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TGF-β superfamily signaling in muscle and tendon adaptation to resistance exercise

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Abstract

Numerous studies in muscle and tendon have identified a central role of the TGF-β superfamily of cytokines in the regulation of extracellular matrix growth and remodeling, protein degradation, and cell proliferation and differentiation. Here we provide a novel framework for TGF-β and myostatin signaling in controlling the coordinated adaptation of both skeletal muscle and tendon tissue to resistance training.

Keywords

Transforming growth factor-β; myostatin; skeletal muscle hypertrophy; tendon hypertrophy; resistance training

Introduction

The ability of the musculoskeletal system to adapt to environmental changes, exercise, injury, illness and other physiological conditions is critical in determining the overall health, mobility and athletic performance of an individual. The formation of cross-bridges between actin and myosin molecules within muscle fibers generates forces that are transmitted through the muscle extracellular matrix (ECM) to tendons, and then to cartilage and bones to allow for locomotion to occur. While tendons are often thought of as distinct anatomical structures from muscles, tendon tissue is really a direct continuation of the muscle ECM, and the mechanical properties of both muscles and tendons must be finely tuned for proper force transmission to occur. Muscle and tendon demonstrate a profound ability to respond to resistance training, with both tissues demonstrating hypertrophy and changes in mechanical properties to optimize force transmission and locomotion (3, 13). Although this is not always the case, in our observations many studies that evaluate the response of muscle and

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tendon to growth stimuli like resistance exercise assess these two tissues separately, and do not consider their combined responses. There has been considerable advancement in our understanding of the cellular and molecular processes that regulate muscle and tendon growth, with the field of tendon biology in particular experiencing a recent and vigorous acceleration in the number of breakthrough studies using sophisticated genetic models and cutting-edge tools of discovery. The transforming growth factor-β (TGF-β) superfamily of signaling molecules in particular appears to play an important role in directing the response of muscle and tendon to mechanical growth stimuli. Based on the numerous but disparate studies exploring TGF-β signaling in skeletal muscle and tendon, and the close anatomical association between these tissues, we hypothesize that TGF-β signaling acts in a coordinated fashion to regulate the synergistic growth and adaptation of muscle and tendon to resistance training. This review will discuss the latest findings in TGF-β signaling in skeletal muscle and tendon physiology, and construct an integrated model of TGF-β superfamily control of ECM growth and remodeling, and turnover of damaged myofibrillar proteins to enhance the combined response of muscle and tendon to resistance training.

TGF-β Superfamily Signal Transduction

Signaling by TGF-β and related factors plays an important role in the adaptation of skeletal muscle and tendon to chronic resistance training. With more than 30 members identified in humans, the TGF-β superfamily orchestrates a diverse array of cellular processes that include proliferation, differentiation, protein metabolism, and growth and remodeling of the ECM (18). Based on similarities in sequence homology, ligands of the TGF-β superfamily can be placed into two groups that include TGF-β/Activin/Nodal and Growth and Differentiation Factor (GDF)/Bone Morphogenetic Protein (BMP). TGF-β exists in three isoforms (TGF-β1, -β2 and -β3), and the TGF-β1 isoform (referred to in this review as TGF-β), along with myostatin (GDF-8), are the most studied superfamily members in skeletal muscle and tendon, and will be the focus of this review. In response to resistance exercise, TGF-β and myostatin initiate signal transduction through complex ligand-receptor interactions that result in the activation of MAPK cascades and nuclear accumulation of Smad proteins, and subsequent activation of target genes that are likely important in the adaptation of skeletal muscle and tendon to resistance training (15, 18). An overview of these pathways is presented in Figure 1 and discussed in detail in the following sections.

