR. PLoS One 11:1–18

Khurana A, Dey CS (2002) Subtype specific roles of mitogen activated protein kinases in L6E9 skeletal muscle cell differentiation. Mol Cell Biochem 238(1–2):27–39

Kjaer M (2004) Role of extracellular matrix in adaptation of tendon and skeletal muscle to mechanical loading. Physiol Rev 84:649–698

Klossner S, Durieux A-C, Freyssenet D, Flueck M (2009) Mechano-transduction to muscle protein synthesis is modulated by FAK. Eur J Appl Physiol 106:389–398

Koskinen SOA et al (2002) Short-term effects of forced eccentric contractions on collagen synthesis and degradation in rat skeletal muscle. Pflugers Arch 444:59–72

Laplante M, Sabatini DM (2009) mTOR signaling at a glance. J Cell Sci 122:3589–3594

Legate KR, Wickstrom SA, Fassler R (2009) Genetic and cell biological analysis of integrin outside-in signaling. Genes Dev 23:397–418

Lessard SJ, MacDonald TL, Pathak P, Han MS, Coffey VG, Edge J, Rivas JDA, Hirshamn MF, Davis RJ, Goodyear LJ (2018) JNK regulates muscle remodeling via myostatin/SMAD inhibition. Nat Commun 9(1):3030

Lillemeier BF, Pfeiffer JR, Surviladze Z, Wilson BS, Davis MM (2006) Plasma membrane-associated proteins are clustered into islands attached to the cytoskeleton. Proc Natl Acad Sci USA 103:18992–18997

Locke L (2008) Heat shock protein accumulation and heat shock transcription factor activation in rat skeletal muscle during compensatory hypertrophy. Acta Physiol (Oxf) 192:403–411

Loenneke JP, Fahs CA, Rossow LM, Abe T, Bemben MG (2012a) The anabolic benefits of venous blood flow restriction training may be induced by muscle cell swelling. Med Hypotheses 78(1):151–154

Loenneke JP, Abe T, Wilson JM, Ugrinowitsch C, Bemben MG (2012b) Blood flow restriction: how does it work? Front Physiol 3:392

Long YC, Widegren U, Zierath JR (2004) Exercise-induced mitogen-activated protein kinase signaling in skeletal muscle. Proc Nutr Soc 63(2):227–232

Low SY, Taylor PM (1998) Integrin and cytoskeletal involvement in signaling cell volume changes to glutamine transport in rat skeletal muscle. J Physiol 512(Pt 2):481–485

Lueders TN, Zou K, Huntsman HD, Meador B, Mahmassani Z, Abel M et al (2011) The alpha7beta1-integrin accelerates fiber hypertrophy and myogenesis following a single bout of eccentric exercise. Am J Physiol Cell Physiol 301:C938–C946

Lundberg TR, Fernandez-Gonzalo R, Tesch PA (2014) Exercise-induced AMPK activation does not interfere with muscle hypertrophy in response to resistance training in men. J Appl Physiol Bethesda Md 1985 116:611–620

Mackey AL, Donnelly AE, Turpeenniemi-Hujanen T, Roper HP (2004) Skeletal muscle collagen content in humans after high-force eccentric contractions. J Appl Physiol 97:197–203

Maniotis AJ, Chen CS, Ingber DE (1997) Demonstration of mechanical connections between integrins, cytoskeletal filaments, and nucleoplasm that stabilize nuclear structure. Proc Natl Acad Sci USA 94(3):849–854

Martin TD, Dennis MD, Gordon BS, Kimball SR, Jefferson LS (2014) mTORC1 and JNK coordinate phosphorylation of the p70S6K1 autoinhibitory domain in skeletal muscle following functional overloading. Am J Physiol Endocrinol Metab 306:E1397–E1405

Martineau LC, Gardiner PF (2001) Insight into skeletal muscle mechanotransduction: MAPK activation is quantitatively related to tension. J Appl Physiol 91(2):693–702

Matheny RW et al (2010) Minireview: mechano-growth factor: a putative product of IGF-I gene expression involved in tissue repair and regeneration. Endocrinology 151(3): 865–875

Mayer C, Grummt I (2006) Ribosome biogenesis and cell growth: mTOR coordinates transcription by all three classes of nuclear RNA polymerases. Oncogene 25(48):6384–6391

McBride TA, Stockert BW, Gorin FA, Carlsen Richard CRC (2000) Stretch-activated ion channels contribute to membrane depolarization after eccentric contractions. J Appl Physiol 88:91–101

