Am J Physiol Cell Physiol 317: C629–C641, 2019.
First published July 17, 2019; doi:10.1152/ajpcell.00009.2019.

THEME | *New and Emerging Roles of the Cytoskeleton in Striated Muscle*

Integrin signaling: linking mechanical stimulation to skeletal muscle hypertrophy

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Submitted 14 January 2019; accepted in final form 11 July 2019

Boppart MD, Mahmassani ZS. Integrin signaling: linking mechanical stimulation to skeletal muscle hypertrophy. *Am J Physiol Cell Physiol* 317: C629–C641, 2019. First published July 17, 2019; doi:10.1152/ajpcell.00009.2019.—The $\alpha_7\beta_1$-integrin is a transmembrane adhesion protein that connects laminin in the extracellular matrix (ECM) with actin in skeletal muscle fibers. The $\alpha_7\beta_1$-integrin is highly expressed in skeletal muscle and is concentrated at costameres and myotendious junctions, providing the opportunity to transmit longitudinal and lateral forces across the membrane. Studies have demonstrated that α_7-integrin subunit mRNA and protein are upregulated following eccentric contractions as a mechanism to reinforce load-bearing structures and resist injury with repeated bouts of exercise. It has been hypothesized for many years that the integrin can also promote protein turnover in a manner that can promote beneficial adaptations with resistance exercise training, including hypertrophy. This review provides basic information about integrin structure and activation and then explores its potential to serve as a critical mechanosensor and activator of muscle protein synthesis and growth. Overall, the hypothesis is proposed that the $\alpha_7\beta_1$-integrin can contribute to mechanical-load induced skeletal muscle growth via an mammalian target of rapamycin complex 1-independent mechanism.

hypertrophy; ILK; integrin; mTORC; skeletal muscle

INTEGRIN STRUCTURE AND ACTIVATION

Integrins are heterodimeric membrane proteins comprised of α- and β-subunits (6, 67). The integrin family consists of 18 unique α-subunits and 8 unique β-units that noncovalently associate into 24 known heterodimers, each expressed by a wide variety of mammalian cell types (6). The structure of each integrin subunit includes a large extracellular domain, a transmembrane domain, and a cytoplasmic domain. A complete description of integrin protein structure and conformational changes that occur upon activation can be found in other reviews (26, 76). The purpose of this review is to provide a brief introduction to integrin activation and then outline our current understanding of integrin expression and its involvement in the initiation of skeletal muscle adaptation in response to a mechanical stimulus in the form of contraction, exercise, or chronic loading.

Integrins adhere the cell cytoskeleton to specific proteins within the extracellular matrix (ECM) for the purpose of stabilization/survival, migration, and proliferation. Integrins are bidirectional signaling molecules, allowing internal cues to regulate external adhesion ("Inside-Out" signaling) and relaying cues from the outside microenvironment to regulate cellular processes ("Outside-In" signaling). Integrins are initially transported from the endoplasmic reticulum to the plasma membrane with the extracellular domains of α- and β-subunits displaying a bent and inactivated or "closed" conformation, while the cytoplasmic domains are linked and stabilized by a salt bridge (28) (Fig. 1). In the case of "Inside-Out" signaling, the presence of intracellular force stimulates molecules such as talin and kindlin to attach to the β-subunit and destabilize the salt bridge, which promotes an extended and activated or "open" conformation allowing interaction with the ECM. The A or I domain (A/I domain) in the β-subunit, and in some cases the α-subunit, includes a metal ion-dependent adhesion site (MIDAS) that can serve as a ligand binding site (86). Following integrin activation, presentation of agonists in the external environment (laminin, collagen, fibronectin) facilitate further opening of the integrin extracellular domain and increased binding to the ECM. This high-affinity binding state then induces integrin clustering and assembly of associated cytoplasmic proteins at concentrated regions along the membrane, or focal adhesions (focal adhesion complex, or FAC), providing the basis for "Outside-In" molecular signaling. Due to the cooperative nature of "Inside-Out" and "Outside-In" conformational changes, endogenously and exogenously applied

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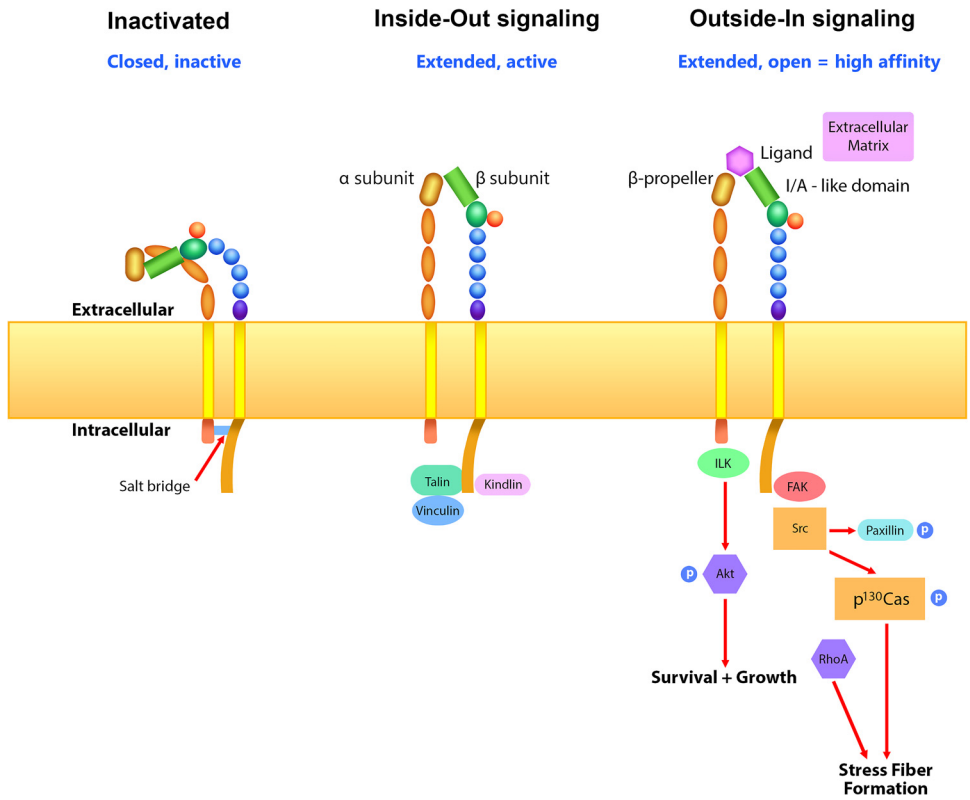

Fig. 1. Integrin activation. Following synthesis and localization at the membrane, the integrin will maintain a bent or "closed" conformation. Association of talin and vinculin, as well as kindlin and α-actinin, with the integrin in response to cytoskeletal tension destabilizes the salt bridge between the α- and β-cytoplasmic tails, allowing the extracellular domains to extend toward proteins within the extracellular matrix (ECM). "Inside-Out" signaling and increased cell-matrix interaction facilitate further opening of the space between α- and β-subunits, integrin clustering, focal adhesion complex formation, and initiation of signaling in response to mechanical strain ("Outside-In") that results in stress fiber formation, survival, and growth. Studies suggest that focal adhesion kinase (FAK), paxillin, Src, p130Cas, and RhoA are important for stress fiber formation, whereas integrin-linked kinase (ILK)-Akt may facilitate survival and growth in response to mechanical strain.

forces similarly impact integrin-mediated adhesion and intracellular signaling in a variety of mammalian cells.