TGF-β is synthesized as a precursor protein with a long N-terminal prodomain, which is also termed the latency-associated peptide (LAP), and a short C-terminal mature domain (8). The LAP facilitates proper folding and disulfide-linked dimerization of the mature domain. Dimeric TGF-β is then processed by furin-like proprotein convertases, which cleave an RXXR consensus sequence between the LAP and mature domain. The LAP remains non-covalently associated with the mature domain to suppress biological activity until activation can occur. TGF-β is secreted from the cell along with its LAP and covalently interacts with the latent TGF-β binding proteins (LTBPs) to form the multiprotein large latent complex (LLC). The LLC binds to other ECM components like fibrillin-1 and fibronectin, and provides a local reservoir of latent TGF-β in the ECM. Active TGF-β can be released from the LLC by mechanical force or proteolytic degradation of the LAP or LTBP. In the case of enzymatic activation of TGF-β, ADAMTS1, MMP-2 and MMP-9 appear to be the main

proteinases that activate TGF-β by degrading the other components of the LLC (9). For mechanical force-mediated TGF-β activation, αvβ6 integrin, which is a transmembrane protein that is connected at the cytosolic end to the actin cytoskeleton and at the extracellular end to the LAP, can pull on the LAP to induce a conformational change that liberates active TGF-β from the LAP (34).

Myostatin is a member of the TGF-β superfamily that shares approximately one-third of its sequence identity with the TGF-β1 isoform. The N-terminal prodomain of myostatin, referred to as the propeptide, assists in folding and dimerization of mature myostatin and helps to maintain myostatin in an inactive form upon secretion from the cell. Myostatin binds to fibromodulin, fibronectin and laminin in the ECM, where it can also remain sequestered with its LAP and other proteins in a latent form (25). Active myostatin can be released from the matrix by proteolytic degradation of the propeptide by the BMP-1/tolloid family of metalloproteinases (35), although the mechanism of release from other matrix proteins is not well understood. It also remains unknown if, similar to TGF-β, mechanical force can liberate active myostatin from binding proteins in the ECM.

All members of the TGF-β superfamily bind to cell surface receptors that form a heterotetrameric complex with two type I and two type II receptors (18). Seven type I and five type II receptors are encoded in humans, and both receptor types consist of an N-terminal extracellular ligand binding domain, a single-pass transmembrane domain and a C-terminal cytoplasmic kinase domain that has serine/threonine protein kinase activity. TGF-β preferentially binds to the type I receptor, TGFBR1, and the type II receptor, TGFBR2, while myostatin preferentially binds to two type I receptors, ALK4 and ALK5, and two type II receptors, ACVR2A and ACVR2B (6, 18). While the type I receptor is normally quiescent in the absence of ligand, the type II receptor is constitutively active. Ligand binding brings the type I and type II receptors in physical proximity, which then allows the type II receptor to phosphorylate the type I receptor and activate the intracellular kinase domain of the type I receptor, that activates downstream intracellular signaling pathways.

Smad-mediated signal transduction is considered the canonical TGF-β signaling pathway. Eight Smad proteins have been described in humans, and they can be broadly categorized as receptor-regulated Smads (R-Smads), inhibitory Smads (I-Smads) and co-mediator Smads (co-Smads) (18). Each Smad protein consists of an N-terminal Mad-homology 1 (MH1) domain and a C-terminal MH2 domain, except for I-Smads, which lack an MH1 domain. The MH1 domain contains a nuclear localization signal and DNA-binding motifs, while the MH2 domain interacts with the type I receptor and directs homo- and hetero-oligomerization of Smad complexes. When activated, the type I receptor recruits and phosphorylates two R-Smads, Smad2 and Smad3. The Co-Smad, Smad4, then associates with Smad2 and Smad3 to form a functional trimeric complex that translocates to the nucleus and activates the transcription of target genes. TGF-β signaling also induces the expression of an I-Smad, Smad7, as part of a negative feedback loop that fine tunes the strength and duration of the propagated signal (18). Smad7 competes against Smad2 and Smad3 for binding sites on Smad4 and the type I receptor, and can also promote the degradation of the type I receptor.

Even though the TGF-β superfamily signals through the action of Smad proteins, TGF-β and related factors can also activate other so-called 'non-canonical' pathways that can function in association with or independent from Smad proteins (18). For instance, the mitogen-activated protein kinase (MAPK) pathway has been shown to regulate many TGF-β-mediated cellular responses such as proliferation, differentiation, apoptosis and epithelial-to-mesenchymal transition (EMT) (12). TGF-β activated kinase 1 (TAK1), a member of the MAPK kinase kinase (MAPKKK) family, is recruited by the activin and TGF-β receptors and leads to activation of p38 MAPK by the intermediate MAPK kinase 3/6 (MKK3/6). Since p38 MAPK does not bind directly to DNA, it regulates transcription of target genes by activation of other transcription factors. There are also several other non-canonical signaling pathways activated by type I receptors, and this is currently one of the intense areas of study in TGF-β signal transduction research (18).