McCarthy JJ et al (2011) Effective fiber hypertrophy in satellite cell-depleted skeletal muscle. Development (Camb, Engl) 138(17):3657–3666

Mei L, Xiong WC (2010) FAK interaction with MBD2: a link from cell adhesion to nuclear chromatin remodeling? Cell Adhes Migr 4:77–80

Milner DJ, Mavroidis M, Weisleder N, Capetanaki Y (2000) Desmin cytoskeleton linked to muscle mitochondrial distribution and respiratory function. J Cell Biol 150(6):1283–1298

Murach KA, Fry CS, Kirby TJ, Jackson JR, Lee JD, White SH et al (2018) Starring or supporting role? Satellite cells and skeletal muscle fiber size regulation. Physiology 33:26–38

Murgia M, Serrano AL, Calabria E, Pallafacchina G, Lomo T, Schiaffino S (2000) Ras is involved in nerve-activity-dependent regulation of muscle genes. Nat Cell Biol 2(3):142–147

Na S, Collin O, Chowdhury F, Tay B, Ouyang M, Wang Y, Wang N (2008) Rapid signal transduction in living cells is a unique feature of mechanotransduction. Proc Natl Acad Sci USA 105(18):6626–6631

Nakada S, Ogasawara R, Kawada S, Maekawa T, Ishii N (2016) Correlation between ribosome biogenesis and the magnitude of hypertrophy in overloaded skeletal muscle. PLoS One 11(1):e0147284

Nicoll JX, Fry AC, Galpin AJ, Sterczala AJ, Thomason DB, Moore CA, Weiss LW, Chiu LZF (2016) Changes in resting mitogen-activated protein kinases following resistance exercise overreaching and overtraining. Eur J Appl Physiol 116(11–12):2401–2413

Nicoll JX, Fry AC, Galpin AJ, Thomason DB, Moore CA (2017) Resting MAPK expression in chronically trained endurance runners. Eur J Sports Sci 17(9):1194–1202

Ohlendieck K (2011) Skeletal muscle proteomics: current approaches, technical challenges and emerging techniques. Skelet Muscle 1(1):6

Pasqualini FS, Nesmith AP, Horton RE, Sheehy SP, Parker KK (2016) Mechanotransduction and metabolism in cardiomyocyte microdomains. BioMed Res Int 2016:4081638

Plopper GE, McNamee HP, Dike LE, Bojanowski K, Ingber DE (1995) Convergence of integrin and growth factor receptor signaling pathways within the focal adhesion complex. Mol Biol Cell 6(10):1349–1365

Qin J, Vinogradova O, Plow EF (2004) Integrin bidirectional signaling: a molecular view. PLoS Biol 2(6):e169

Ramaswamy KS, Palmer ML, van der Meulen JH, Renoux A, Kostrominova TY, Michele DE, Faulkner JA (2011) Lateral transmission of force is impaired in skeletal muscles of dystrophic mice and very old rats. J Physiol 589:1195–1208

Rindom E, Vissing K (2016) Mechanosensitive Molecular networks involved in transducing resistance exercise-signals into muscle protein accretion. Front Physiol 7:547

Roman W, Gomes ER (2018) Nuclear positioning in skeletal muscle. Semin Cell Dev Biol 82:51–56

Romero MA, Mobley CB, Linden MA, Meers GM, Martin JS, Young KC, Rector RS, … Roberts MD (2017) Endurance training lowers ribosome density despite increasing ribosome biogenesis markers in rodent skeletal muscle. BMC Res Notes 10(1):399

Sabatini DM (2017) Twenty-five years of mTOR: uncovering the link from nutrients to growth. Proc Natl Acad Sci 114(45):11818–11825

Saxton RA, Sabatini DM (2017) mTOR signaling in growth, metabolism, and disease. Cell 168(6):960–976

Schiaffino S, Sandri M, Murgia (2007) Activity-dependent signaling pathways controlling muscle diversity and plasticity. Physiology (Bethesda) 22:269–278

Schwartz MA (2010) Integrins and extracellular matrix in mechanotransduction. Cold Spring Harb Perspect Biol 2:a005066

Senf SM (2013) Skeletal muscle heat shock protein 70: diverse functions and therapeutic potential for wasting disorders. Front Physiol 4:330

Shah SB, Davis J, Weisleder N, Kostavassili I, McCulloch AD, Ralston E, Lieber RL et al (2004) Structural and functional roles of desmin in mouse skeletal muscle during passive deformation. Biophys J 86(5):2993–3008

Shi H, Scheffler JM, Pleitner JM, Zeng C, Park S, Hannon KM, Grant AL, Gerrard DE (2008) Modulation of skeletal muscle fiber type by mitogen activated protein kinase signaling. FASEB J 22:2990–3000