IMPACT OF MECHANICAL STRAIN ON INTEGRIN-MEDIATED STRESS FIBER FORMATION AND SIGNALING

Talin is a large, 270 kDa scaffold protein, consisting of *1*) a head region that binds to the NPxY motif on the β-subunit cytoplasmic domain, forcing the separation of α- and β-subunits, and *2*) a long tail region that directly binds two F-actin sites and vinculin (11 sites) (120). Thus talin serves as a scaffold protein necessary for the initial stages of cell-matrix interactions. Talin-integrin interaction induces a conformational change in talin that exposes vinculin binding sites, allowing vinculin to further facilitate talin and F-actin interaction (40). Dependent on substrate stiffness, proteins other than talin may serve as primary F-actin binding proteins, such as kindlin, α-actinin, and the integrin-linked kinase (ILK)-PINCH-parvin complex (15, 40, 113, 138). Kindlin, for example, can bind a unique conserved NPxY sequence motif on the integrin β-subunit (membrane-distal site versus the membrane-proximal side required for talin) and can initiate integrin-mediated actin fibril formation independent of talin (124). Upon high-affinity ligand binding, activated integrins recruit numerous proteins to their short cytoplasmic tails. The precise composition of proteins that associate the nascent adhesions varies considerably based on cell type and environmental conditions, yet talin and vinculin are consistently represented and the majority also bind actin (25).

The application of force in the form of mechanical strain can allow prestressed, nascent adhesions to grow in size and form larger focal adhesion complexes via integrin clustering, F-actin bundling, and stress fiber formation (95, 120). Mechanical stretch on integrins can increase integrin-bound and autophosphoryated (Tyr397) focal adhesion kinase (pp125^{FAK} or FAK), as well as stimulate Src family kinases to phosphorylate the docking protein p130Cas on multiple tyrosine residues (122). FAK can similarly phosphorylate paxillin, a key adaptor molecule containing a variety of interacting domains (LIM, SH2, SH3) (75). These events ensure recruitment of proteins to the maturing FAC that then induce strain-induced intracellular signaling. In addition to FAK, ILK can similarly bind to the integrin and facilitate phosphorylation of numerous downstream targets including Akt and GSK-3, as well as PINCH and other LIM-domain containing proteins, which allow for cell survival, migration, and spreading (7, 35, 59, 125, 126). ILK, although initially characterized as a serine/threonine kinase (59), appears to primarily serve as a scaffold protein, as mammalian ILK lacks catalytic activity (84, 139).

The signaling pathways that control stress fiber assembly can vary based on cell type (mobile versus nonmobile) and may or may not involve the integrin. However, the Ras homolog gene family, member A (RhoA), a small GTPase protein, appears to be universally important for actin assembly. RhoA can activate RhoA kinase (ROCK), a kinase that can inhibit the actin severing activity of cofilin, which ultimately prevents actin depolymerization and promotes stress fiber formation (61, 102, 61). The striated muscle activator of Rho signaling (STARS) protein, which is localized to I bands in cardiac and skeletal muscle, may be the primary mechanism for stress fiber formation in these cell types (2). Stress fiber formation in response to strain is important. Not only does it provide a means to resist force and protect against cytoskeletal disruption, it may provide a physical structure for transmission

of mechanical signals to the nucleus for direct control of gene transcription and adaptation (29, 121).

INTEGRIN SPECIFICITY

In 1977, Richard Hynes reported the ability for fibronectin to induce the rearrangement of actin filaments (1), providing the first evidence for ECM-mediated control of cell function through a mechanism involving a yet unknown transmembrane protein. A fascinating history of the discovery of integrins is provided by Hynes in a personal account, including the eventual cloning of the fibronectin receptor (β_1-integrin subunit), appropriately termed "integrin" to reflect its role in maintaining the cell-matrix interaction (68, 123). This personal perspective describes some of the challenges and delays faced in the identification of integrin subunits, including the complexity of integrin subunit specificity. Hynes and others revealed through their work that integrins can bind to multiple ECM ligands and more than one integrin may exist in the cell membrane. Integrin complexity, including the ability for multiple heterodimers to recognize and respond to dynamic changes in the ECM environment, continues to provide challenges to elucidating a precise role for integrins in a variety of cell types. Despite remaining questions, our current understanding is that β_1-integrins, β_2-integrins, and α_v-containing integrins represent the majority of integrin heterodimers in vertebrates, with β_1-integrins forming heterodimers with α-subunits 1–9 and v (6). Whereas $\alpha_4\beta_1$- and $\alpha_5\beta_1$-heterodimers primarily recognize fibronectin, $\alpha_6\beta_1$- and $\alpha_7\beta_1$-heterodimers exhibit preferential binding to laminin. An extensive review of the different integrin complexes and our current understanding of each is provided elsewhere (6).

Each cell in an organism possesses a specific integrin signature at the membrane that is dependent on factors such as development and tissue-specific microenvironmental cues, including ECM composition, elastic modulus, and topography. Whereas fibroblasts predominantly express α_{11}-, α_2-, α_1-, and α_5-integrin subunits, myogenic progenitor cells (satellite cells) (97, 98, 114) and skeletal muscle fibers (4, 5, 94, 129) predominantly express the α_7-integrin subunit. A switch in integrin signature is observed in myoblasts during development, specifically during the stages of myoblast fusion and myotube formation, such that the fibronectin receptor $\alpha_5\beta_1$ is downregulated to inhibit proliferation (14) and the laminin receptor $\alpha_7\beta_1$ is upregulated to enhance differentiation (118). The switch in integrin expression is believed to occur in direct response to changes in the muscle cell ECM microenvironment during development, initially fibronectin rich to support myoblast proliferation and then changing to a laminin-rich environment to enhance differentiation (80). The $\alpha_7\beta_1$-integrin is highly expressed in differentiated myotubes and is the major, if not exclusive, integrin receptor found in the adult myofiber across different species.