Skeletal Muscle Response to Resistance Training

Skeletal muscle consists of hundreds to millions of long, multinucleated fibers that are organized by an ECM (3). The primary constituents of the muscle ECM are the fibrillar collagens, type I and III. These fibrillar collagens act as molecular springs and exist in parallel with the muscle fibers. The basement membrane that directly surrounds muscle fibers is composed mostly of type IV and VI collagen, which have important roles in transmitting forces generated within muscle fibers to the fibrillar collagens, and eventually to the tendons (3). Type IV and VI collagen allow for the lateral transmission of forces generated within activated muscle fiber sarcomeres to the overall ECM. In addition to collagens, there are various other proteins in the ECM that help to determine the mechanical properties of the matrix, such as elastin, proteoglycans and hyaluronic acid.

Mechanical damage to skeletal muscle fibers can initiate a series of events that lead to muscle hypertrophy and increases in force production. There are three general types of muscle contractions: (i) isometric, in which muscle fibers are actively generating force but are not undergoing a change in length; (ii) shortening or concentric, in which muscle fibers are shortening while actively generating force; (iii) lengthening or eccentric, in which muscle fibers are lengthening while actively generating force. While isometric and concentric contractions can result in some early strength gains when starting an exercise program, but major gains in strength and muscle hypertrophy often occur through eccentric exercise. Eccentric contractions can directly mechanically damage sarcomeres and the muscle fiber plasma membrane, or sarcolemma, and this damage sets off a series of signaling cascades that are responsible for degrading and recycling damaged proteins.

The regulation of muscle growth and atrophy involves a sensitive balance between protein synthesis and degradation. With repetitive minor damage, such as the damage that occurs during exercise sessions that involve repeated eccentric contractions, muscle protein turnover is increased due to activation of both protein synthesis and degradation pathways. With time, repetitive resistance training results in a more efficient protein turnover with less protein degradation and more protein synthesis, leading to a subsequent increase in the size and force generating capacity of muscle fibers. However, even in highly resistance-trained individuals, myofibrils are still damaged as a result of lengthening contractions, and the

damaged proteins within these myofibrils must be targeted for degradation. Resistance exercise also causes changes to the size and mechanical properties of the ECM surrounding muscle fibers. Myostatin and TGF-β play central roles in the activation of proteolytic systems within muscle fibers and regulation of ECM synthesis and remodeling (Figure 2, (6)). While many studies have focused on the role of these proteins in severe muscle injuries, less attention has been paid to their function in the physiological responses of skeletal muscle and the ECM to eccentric exercise.

As discussed above, eccentric contractions can induce damage to both the sarcolemma and the sarcomeres. Damage to the sarcolemma allows for an influx of extracellular Ca^{2+} into the fiber and activation of an important protease, m-calpain (11). Once active, m-calpain will degrade titin, which is a key protein that helps to organize and provide passive mechanical properties to the sarcomere. Proteolytic degradation of titin by m-calpain likely assists in the disassembly of damaged myofibrils and subsequent physical release of sarcomeric proteins so that they can be fully broken down. Interestingly, myostatin is also localized at the sarcomere RecNum><DisplayText>(24)</DisplayText>(27) in addition to the extracellular pool of myostatin. Once titin is cleaved, this allows the dissociation of titin-cap from titin, and also liberates myostatin bound at the sarcomere. While the specific function of this sarcomeric-localized myostatin is not known, it is likely transported out of the cell where it can participate either in an autocrine or paracrine fashion to activate intracellular signaling cascades. This pool of myostatin is therefore likely important in activating the subsequent steps of protein degradation, and also for regulating the activity of satellite cells and fibroblasts in the area of damage.

