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Emerging role of TAK1 in the regulation of skeletal muscle mass

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Abstract

Maintenance of skeletal muscle mass and strength throughout life is crucial for heathy living and longevity. Several signaling pathways have been implicated in the regulation of skeletal muscle mass in adults. TGF-β-activated kinase 1 (TAK1) is a key protein, which coordinates the activation of multiple signaling pathways. Recently, it was discovered that TAK1 is essential for the maintenance of skeletal muscle mass and myofiber hypertrophy following mechanical overload. Forced activation of TAK1 in skeletal muscle causes hypertrophy and attenuates denervation-induced muscle atrophy. TAK1-mediated signaling in skeletal muscle promotes protein synthesis, redox homeostasis, mitochondrial health, and integrity of neuromuscular junctions. In this article, we have reviewed the role and potential mechanisms through which TAK1 regulates skeletal muscle mass and growth. We have also proposed future areas of research that could be instrumental in exploring TAK1 as therapeutic target for improving muscle mass in various catabolic conditions and diseases.

Graphical Abstract:

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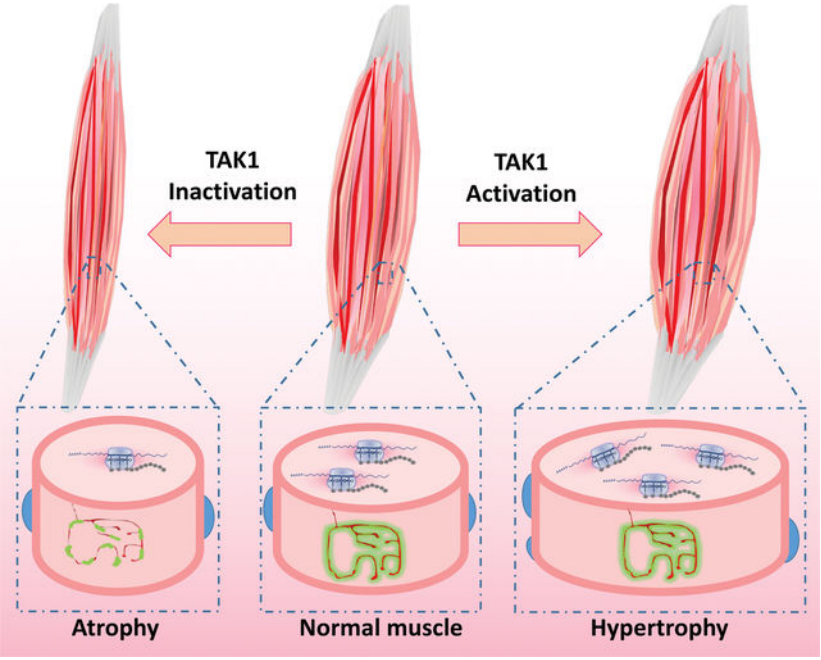

TAK1 is a central kinase that lies at the intersection of multiple signaling pathways. Accumulating evidence suggests that TAK1 is essential for the growth and maintenance of skeletal muscle mass. Here we have reviewed the current understanding about the role and mechanisms of action of TAK1 in skeletal muscle homeostasis.

Keywords

Skeletal muscle atrophy; Hypertrophy; TAK1; protein synthesis; neuromuscular junctions; signaling

Introduction

Skeletal muscle, a strong predictor of longevity and health in humans, is a highly plastic multicellular tissue composed of individual multinucleated myofibers, neuronal supply, and vasculature. While the number of myofibers remain constant after attaining adulthood, several intrinsic and extrinsic factors regulate the area of individual myofibers in skeletal muscle tissue (1–3). Loss of muscle mass is a major determinant of morbidity and mortality in the elderly and in various conditions, including nerve injury, limb immobilization, prolonged bed rest, and in chronic diseases, such as cancer, diabetes, and heart failure (1, 4, 5).

Skeletal muscle mass is governed by a delicate balance between the rate of protein synthesis and degradation that is regulated through coordinated activation of many intracellular pathways. Anabolic stimuli induce translational machinery to trigger protein synthesis. By contrast, catabolic stimuli augment the rate of myofibril protein degradation leading to skeletal muscle atrophy (6, 7). The ubiquitin-proteasome system (UPS) is the most important mechanism that causes degradation of many short- and long-lived proteins in

atrophying skeletal muscle (1, 8). The major component of the UPS are the E3 ubiquitin ligases, which catalyze the transfer of the ubiquitin chains to the target protein (1, 2, 9, 10). Levels of several E3 ubiquitin ligases, such as MAFbx, MuRF1, MUSA1, TRAF6, and UBR2 are dramatically increased in skeletal muscle in diverse catabolic states (1, 2, 9–12). Autophagy is another proteolytic system through which protein aggregates and defunct organelles are eliminated in mammalian cells. While basal level of autophagy is essential for the maintenance of skeletal muscle mass and health, excessive activation of autophagy that occurs in many catabolic conditions, such as cancer, sepsis, and functional denervation mediates the pathological loss of skeletal muscle mass (1, 13). In addition, other proteolytic enzymes, including Caspase-3 and calpains also contribute to protein degradation in conjunction with the UPS and autophagy in skeletal muscle (1, 14).