The $\alpha_7\beta_1$-integrin preferentially binds laminin (LM-211 and LM-221) in the basal lamina and is concentrated at costameres (subsarcolemmal protein assembly between the membrane and Z bands), myotendinous (MTJ), and neuromuscular junctions (NMJ) (4, 22, 94, 105). Alternative splice variants exist for the α_7-subunit, including the mutually exclusive X1 and X2 extracellular domains and the A and B cytoplasmic domains (30, 118, 148). Both A and B isoforms are expressed in skeletal muscle, whereas only the X2 isoform is expressed in adult skeletal muscle. While the A isoform is unique to adult skeletal muscle, B appears to be the predominant isoform present in the sarcolemma (22) and is also expressed in cardiac myocytes, intestinal cells, vascular smooth muscle cells, and neuronal cells (8, 30 129, 136, 143). Of the two β_1-isoforms known to exist (A and D), the β_{1A}-subunit is downregulated during myoblast differentiation and only the β_{1D}-integrin subunit is expressed in mature myotubes (9, 128). Additionally, only the β_{1D}-isoform is expressed in striated skeletal muscle and cardiomyocytes, where it is localized to costameres, MTJs, and NMJs (9, 128). These data suggest the $\alpha_{7BX2}\beta_{1D}$-integrin is highly expressed and serves an important functional role in adult skeletal muscle.

THE $\alpha_7\beta_1$-INTEGRIN AND NEUROMUSCULAR DISEASE

The dystrophin-glycoprotein (DGC) complex and the $\alpha_7\beta_1$-integrin serve as the two primary laminin receptors in skeletal muscle, ultimately responsible for myofiber adhesion and cytoskeletal integrity. Genetic mutations in the components of either protein complex provide the basis for myopathies in humans and murine model systems, the majority of which are progressive in nature and exacerbated by mechanical strain during contraction (22, 62 98). Endogenous $\alpha_7\beta_1$-integrin mRNA and protein are upregulated in skeletal muscle in humans and mice lacking the DGC (*mdx* mice) in an attempt to compensate for the absence of transmembrane adhesion (63). Talin and vinculin, which are necessary for integrin linkage to the cytoskeleton as described above, are similarly increased ~200% in *mdx* muscle at the MTJ, suggesting reinforcement of the FAC (85, 117). Muscle-specific overexpression of the α_{7BX2}-integrin can ameliorate pathology (kyphosis, gait, contractures, NMJ, and MTJ structure) and extend the lifespan of mice with a severe form of dystrophy (*mdx/utr*$^{-/-}$) (23, 24). The fact that a reciprocal increase in endogenous dystrophin protein does not occur in mice lacking the α_7-integrin subunit suggests that the integrin and DGC complexes independently support adhesion and maintain muscle integrity. Together these studies provide irrefutable evidence that α_7-integrin localization and FAC development at the fiber membrane are not only protective but necessary for muscle health.

DGC deficiency stimulates an increase in the synthesis and/or presence of numerous integrin-related focal adhesion proteins, and this complex may serve to initiate critical signaling pathways necessary for actin remodeling and cell survival. Hyperphosphorylation of FAK (Tyr577, Try397, and Tyr722), paxillin (Tyr118 and Tyr31), protein kinase-Cα (PKCα; Ser657), and the mitogen-activated kinase-activated protein kinase 2 (MAPKAPK2; Thr222) has been noted in *mdx* mice (117). Paxillin may be an important downstream effector of the integrin, as phosphorylation on Tyr31 has been shown to be necessary for myofibrillar protein organization and sarcomere formation in myotubes (117). In addition to these findings, we have reported that ILK expression and kinase activity are markedly increased in *mdx/utr*$^{-/-}$ and *mdx/utr*$^{-/-}$ muscle that overexpress the α_{7BX2}-integrin (α_{7BX2}-*mdx/utr*$^{-/-}$) compared with wild-type (WT) and additional enhancement of the Akt (Ser473) phosphorylation-to-total Akt ratio is observed in α_{7BX2}-*mdx/utr*$^{-/-}$ compared with *mdx/utr*$^{-/-}$. In this study, we probed phosphorylation and total amounts of FAK at

Tyr397, but the results were highly variable and thus not reported (unpublished observations). The α_7-integrin subunit and ILK are preferentially coexpressed in glycolytic muscle fibers (96) and directly bind to each other through a critical tyrosine residue on the B cytoplasmic domain (21), providing additional support for an α_7-integrin-ILK-Akt mediated pro-survival pathway.

While skeletal muscle-specific loss of ILK does not impact $\alpha_7\beta_1$-integrin protein expression, widespread defects in FAC-associated protein localization at the MTJ and disruption of the actin cytoskeleton are readily apparent (51, 132). The progressive form of myopathy that develops and the increased susceptibility to mechanical strain-induced damage are highly reminiscent of the $\alpha_7\beta_1$-integrin deficient mouse phenotype (22, 41, 98). All together, these studies point to ILK as an important downstream effector of the $\alpha_7\beta_1$-integrin in skeletal muscle, and upregulation of the α_7-integrin-ILK-Akt signaling pathway represents an important compensatory mechanism to stabilize and repair sarcomeric structure in the face of dystrophin deficiency.

THE $\alpha_7\beta_1$-INTEGRIN AND PROTECTION FROM EXERCISE-INDUCED MYOFIBER DISRUPTION

Engagement in resistance exercise training can initiate an adaptive response in skeletal muscle that can provide protection from myofibril disruption, as well as increase myofiber size and enhance strength. The early cellular and molecular events responsible for training-induced adaptations have not been fully elucidated. However, an acute bout of (unaccustomed) exercise, particularly a session that incorporates eccentric or lengthening contractions, can cause localized membrane and myofibril disruption and subsequently elicit a stress response in an effort to facilitate repair.

We and others have demonstrated that an acute bout of eccentric exercise induces an increase in $\alpha_7\beta_1$-integrin mRNA and protein in skeletal muscle of healthy humans and mice (20, 22, 34, 66). All isoforms of α_7-integrin mRNA, including A, B, X1, and X2, are increased in muscle 3 h posteccentric exercise (30 min, downhill running) (22), and a 70% increase in α_{7B}-integrin protein is observed by 24 h postexercise (20). Interestingly, only the α_7-integrin subunit is responsive to exercise, as no change was observed in α_5- and α_6-mRNA and a decrease was observed in α_4-mRNA (22). In young men, a more dramatic 3.8-fold increase in α_7B-protein was reported at 24 h posteccentric exercise (15 sets of 10 repetitions, unilateral maximal contractions using an isokinetic dynamometer), including a reciprocal 3.9-fold increase in the β_{1D}-subunit (34). The upregulation of the α_{7BX2}-integrin subunit appears to be necessary for membrane repair and protection from subsequent myofiber disruption normally observed in healthy WT muscle postexercise, as α_7-integrin knockout mice (α_7-integrin$^{-/-}$) are highly susceptible to muscle injury and compromised membrane integrity with a second (or repeat bout) of eccentric exercise (30 min, downhill running) 24 h later (22). We have also demonstrated that transgenic overexpression of the α_7BX2-integrin in mouse muscle (muscle creatine kinase, MCK:α_{7BX2} integrin; α_7Tg) can prevent decreases in membrane integrity and force, as well as mitigate an inflammatory response, following an acute bout of eccentric exercise (60 min, downhill running) (89). Given the localization and concentration of the integrin at the costamere, MTJ, and NMJ, it is assumed that the integrin serves as an anchor to resist forces present during contraction, ultimately preserving membrane, cytoskeletal, and sarcomeric structure.