In addition to the pool of myostatin located at the sarcomere, there are caches of TGF-β and myostatin located throughout the ECM. Several factors can regulate the extracellular activation of TGF-β and myostatin. Many of the proteolytic enzymes discussed in the previous section that cleave the LAP or propeptide are activated by reactive oxygen species, which are often induced after muscle injury. While this has not been specifically demonstrated in skeletal muscle, mechanical stretch of the ECM can also physically liberate active TGF-β from the LTBP/LAP complex (34). Once activated from their latent form, TGF-β and myostatin can bind to their receptors and promote the process of protein degradation in muscle fibers through induction of the E3 ubiquitin ligases, atrogin-1 and MuRF-1 (30). These ligases direct the polyubiquination of damaged sarcomeric proteins, which then targets these proteins for degradation in the 26S proteasome (2, 6). While these findings are largely based on in vitro data, and further in vivo studies are necessary to determine the specific molecular targets of these different E3 ligases (2), atrogin-1 and MuRF-1 likely serve a critical role in muscle protein turnover by recycling dysfunctional proteins into free amino acids, which can be used subsequently for the synthesis of new proteins. The importance of myostatin signaling in muscle protein turnover is demonstrated well in studies of single fibers from wild type and myostatin deficient mice. While myostatin deficient mice have a reduction in atrogin-1 levels and muscle fiber hypertrophy, despite having bigger fibers, there is no change in maximum isometric force production between the two groups of mice (23). The prolonged absence of myostatin, coupled with low levels of atrogin-1, result in an accumulation of non-functional proteins that would otherwise be targeted for protein degradation. Additionally, the inhibition of TGF-β signaling after

eccentric loading results in an initial improvement, but long term deficit in muscle function and delayed activation of atrogin-1 (5). Based on these findings, TGF-β and myostatin signaling, and the subsequent activation of atrogin-1 and MuRF-1 are likely integral for the full functional recovery of muscle after eccentric injury.

In addition to regulating the adaptation of muscle fibers to resistance training, TGF-β and myostatin signaling regulate the activity of other cell types in skeletal muscle tissue. Satellite cells, which are a resident pool of myogenic stem cells located between the sarcolemma and basal lamina, contribute to muscle fiber hypertrophy by providing a source of new nuclei to muscle fibers. The reactive oxygen species and mechanical stretch of muscle tissue liberates hepatocyte growth factor (HGF) from the ECM, which then awakens quiescent satellite cells and allow them to migrate to the site of injury, undergo proliferation, and eventually withdraw from the cell cycle to fuse with the damaged muscle fiber (32). TGF-β and myostatin generally act as a brake on satellite cell activity, by inhibiting the activity of cyclin dependent kinases and reducing the expression of the myogenic transcription factor MyoD (19). They also limit satellite cell differentiation and fusion by downregulating the expression of myogenin (19). While the combined effects of TGF-β and myostatin on satellite cell activity is often described as having a negative effect on muscle regeneration, we posit that this is effect has more to do with optimizing the actions of satellite cells. Premature proliferation, differentiation and fusion of satellite cells result in improperly regenerated and diminutive muscle fibers (26). The precise timing of satellite cell activation is critical to full regeneration, and in the context of resistance training, TGF-β and myostatin likely act to temporally regulate the activity of satellite cells to ensure muscle fibers have finished breaking down damaged sarcomeric proteins prior to ramping up the process of hypertrophy.

Resistance training also changes the structure and function of the muscle ECM, typically causing an increase in the collagen content and stiffness of the matrix. Individual fibers transmit forces longitudinally along the muscle, and also laterally between muscle fibers (13, 29). The lateral transmission of force stabilizes load and strain distribution across the fibers in a muscle (29). Since the amount of strain a muscle undergoes during eccentric contractions is the best predictor of the amount of damage to myofibrillar proteins, efficient lateral force transmission helps to protect individual muscle fibers from injury (29). Fibroblasts are the cells within muscle that are thought to be chiefly responsible for the regulation of ECM synthesis, breakdown and remodeling. Fibroblasts expand in close proximity with satellite cells can also indirectly regulate myogenesis through their interactions with satellite cells (26). TGF-β and myostatin promote fibroblast proliferation and the expression of the chief structural ECM proteins, type I and III collagen (3). In addition to promoting ECM synthesis, TGF-β and myostatin also induce the expression of several MMP enzymes that can directly breakdown collagen (3). The concomitant induction of fibroblast proliferation, collagen synthesis and degradation indicates that in addition to regulating the adaptation of muscle fibers, TGF-β and myostatin function to remodel the muscle ECM in response to resistance training.