Spangenburg EE, McBride TA (2006) Inhibition of stretch-activated channels during eccentric muscle contraction attenuates p70S6K activation. J Appl Physiol 100:129–135

Spiering BA, Kraemer WJ, Anderson JM, Armstrong LE, Nindl BC, Volek JS, Maresh CM (2008) Resistance exercise biology: manipulation of resistance exercise programme variables determines the responses of cellular and molecular signalling pathways. Sports Med 38:527–540

Stary CM, Hogan MC (2016) Cytosolic calcium transients are a determinant of contraction-induced HSP72 transcription in single skeletal muscle fibers. J Appl Physiol 120:1260–1266

Stary CM, Walsh BJ, Knapp AE, Brafman D, Hogan MC (2008) Elevation in heat shock protein 72 mRNA following contractions in isolated single skeletal muscle fibers. Am J Physiol Regul Integr Comp Physiol 295(2):R642–R648

Stiber JA, Seth M, Rosenberg PB (2009) Mechanosensitive channels in striated muscle and the cardiovascular system: not quite a stretch anymore. J Cardiovasc Pharmacol 54(2):116–122

Tajik A, Zhang Y, Wei F, Sun J, Jia Q, Zhou W, Wang N (2016) Transcription upregulation via force-induced direct stretching of chromatin. Nat Mater 15(12):1287–1296

Takada Y, Takada YK, Fujita M (2017) Crosstalk between insulin-like growth factor (IGF) receptor and integrins through direct integrin binding to IGF1. Cytokine Growth Factor Rev 34:67–72

Tan J, Kuang W, Jin Z, Jin F, Xu L, Yu Q, Kong L, Zeng G, Yuan X, Duan Y (2009) Inhibition of NFkappaB by activated c-Jun NH2 terminal kinase 1 acts as a switch for C2C12 cell death under excessive stretch. Apoptosis 14(6):764–770

Thalacker-Mercer A, Stec M, Cui X, Cross J, Windham S, Bamman M (2013) Cluster analysis reveals differential transcript profiles associated with resistance training-induced human skeletal muscle hypertrophy. Physiol Genom 45(12):499–507

Vera M, Singer RH (2014) Gene regulation: the HSP70 gene jumps when shocked. Curr Biol 24(10):R396–R398

Wang N, Tolic-Norrelykke IM, Chen J, Mijailovich SM, Butler JP, Fredberg JJ, Stamenovic D (2002) Cell prestress. I. Stiffness and prestress are closely associated in adherent contractile cells. Am J Physiol Cell Physiol 282:C606–C616

West DWD, Burd NA, Staples AW, Phillips SM (2010) Human exercise-mediated skeletal muscle hypertrophy is an intrinsic process. Int J Biochem Cell Biol 42:1371–1375

West DW, Baehr LM, Marcotte GR, Chason CM, Tolento L, Gomes AV, Bodine SC, Baar K (2016) Acute resistance exercise activates rapamycin-sensitive and -insensitive mechanisms that control translational activity and capacity in skeletal muscle. J Physiol 594:453–468

Wu Z, Woodring PJ, Bhakta KS, Tamura K, Wen F, Feramisco JR, Karin M, Wang YG, Puri PL (2000) p38 and extracellular signal-regulated kinases regulate the myogenic program at multiple steps. Mol Cell Biol 20(11):3951–3964

Yamada M, Tatsumi R, Kikuiri T, Okamoto S, Nonoshita S, Mizunoya W et al (2006) Matrix metalloproteinases are involved in mechanical stretch-induced activation of skeletal muscle satellite cells. Muscle Nerve 34:313–319

Ye GJ, Nesmith AP, Parker KK (2014) The role of mechanotransduction on vascular smooth muscle myocytes' [corrected] cytoskeleton and contractile function. Anat Rec (Hoboken) 297:1758–1769

You J-S, Lincoln HC, Kim C-R, Frey JW, Goodman CA, Zhong X-P et al (2014) The role of diacylglycerol kinase ζ and phosphatidic acid in the mechanical activation of mammalian target of rapamycin (mTOR) signaling and skeletal muscle hypertrophy. J Biol Chem 289:1551–1563

Zou K, Meador BM, Johnson B, Huntsman HD, Mahmassani Z, Valero MC, Huey KA, Boppart MD (2011) The $\alpha_7\beta_1$-integrin increases muscle hypertrophy following multiple bouts of eccentric exercise. J Appl Physiol 111:1134–1141