The immediate upregulation of α_7-integrin subunit mRNA and protein, as well as concomitant increases in talin and vinculin protein (48), are reminiscent of the response to DGC deficiency (85, 117). Loss of dystrophin and related dystrophin-associated proteins has been observed in rodent muscle in response to lengthening contractions (13), an observation that we have also noted in mouse muscle. Thus α_7-integrin upregulation is likely a compensatory mechanism necessary to stabilize the cytoskeleton and prevent Z-band disruption posteccentric exercise. A question that remains to be addressed, however, is whether α_7-integrin upregulation provides a mechanism for long-term reinforcement of Z bands and recruitment of unique signaling proteins to the costamere that facilitate additional benefits associated with resistance exercise training, including long-term structural and functional gains.

MECHANISMS DRIVING MECHANICAL LOAD-INDUCED PROTEIN SYNTHESIS AND SKELETAL MUSCLE HYPERTROPHY

Mammalian Target of Rapamycin Complex

The mammalian target of rapamycin (mTOR) is a critical regulator of protein synthesis and myofiber growth in response to anabolic stimuli, such as insulin, growth factors (IGF-1, IGF-2), certain amino acids, and mechanical force (54, 144). mTOR, a serine/threonine protein kinase, serves as a core component of two distinct multiprotein complexes, including mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) (71, 115). Both complexes share association with DEP domain-containing mTOR-interacting protein (DEPTOR) and mammalian lethal with SEC13 protein 8 (mLST8), which serve to regulate mTOR kinase activity (144). The regulatory-associated protein of mTOR (RAPTOR) and the proline-rich Akt substrate of 40 kDa (PRAS40) specifically regulate mTORC1 activity, whereas rapamycin-insensitive companion of mTOR (RICTOR), stress-activated protein kinase-interacting protein 1 (mSIN1), and the RICTOR-binding proteins Protor-1/2 are unique to mTORC2 (111, 115). mTORC1 and mTORC2 can be distinguished based on sensitivity to rapamycin. FKBP12-rapamycin can allosterically interact with mTORC1 and destabilize RAPTOR-mTOR interaction, whereas rapamycin does not significantly impact mTORC2 (111). In general, the two complexes are responsive to different signals and exhibit specificity for different downstream effectors, with mTORC1 a primary coordinator of protein synthesis and autophagy (50, 90) and mTORC2 a primary regulator of cytoskeletal structure and cell survival (31, 71, 110).

mTORC complexes are localized to distinct subcellular compartments to allow spatial and temporal control of cell growth (11). mTORC1 translocation to the lysosomal membrane is observed in response to amino acids and mechanical stimulation in the form of eccentric contraction (73). This translocation event, which is controlled by the Rag GTPase and the GEF and lysosomal anchor for Rag (Ragulator), is important because it enhances proximity between mTOR and the GTP-bound form of Ras homolog enriched in brain (RHEB), which is required for mTOR activation. Following mTOR phosphor-

ylation, RAPTOR binds a conserved TOR signaling (TOS) motif in downstream targets p70S6 kinase 1 (p70S6K) and the eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1) (108), facilitating phosphorylation events that increase capacity and efficiency of protein translation (90).

Several studies have now demonstrated a central role for mTORC1 in mechanical load-induced skeletal muscle growth (16, 36, 54, 79, 145). However, recent studies suggest an additional role for an mTORC1/RAPTOR-independent mechanism in skeletal muscle adaptation (109, 145). For example, Ogasawara et al. (109) recently demonstrated that while early hypertrophic signaling (<3 h postcontraction) was sensitive to rapamycin, later increases in protein synthesis (>6 h postcontraction) remained insensitive to rapamycin administration. Similarly, You et al. (145) reported that skeletal muscle-specific and conditional ablation of RAPTOR eliminates mTOR localization to the lysosome, p70S6K (Thr389) phosphorylation, and increased myofiber cross-sectional area (CSA) in response to high-intensity contraction and/or chronic mechanical loading in mouse plantaris muscle, yet phosphorylation of S6 (Ser235/236; Serine240/244) and 4E-BP1 (Thr36/45) and enhanced protein synthesis, as assessed by puromycin labeling, were not inhibited. These studies suggest a role for mTORC1-independent mechanisms in the regulation of protein turnover, an event that may be necessary for maintenance of beneficial structural and functional gains postexercise.

Mammalian Target of Rapamycin Complex 2

Minimal information exists regarding a role for mTORC2 in skeletal muscle, particularly in response to contraction and exercise. In nonmuscle cell types, endogenous mTORC2 is localized to the plasma membrane, outer mitochondrial membranes, and a subpopulation of endosomal vesicles (39). Similar to mTORC1, it is thought that partitioning of mTORC2 may allow for preferential activation of downstream targets, such as Akt (Ser473), serum- and glucocorticoid-regulated kinase 1 (SGK1; Ser422), protein kinase C (PKC; Ser657), and 4E-BP1 (multiple phosphorylation sites) (58, 71, 72, 77, 115, 116).

Unbiased proteomic screening experiments have demonstrated that ILK, presumably associated with integrins at the FAC, can directly bind RICTOR and facilitate mTORC2-mediated Akt phosphorylation and cell survival in cancer cells (101). In addition, early experiments in HeLa cells highlighted a role for RICTOR in PKC activation and cytoskeletal organization (115). Specifically, lentivirus knockdown of RICTOR reduced PKCα activity and induced reorganization of actin from the cell periphery to thick bundles in the cytoplasm with no clear connection to the remaining actin cytoskeleton. These studies suggest that an integrin-ILK-RICTOR complex may exist in a variety of mammalian cell types to ensure cytoskeleton integrity. However, whether this complex is augmented in skeletal muscle in response to mechanical load and the extent to which it serves a structural (protection against disruption) or functional (hypertrophic signaling) role in the context of loading are not known.