Tendon Response to Resistance Training

Tendon tissue is an extension of the muscle ECM, and adapts mechanically and structurally in a coordinated fashion with muscle to mechanical loading. Tendon is composed mostly of type I collagen, with various other proteins and glycosaminoglycans (3). Traditionally tendon was thought to be a metabolically inert tissue, but recent studies have demonstrated tendon is a dynamic tissue whose metabolic activity increases with mechanical loading (14). Following a single bout of exercise, tendon increases glucose uptake and collagen synthesis, persisting for up to 2–3 days after loading (14). Prolonged eccentric training results in increased tendon cross-sectional area (CSA) and stiffness, which allows the tendon to handle the greater loads from the hypertrophied muscle and store elastic energy in a more efficient manner (14). An increase in tendon CSA following training will reduce the stress applied to the tendon for any given load, which will decrease the probability for tendon rupture under large loads (16). Eccentric training is also accompanied by proliferation of fibroblasts, which synthesize collagen in response to mechanical loading (14, 21). In contrast, repetitive microtrauma and overuse can lead to irregular fibroblast cellularity, increased neovascularization, and disorganized collagen fibrils in tendon (3). Because of this, eccentric exercise is often used in a rehabilitation program for the treatment of chronic tendinopathy to restore tendon fibril alignment and function (3).

While the mechanical and morphological changes that occur in tendons in response to eccentric training are well documented, an important area of focus is now on the underlying cellular, molecular and genetic mechanisms that regulate this response. TGF-β superfamily signaling appears to play a central role in tendon adaptation to resistance exercise (Figure 2). TGF-β and myostatin both stimulate tendon fibroblast proliferation and type I collagen synthesis (20, 22). TGF-β also induces the expression of the bHLH transcription factor scleraxis, which is critical for the proper formation of tendons during development (28). Mice with a targeted inactivation of either scleraxis or the type II TGF-β receptor fail to form limb tendons and have a severely disrupted limb phenotype (28). While mice deficient in scleraxis are embryonically viable and demonstrate joint contractures and markedly altered gait, deletion of the type II TGF-β receptor in the limb bud mesenchyme results in embryonic lethality. The genetic inactivation of myostatin also alters tendon development, resulting in a small, stiff, brittle and hypocellular tendon ECM (20), although the phenotype is not nearly as what is observed in the type II TGF-β receptor mutants. The diminutive tendon phenotype in the myostatin-deficient mice is in stark contrast to the muscle phenotype, which has a profound increase in both the number and size of muscle fibers. While TGF-β and myostatin signaling appear important for the recruitment and maintenance of tendon fibroblasts during development (20, 28), and there have been numerous studies demonstrating the ability of these cytokines to induce fibroblast proliferation and type I collagen synthesis in vitro (3), there is of yet no in vivo studies to our knowledge that have evaluated whether these signaling pathways play an important role in adult tendon growth and remodeling. Based on the development literature, the in vitro studies of adult tendon fibroblasts, and the studies of collagen synthesis in adult humans in response to resistance exercise, we posit that TGF-β and myostatin play important roles in the growth and adaptation of adult tendons to resistance exercise.

The prenatal and postnatal growth and remodeling of many tissues, including skeletal muscle, bone and cartilage are largely made possible by a resident population of tissue stem cells. In the past decade there has been a robust increase in the number of papers that have studied the origin, location and function of stem cells in tendon. By enzymatically digesting whole tendons and culturing the cells released from this process, a pool of stem cells was identified and characterized from mouse and human tendons (1). These cells demonstrated many of the characteristics of other stem cells in culture, including self-renewal, the ability to form colonies, and the ability to differentiate into multiple tissue types, including tendon, bone, cartilage and fat. While there appear to be resident stem cells in tendon, their anatomical location within the tendon and surrounding connective tissue is an area of ongoing study.

The most superficial layers of the tendon, consisting of the epitenon, peritenon and paratenon, appear to be at least one source of progenitor cell populations. The first evidence for this came from studies of tendon explants maintained in culture, which identified a rapidly proliferating cell population that originated in the outer layer of tendon connective tissue and migrate deeper into the tendon substance proper (17). More recently, several groups identified a population of proliferating cells in the superficial layers of the tendon that appear to contribute to postnatal growth (4, 21). This superficial layer of tendon tissue contains a basement membrane epithelium (33), and while scleraxis expression in the interior of the tendon decreases with adulthood, there are scleraxis expressing cells that persist in the epitenon (21). In response to chronic treadmill training, these scleraxis expressing cells migrate into the tendon proper, where presumably they participate in matrix turnover and synthesis (21).

For many tissues in the body, TGF-β can induce growth and remodeling of the ECM through a process known as the epithelial-to-mesenchymal transition (EMT, (12)). EMT programs are canonically driven by the transcription factor, Snail1 (12), which is a downstream target of TGF-β signaling. Using an a tendon injury model, we identified that Snail1, and other genes that play a role in EMT-related processes such as Slug, Goosecoid and Twist1 are coordinately regulated throughout the tendon repair and remodeling process (31). These EMT-related genes not only play a central role in the EMT program, but also in well-established, EMT-independent functions including ECM remodeling, cell lineage specification and cell cycle regulation (12). Similar to other tissues, there is likely not a single stem cell population in tendons, but probably multiple cell populations that can contribute to tendon growth and remodeling (7). Interestingly, although tendon tissue as a whole is metabolically active and various metabolites and markers of collagen turnover can be detected using dialysis probes, the inner core of human tendon is not very metabolically active once adulthood is reached (10). Combined with data from animal models demonstrating that the most superficial regions of the tendon experience high rates of cell proliferation and collagen synthesis (7), we propose that tendon tissue likely grows in a fashion similar to the rings of a tree, where increases in CSA occur in the outermost layers of the tendon, while the core itself remains idle. Further, we posit TGF-β signaling is likely to be a central regulator in tendon growth and remodeling in adult organisms, by inducing the proliferation, migration and eventual differentiation of tendon fibroblast progenitor cells.

The development of complex genetic mouse models using conditionally active Cre and Flp models that allow for the spatial and temporal inactivation of various genes will no doubt aid in the understanding of TGF-β superfamily signaling in the adaptation of adult tendon tissue following eccentric loading, and identify the progenitor cell populations required for tendon growth and remodeling.

Conclusions

Skeletal muscle and tendon demonstrate a robust response to resistance training. Given the close anatomical association between muscle and tendon, and the shared microcirculation and interstitial fluid, activated TGF-β and myostatin are likely to circulate easily between the two tissues. The physiological processes that are downstream of TGF-β and myostatin signaling, namely the efficient recycling of damaged contractile proteins, the coordinated regulation of myoblast and fibroblast progenitor cell activity, and the induction of collagen synthesis and ECM remodeling, all induce favorable changes to the entire musculotendinous unit that allow for greater and more efficient force transmission throughout the kinetic chain.

Given the dramatic hypermuscular phenotype that occurs in animal models of myostatin deficiency, there has been concern in collegiate and professional sports about the potential use of myostatin inhibitors for doping purposes. This has lead to the World Anti-Doping Agency to ban the use of myostatin inhibitors in sport. As of yet, however, there is no data in human subjects which demonstrate that inhibiting myostatin leads to increased athletic performance. Based on the available data discussed in this review, we suggest that inhibition of myostatin in athletes undergoing a resistance training program would probably be detrimental to gains in force production and changes in the mechanical properties of the ECM, resulting in maladaptations that are likely to detract from athletic performance. While inhibition of myostatin in otherwise healthy muscle could result in an increase in muscle fiber size in humans, this hypertrophy is unlikely to be accompanied by an increase in force production. For some moderate to severe muscle and joint injuries that have associated muscle wasting or fibrosis caused by an upregulation in myostatin or TGF-β, such as what occurs in patients with knee ligament tears (24), the short term inhibition of these proteins may enhance recovery and prevent the persistent loss in force production that is frequently observed after these injuries.

Much is still unknown about the regulation of TGF-β and myostatin signaling at the systems level. Understanding genetic and molecular networks that regulate the expression and activity of TGF-β and myostatin, such as miRNAs and lncRNAs, will also help identify potential regulatory steps that are altered in response to mechanical loading. The genetic promoters that label most of the specific cell populations in muscle have been identified, and for tendon there are promoters available for several cell populations, but more work is needed in this area. These promoters will be useful in developing transgenic animals to enhance our understanding of the basic biology of muscle and tendon adaptation to resistance training, but ultimately this work needs to be translated to human subjects to have the greatest impact. The insight gained from studies of the role of TGF-β superfamily signaling in controlling the adaptation of skeletal muscle and tendon to mechanical loading is likely to shape applied exercise physiology and clinical musculoskeletal medicine.