Hodson et al. (64), recently evaluated RICTOR localization in human skeletal muscle 1 and 3 h following an acute bout of resistance exercise (4 sets, unilateral leg extension at 70% RM until volitional failure, 2-min recovery between sets) in recreationally active young men. No change in mTOR-RICTOR colocalization was observed, yet complex formation may be dependent on training status, as well as the time course for evaluation (later time points are required). Conditional, muscle-specific RICTOR knockout mice exist (10, 77) that may be useful, but the effectiveness of this mouse model would depend on the extent of damage following application of a mechanical stimulus. Currently, RICTOR$^{-/-}$ mice do exhibit progressive myopathy or a negative phenotype with the application of aerobic exercise, but these mice have not yet been subjected to a load that would represent a significant challenge to muscle structure. A muscle-specific RICTOR transgenic mouse could also be generated to address a more precise role for mTORC2 in load-induced growth.

Serum Response Factor

Other mTORC1-independent mechanisms exist that may also contribute to load-induced growth. RhoA-mediated stress fiber formation can stimulate translocation of serum response factor (SRF) to the nucleus, where it can induce transcription of skeletal muscle-specific genes [skeletal α-actin, α-myosin heavy chain (MHC), myogenin] and initiate myoblast differentiation (134). Dominant negative mutants of the β_1-integrin and inhibition of actin polymerization by cytochalasin D significantly reduce RhoA-induced gene expression in cardiac myocytes (135), suggesting an important role for the integrin in the regulation of muscle-specific protein expression. Functional overload can induce a RhoA protein expression at the sarcolemma in rat plantaris muscle at 3 days, as well as increase SRF protein in nuclear and cytoplasmic fractions in rooster anterior latissimus dorsi (ALD) muscle 7 days poststretch (42, 100). In humans, 8 wk of resistance exercise increased SRF, α-actin, and MHCIIa mRNA, as well as RhoA and nuclear SRF protein levels in quadriceps muscle (83). Induction of SRF loss in adult myofibers results in a progressive myopathy, characterized by an altered regenerative response and accumulation of fibrosis in mice (82). Loss of SRF also inhibits load-induced hypertrophy via lack of satellite cell fusion (57). However, the role of satellite cell fusion in load-induced growth is controversial (49, 99, 106) and the lack of growth response to mechanical load in this study likely reflects the requirement for satellite cells in very young animals (2 mo old). Thus the extent to which the integrin-RhoA-SRF signaling pathway contributes to load-induced growth in adult skeletal muscle remains questionable.

THE $\alpha_7\beta_1$-INTEGRIN AND MECHANICAL LOAD-INDUCED SKELETAL MUSCLE HYPERTROPHY

The integrin is assumed to serve as a primary mechanosensor and regulator of mechanical load-induced growth, as depicted in nearly all illustrations presented in relevant reviews. However, our current understanding of the integrin role in growth is incomplete, which is also represented by the question marks that connect the integrin to mTORC signaling in illustrations of relevant reviews. Currently, minimal in vivo data exist to provide evidence of increased talin association with the integrin, integrin conformational changes, integrin clustering, or FAC assembly at the sarcolemma in response to mechanical load. FAK and ILK phosphorylation events have been used as

indirect indicators of integrin activation, yet these correlational studies are not sufficient to confer a causal relationship between the integrin and load-induced growth. In this section, we will review the literature that examine a role for the integrin and integrin-associated proteins in load-induced skeletal muscle hypertrophy.

The creation of mice overexpressing the α_{7BX2}-integrin subunit in skeletal muscle (MCK:α_{7BX2}-integrin; α_7Tg) provided the first opportunity to examine a direct role for the integrin in exercise-mediated adaptation (20, 89). The paradigm of acute downhill running (−20° decline, 17 m/min, 30–60 min) was originally chosen to discern a role in the protection from myofiber disruption consistently observed with muscle lengthening, a role that was outlined earlier in this review. Unexpected phenotypes were observed in α_7Tg muscle following exercise, including an increase in the mean fiber CSA and accumulation of $Pax7^+$ satellite cells and newly formed fibers ($eMHC^+$) compared with WT muscle (89). The increase in satellite cell content and new fiber synthesis in the absence of disruption still cannot be explained by integrin overexpression given its restricted expression within the adult myofiber (MCK promoter). The increase in fiber CSA was similarly perplexing for two reasons. First, one would not expect fiber growth to occur with a single bout of exercise, particularly a type of exercise that includes an aerobic component. Second, our prior work demonstrated a decrease in mTOR signaling, including reductions in the phosphorylation of Akt (Ser473), mTOR (Ser2448), and p70S6K (Thr389), in α_7Tg muscle immediately and 3 h postexercise (20). Therefore, if the α_7-integrin were to increase protein synthesis (not assessed in this study) and fiber hypertrophy in the context of eccentric exercise, a mechanism other than mTORC1 signaling would likely be required.

The results from the first study provided the incentive to conduct an eccentric exercise training study to determine the full extent to which α_7-integrin overexpression could induce skeletal muscle growth and other exercise-specific phenotypes (149). Downhill running (3×/wk; 4 wk) did not promote muscle growth in WT, yet resulted in a significant increase in the mean fiber CSA and percentage of large caliber fibers ranging >3,000 μm^2 in α_7Tg muscle. A significant increase in the fiber CSA was also observed in the sedentary state of α_7Tg muscle compared with WT, yet mice were fasted for 24 h in this study before dissection, and this observation may simply reflect the ability for the integrin to prevent a decrease in CSA due to atrophy. This rationale is supported by the relatively low mean fiber CSA values recorded. Regardless, preferential enhancement of myofibrillar protein content and whole muscle CSA in α_7Tg compared with WT provide additional evidence for integrin-mediated growth in response to load (149). Increases in mTOR signaling were observed in this training study, but the extent to which these late, long-term changes in signaling are meaningful is not known. Finally, enhanced vascular remodeling and arteriogenesis was also observed in α_7Tg muscle following acute (7 days post exercise) and repeated bouts of eccentric exercise, an adaptation that may occur to ensure proper nutrient and oxygen delivery to hypertrophied fibers (65).

Surgical ablation of the gastrocnemius muscle and chronic loading of the compensatory plantaris muscle (and or soleus muscle) is traditionally used to discern the mechanistic basis for mechanical strain-induced growth. Myotenectomy (MTE) is a modified version of synergist ablation in which the gastrocnemius muscle is severed and the tendon is removed, resulting in loading of the remaining plantaris and soleus muscles, a procedure that can minimize damage while maximizing the potential for growth. Our laboratory recently completed a study in which α_7Tg mice were subjected to MTE and then chronically loaded for 1 day (to evaluate signaling and growth) or 14 days (to evaluate growth) (unpublished observations). In this study, a preferential increase in muscle weight was observed in α_7Tg muscle compared with WT at 1 and 14 days. The impact of α_7-integrin overexpression on mechanical load-induced growth was only apparent in the glycolytic plantaris muscle and not the oxidative soleus muscle, appropriately reflecting preferential expression of MCK and transgene expression in type 2 muscle fibers (soleus was used as a control). Unlike downhill running, an increase in mean fiber CSA was not observed with chronic load in α_7Tg muscle, likely the result of extensive fiber splitting that occurred in α_7Tg mice compared with WT in response to this supraphysiological stimulus. mTORC1 signaling was elevated in both WT and α_7Tg muscle 1 day postload, but no enhancement was observed and a trend toward a decrease was noted in α_7Tg, consistent with our prior results (20). Interestingly, in light of findings reported by You et al. (145) described above, S6 (Ser235/236) phosphorylation was not suppressed and 4E-BP1 (Ser65) phosphorylation was increased in α_7Tg muscle. The results from these studies support a role for the $\alpha_7\beta_1$-integrin in the induction of load-induced growth, but the primary mechanisms driving integrin-mediated responses are not yet known.