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Summary Statement

We provide an integrated framework for TGF-β signaling in controlling skeletal muscle and tendon adaptation to resistance training.

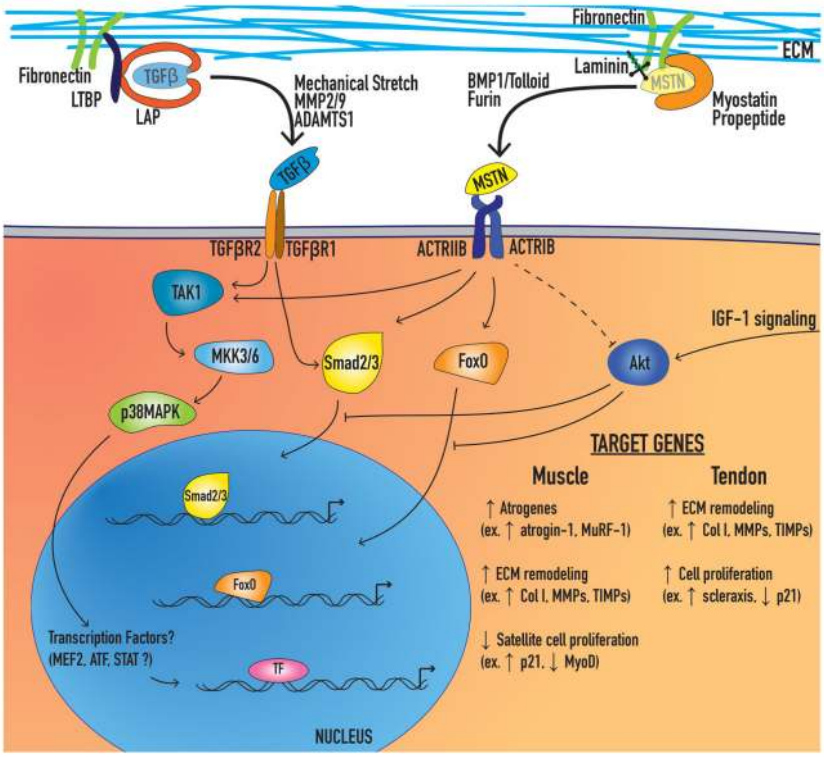

Figure 1.
Overview of TGF-β and myostatin signaling pathways.

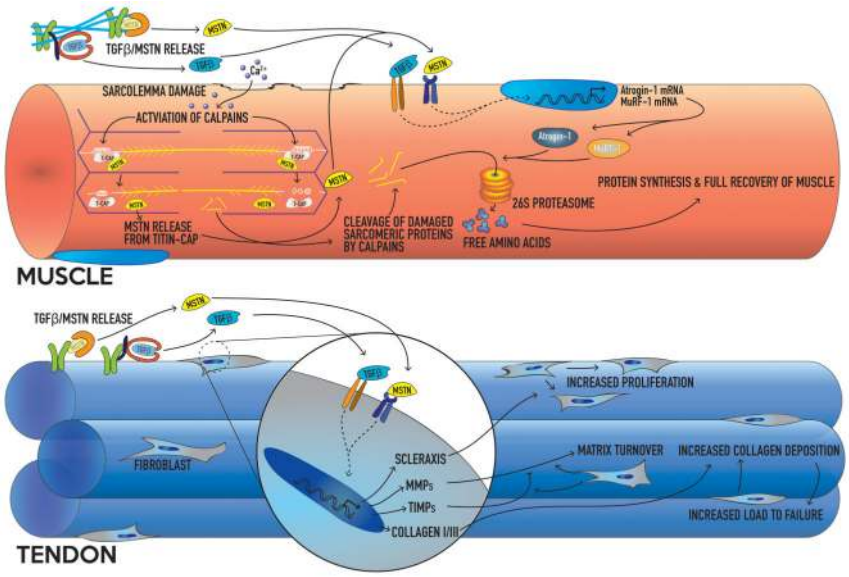

Figure 2.
Overview of muscle fiber and tendon responses to TGF-β and myostatin signaling.