MECHANISTIC BASIS FOR $\alpha_7\beta_1$-INTEGRIN-MEDIATED SKELETAL MUSCLE GROWTH

Focal Adhesion Kinase

Mechanical stimulation can increase FAK activity in a variety of cells, suggesting a role for FAK in load-induced growth. In fact, FAK autophosphorylation has been used as a readout for integrin activation in response to mechanical load, yet we are not aware of any studies that demonstrate a direct linkage between the $\alpha_7\beta_1$-integrin and FAK in skeletal muscle nor activation of FAK by the integrin.

Flück et al. (43) were the first to report an increase in FAK protein expression (~80%) and autophosphorylation (Tyr397, ~3-fold) in rooster anterior latissimus dorsi (ALD) muscle 1.5, 7, and 13 days following initiation of chronic stretch. FAK colocalized with vinculin at the sarcolemma, and paxillin protein content was similarly increased (~2-fold). FAK and paxillin protein expression as well as FAK phosphorylation (Tyr397) were also increased in rat soleus muscle 1 and 8 days following chronic overload induced by surgical ablation of the synergistic gastrocnemius muscle (43, 53). Subsequent studies using the hindlimb suspension-reload model demonstrated that FAK overexpression via transfection of pCMV-FAK plasmid can enhance p70S6K phosphorylation and activity (S411 at 6 h, T421/S424 and total S6K activity at 24 h) in the tibialis anterior (TA) muscle during the reload phase compared with contralateral controls receiving pCMV empty vector (78). This event was not dependent on Akt activity and did not elicit any change in downstream phosphorylation of 4E-BP1 (Thr37/46). In a follow up study, overexpression of FAK (pCMV-FAK

plasmid), which was exclusively localized to the sarcolemma and sarcoplasm, led to a small (6%) increase in mean myofiber CSA in soleus muscle during normal weight bearing (38). Overexpression of FAK also facilitated a 16% increase in the mean fiber CSA 1 day following reload in FAK^+ fibers compared with FAK^- fibers, yet comparison to contralateral controls was not provided to discern the extent of growth that occurred in response to load. In addition, the impact of FAK overexpression in response load in healthy muscle (outside the context of unload-reload) has not been established nor have any changes in muscle weight or protein synthesis been reported. Overall, these data suggest that FAK and paxillin are responsive to chronic mechanical loading and correlate with muscle hypertrophy, yet evidence that FAK is the mechanosensitive target of the integrin is weak.

Study results also exist that contradict a role for FAK in load-induced growth. First, total FAK protein and FAK phosphorylation at Tyr397 are decreased 90 min following downhill running in rat soleus muscle compared with nonexercised controls (56). We have observed similar decreases in the plantaris muscle of WT mice 1 day following chronic mechanical loading (unpublished observations). Increases in FAK phosphorylation have been observed in the distal region of human muscle compared with the midbelly region following unilateral eccentric exercise training (3×/wk, 8 wk), yet no differences in the rates of protein synthesis were observed between sites (47). Finally, the finding that FAK can facilitate insulin-like growth factor I (IGF-I)-mediated myotube growth via inhibition of tuberous sclerosis complex 2 (TSC2) and activation of mTOR signaling is tempered by studies that demonstrate no requirement for IGF-I or systemic factors in load-induced muscle hypertrophy (119, 137). Thus additional studies are needed to demonstrate a definitive role for FAK as a primary mechanism for integrin-mediated growth in response to a mechanical stimulus.

Integrin-Linked Kinase

In the context of mechanical loading, cardiac-specific overexpression of a constitutively active form of ILK (Ser343D) in mice can induce myocardial cell hypertrophy (88), yet this event occurred independent of a significant increase in Akt phosphorylation and the extent to which this information translates to skeletal muscle is not known. ILK mRNA is robustly increased 3–7 days postload in mouse skeletal muscle (27), suggesting some potential for involvement. We have observed a drop in total ILK protein expression 1 day postload (unpublished observations), which may provide the rationale for increased transcription 3–7 days later (27). In addition, ILK protein expression appears to recover faster in α_7Tg mice compared with WT by 14 days. It is tempting to speculate that temporary membrane disruption is responsible for ILK depletion and that integrin-mediated repair can restore the integrin-ILK complex and its potential involvement in training-induced skeletal muscle adaptation. Overall, ILK may contribute to integrin-mediated growth, but more evidence is needed.

Serum Response Factor and Unfolded Protein Response

A microarray analysis was recently performed using RNA extracted from skeletal muscle of WT and α_7Tg mice under sedentary conditions and 3 h following an acute bout of downhill running exercise to elucidate some of the mechanisms driving integrin-mediated skeletal muscle growth (93). We did not observe any increase in SRF-mediated transcriptional products in the microarray, suggesting no involvement of SRF. Alternatively, KEGG pathway analysis detected an overrepresentation of genes related to protein processing in the endoplasmic reticulum (ER) pathway in α_7Tg mice in the absence of exercise. Indeed, upregulation of heat shock protein mRNA, including Hsp40 and Hspa5/BiP, was verified, and decreased CHOP protein was detected in α_7Tg mice suggesting a preferential unfolded protein response (UPR). We reasoned that a decrease in misfolded protein abundance would serve to increase protein quality and incorporation during myofibrillar protein synthesis. Using a shRNA knockdown approach in myotubes, however, several of the top differentially expressed genes related to protein processing in the ER were not directly regulated by the integrin, suggesting contribution of nonmyofiber cells (stem cells, fibroblasts) to the beneficial UPR observed. While interesting, it is unclear how this event may benefit muscle in the context of mechanical loading.

Other Potential Mechanisms

The microarray analysis detected differential expression of additional genes related to stress resistance and protein translation. Significant increases in angiogenin (Ang) and solute carrier family 7 member 5 (Slc7a5) mRNA, as well as a decrease in N-myc downregulated gene 2 (Ndrg2) mRNA, were detected in α_7Tg muscle postexercise. These changes are particularly relevant to growth, as angiogenin is a ribonuclease that can increase translation of mRNAs with an internal ribosome entry site (IRES) and can serve as a transcription factor to increase ribosomal RNA (rRNA) during periods of stress (69, 112, 142). Slc7a5, or the L-type amino acid transporter 1 (LAT1), is enhanced in human and rat skeletal muscle postexercise (12, 91) and can activate mTOR activity via leucine uptake or leucine efflux from lysosomes (103, 140). Finally, Ndrg2 is a negative regulator of muscle protein synthesis (45, 46). Of these candidate genes, Slc7a5 and Ndrg2 were appropriately downregulated and upregulated, respectively, by integrin knockdown in myotubes. The fact Ndrg2 may be regulated by mTORC2 activity via SGK (107) suggests some potential for the integrin to regulate growth via an integrin-ILK-mTORC2-mediated pathway. In addition, Slc7a5 is a downstream transcriptional target of the Yes-associated protein (YAP), which can also induce muscle growth independent of mTORC1 (55).

The Yes-associated protein (YAP) is a transcriptional coactivator expressed in a variety of mammalian cells that is strongly associated with tissue growth in a manner that is dependent on cell attachment. YAP is normally retained in an inactive state in the cytoplasm and may be targeted for degradation via phosphorylation by the mammalian STE20-like protein kinase 1 (MST1/2) and subsequent phosphorylation of large tumor suppressor 1 kinases (LATS1/2), integral members of the Hippo signaling pathway (74). Ser112 phosphorylation (Ser127 in humans) by LATS1/2 is responsible for cytoplasmic retention, whereas Ser381 mediates recruitment of an E3 ubiquitin ligase that targets YAP for degradation (60, 74, 133). Upon inactivation of Hippo signaling or alternative mechanisms for dephosphorylation, YAP translocates to the nucleus

where it serves as a transcriptional coactivator in association with TEA domain family members 1–4 (TEAD1–4) and other transcription factors (74). Downstream effectors of YAP include transcription of genes necessary for cell survival, stabilization and growth, including Runx (141), Smads (55), ankyrins (37), connective tissue growth factor, amphiregulin (146), c-myc (55), and Slc7a5 (60). Studies have demonstrated that cell attachment and actin stress fiber formation promotes YAP nuclear accumulation, while actin destabilization and detachment leads to phosphorylation and cytoplasmic retention via the Hippo pathway (37, 74, 130, 147. A recent study demonstrated that F-actin abundance and cytoskeleton integrity can promote YAP nuclear translocation and activity in a manner independent of contractility and Ser112 phosphorylation (32). Thus integrin-mediated stress fiber formation in response to a mechanical stimulus can promote YAP activity, regardless of phosphorylation status.

Goodman et al. (55) recently reported significant upregulation of total and phosphorylated YAP (Ser112) in response to chronic overload. The time course for stimulation was distinct from mTORC1, such that p70S6K phosphorylation (Ser389) was optimal 2 days postload and YAP increased in parallel with Akt phosphorylation (Thr308) 4–10 days postload. Transfection of YAP (unphosphorylated) in the tibialis anterior muscle resulted in a rapamycin-insensitive increase in myofiber CSA in the absence of a mechanical stimulus, which also resulted in an increase in c-Myc protein (55). These data support other studies that demonstrate the ability for YAP to directly promote an increase in muscle mass via interaction with TEAD transcription factors (133). In addition, we have

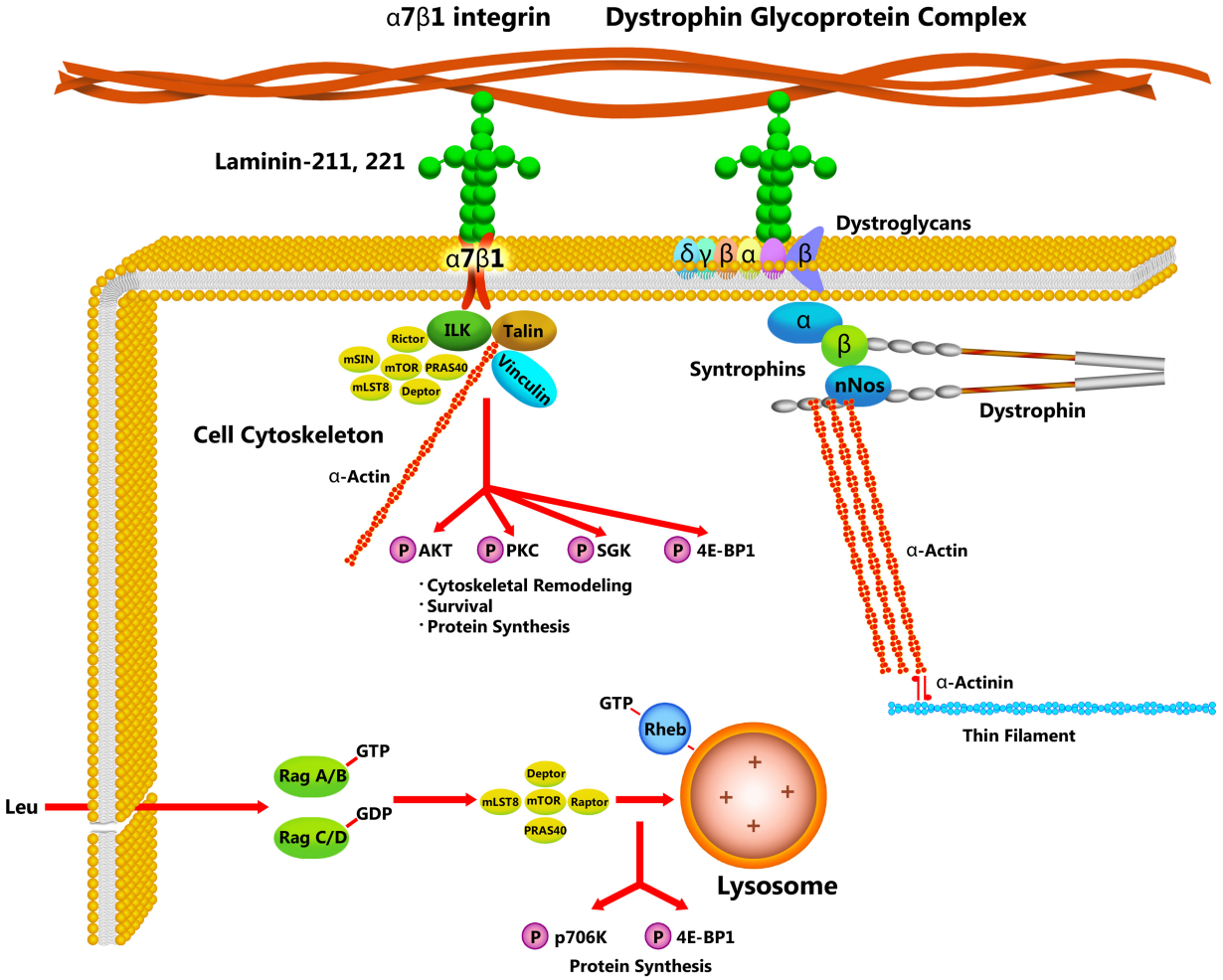

Fig. 2. Hypothetical role for the $\alpha_7\beta_1$-integrin in the induction of skeletal muscle hypertrophy in response to mechanical stimulation. Two mammalian target of rapamycin complexes (mTORC) exist in skeletal muscle: *1*) one that can localize to the lysosomal membrane in response to increased amino acid concentration (via uptake through LAT1/Slc7a5 or lysosomal efflux) and includes Raptor (mTORC1), and 2) another that can localize to the plasma membrane and associate with Rictor, likely via direct association with the integrin-linked kinase (ILK) (mTORC2). Immediately following exercise (rapamycin-sensitive phase), mTORC1 is transported to the lysosome via Ragulators (Rag), where mTOR is activated by the GTP-bound form of Ras homolog enriched in brain (Rheb), allowing phosphorylation of p70S6K and eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1) and increased capacity and efficiency of protein translation. Activation of mTORC1 is essential for postexercise enhancement of myofiber hypertrophy. Studies demonstrate that the $\alpha_7\beta_1$-integrin can also increase muscle hypertrophy in response to mechanical stimulation, yet it appears to facilitate this event independent of mTORC1. In this review, we propose that the $\alpha_7\beta_1$-integrin tethers mTORC2 to the sarcolemma via association of Rictor with ILK in the hours following exercise (rapamycin insensitive phase) and that mTORC2 localization at the membrane allows for activation of downstream signaling pathways that promote survival (Akt), cytoskeletal remodeling, and stability (PKC; which may impact Yes-Associated Protein or YAP), and long-term enhancement of protein translation (SGK and 4E-BP1). nNOS, neuronal nitric oxide synthase.

observed higher total YAP expression in α_7Tg skeletal muscle compared with WT skeletal muscle (unpublished observations), which is consistent with constitutively elevated expression of YAP in *mdx* muscle (where integrin expression is enhanced to compensate for loss of dystrophin) (70). Overall, these data suggest that the integrin may serve to promote cytoskeletal integrity, YAP expression and/or activity, and growth in a manner that does not require mTORC1 activity.

CLINICAL CONSIDERATIONS

Immobilization and bed rest following severe injury or disease can result in significant alterations in body composition, including loss of muscle mass and strength, as well as loss of bone density and an increase in fat and collagen accumulation (131). Several mechanisms appear to account for the decrease in muscle fiber size during disuse atrophy, including increased protein degradation and suppression of muscle protein synthesis (3, 18). Upregulation of forkhead box O (FoxO) transcription factors can increase gene expression of muscle-specific E3 ubiquitin ligases, *MuRF1* and *MAFbx/atrogin*, as well as autophagy-related genes, *LC3* and *Bnip3* (19). Significant muscle sparing is observed in MuRF1$^{-/-}$ and MAFbx$^{-/-}$ mice following hindlimb unloading and denervation (17, 81). However, deletion of MuRF1 does not fully suppress the ubiquitin proteasome pathway (UPP) in mice, suggesting that E3 ligase-independent pathways contribute to atrophy (19). Reproducible reductions in the rate of muscle protein synthesis have been observed in human skeletal muscle with disuse (33). Thus loss of a mechanosensing pathway may contribute to significant declines in muscle mass observed following an extended period of inactivity.

We are only aware of one study that has examined α_7-integrin subunit mRNA following a period of unloading in mice (104). In this study, α_7-integrin mRNA was significantly decreased in rat gastrocnemius muscle following 2 wk of hindlimb suspension, which correlated with significant declines in 45S pre-rRNA abundance, muscle protein synthesis (myofibrillar, cytoplasmic, and mitochondrial fractions), and myofiber CSA (104). Reductions in the phosphorylation of Akt (Ser473) and total FAK were observed, but a significant decline in FAK phosphorylation was not. These results are consistent with data by Li et al. (87), demonstrating a decrease in total FAK, but no change in FAK phosphorylation, in human vastus lateralis muscle following 10 and 21 days of bedrest. The results for FAK phosphorylation are not consistent throughout the literature, however, as decreases or no change have been reported in other studies (33, 44, 52). Further support for a decline in α_7-integrin -ILK complex formation with disuse is provided by a recent human study (92). In this study, decreases in ILK, RhoA, and actin cytoskeleton signaling were observed in young and old muscle via RNA sequencing following 5 days of bed rest. In addition, a significant decrease in α_7-integrin mRNA (28%) was observed in old skeletal muscle following disuse.

One potential confounding factor in the evaluation of integrin and costamere-associated protein with disuse atrophy is the fact that specific integrin isoforms (α_{7B}), FAK and paxillin are expressed in microvascular endothelial cells and vascular smooth muscle cells. Thus any decline in the total or phosphorylated amount of any of these proteins may occur as a result of capillary refraction, which can occur with disuse muscle atrophy (127). Thus lineage tracing or genetic manipulation of the integrin would provide the best approach to elucidating a role for a mechanosensing pathway in loss of muscle mass with long-term disuse.

CONCLUSIONS

The $\alpha_7\beta_1$-integrin represents the predominant integrin heterodimer expressed in skeletal muscle. While our studies demonstrate an important role for the integrin in promoting skeletal muscle hypertrophy in response to a mechanical stimulus, the detailed intracellular signaling events responsible for adaptation remain unknown. In this review, we provide the suggestion that the $\alpha_7\beta_1$-integrin does not promote myofiber growth via FAK, SRF, or mTORC1, the canonical integrin-mediated pathways highlighted in the current literature. Upregulation of the $\alpha_7\beta_1$-integrin following an acute bout of unaccustomed eccentric exercise likely allows for ILK binding, reinforcement of the cytoskeleton at the costamere, and increased YAP activity, a mechanosensing mechanism that may or may not involve RICTOR and mTORC2 activity. We envision a two-step process following mechanical loading in which mTORC1 is activated by amino acid uptake or release from the lysosome to rapidly increase protein synthesis to establish homeostasis, then sustained maintenance and remodeling of muscle structure via an integrin-ILK-mTORC2-YAP-driven mechanism (Fig. 2). Further delineation of a role for the integrin in mTORC1-independent muscle growth following a mechanical stimulus will not only allow for enhanced sport performance but provide impactful knowledge toward mitigating loss of muscle mass in the context of disuse and aging.

GRANTS

This work was supported National Institute of Arthritis and Musculoskeletal and Skin Diseases Grant R21-AR-065578 (to M. D. Boppart).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

M.D.B. prepared figures; M.D.B. and Z.S.M. drafted manuscript; M.D.B. and Z.S.M. edited and revised manuscript; M.D.B. and Z.S.M. approved final version of manuscript.

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