The insulin-like growth factor 1 (IGF1)-phosphatidylinositol-3-kinase (PI3K)-Akt is one of the most important signaling pathways that induces protein synthesis and muscle hypertrophy mainly through activation of mechanistic target of rapamycin (mTOR) complex 1 (mTORC1). Activation of IGF1-PI3K-Akt pathway also inhibits muscle proteolysis through inhibiting FoxO family transcription factors, which augment the gene expression of muscle-specific E3 ubiquitin ligases and autophagy-related molecules in skeletal muscle (1, 15). Akt-mediated phosphorylation of FoxOs sequesters them in cytoplasm and hence prevents their entry into the nucleus to induce gene expression of various atrogenes (15, 16). Recent studies have also provided evidence that bone morphogenetic proteins (BMPs) augment skeletal muscle growth and inhibits atrophy through the activation of Smad1/5/8 signaling (1, 17, 18). In contrast, myostatin-Smad2/3, nuclear factor-kappa B (NF-κB), p38 MAPK, and STAT3-IL-6 signaling stimulate myofibril proteolysis leading to muscle wasting (6, 7, 19–21). Accumulating evidence also suggests that the components of endoplasmic reticulum (ER) stress-induced unfolded protein response (UPR) pathways regulate skeletal muscle mass and function in distinct conditions (7, 22–25). Finally, oxidative stress and mitochondrial dysfunction are also important determinants of skeletal muscle atrophy (1, 26, 27).

TAK1, along with its binding partners TAK1-binding proteins (TAB1, TAB2, and TAB3), is a major signalosome, which fine-tune the activation of many signaling pathways in mammalian cells (28). Previous studies demonstrated that TAK1 is essential for myogenic differentiation (29, 30). In addition, TAK1 promotes survival, self-renewal, and regenerative potential of muscle stem cells in skeletal muscle of adult mice (31). Accumulating evidence suggests that TAK1 is essential for postnatal skeletal muscle growth and the maintenance of skeletal muscle mass in adult animals. In the following sections, we provide a succinct overview of the molecular and signaling mechanisms through which TAK1 controls skeletal muscle mass and function in adults.

Overview of TAK1 signaling.

TAK1 (also known as MAP3K7) is a serine/threonine kinase that was originally identified as a MAPK kinase kinase, a downstream kinase of the non-canonical TGF-β signaling (32, 33). Subsequently, it was found that TAK1 is also highly activated to mediate activation of downstream signaling in response to various cytokines, growth factors, lipopolysaccharides,

and environmental stress (28, 34, 35). TAK1 forms a heterotrimeric complex with TAK1-binding protein (TAB)1 and either TAB2 or TAB3, which bind to the N- and C-terminus of TAK1, respectively (36). Activation of the TAK1 signalosome is triggered by K63-linked poly-ubiquitination reactions catalyzed by the E2 ligase UBC13/UEV1A and the RING finger E3 ligases TNF receptor-associated factor (TRAF) 2 or TRAF6 in response to pro-inflammatory stimuli, such as TNF-α. K63-linked poly-ubiquitination of TAK1 by TRAF6/UBC13/UEV1A is an important event following stimulation by TNF-α (37, 38). Once TAK1 is polyubiquitinated, it auto-phosphorylates itself at Thr187 within its activation loop followed by sequentially phosphorylation at other sites, including Thr184 and Ser192 (39, 40). TAK1 mediates the activation of many signaling cascades, including the MKK4/7-JNK, MKK3/6-p38 MAPK, and IκB kinase β (IKKβ)-NF-κB (34, 41–43). Interestingly, there is also a feedback control loop where binding by TAB1 induces the auto-phosphorylation of p38α MAPK at Thr180 and Tyr182 residues, which suppresses the activation of TAK1. Indeed, genetic deletion or pharmacological inhibition of p38α MAPK causes hyper-activation of TAK1 which leads to the spurious activation of JNK and IKKβ (44–46). AMP-activated kinase (AMPK) agonist and ischemia can also activate TAK1, which in turn activates the LKB1/AMPK pathway, a major sensor of cellular energy levels (47). Extracellular matrix proteins bind to integrin receptors and intracellular tyrosine kinases to activate TAK1 during wound healing (48). In addition, Wnt ligands activate TAK1 which downregulates transcriptional activation mediated by β-catenin and T-cell factor/lymphoid enhancer factor (TCF/LEF) transcription factors through stimulating MAPK-related NEMO-like kinase (49). Furthermore, TAK1 is involved in the regulation of Smad signaling (50–55) suggesting that TAK1 is a point of convergence in various pathways to produce specific cellular responses (FIGURE 1).

TAK1 controls skeletal muscle mass.

TAK1 signalosome plays a critical role in mammalian development evidenced by the findings that germline deletion of *Tak1*, *Tab1,* or *Tab2* in mice leads to embryonic lethality (34, 56). Studies using tissue-specific knockout mice have demonstrated that TAK1 regulates adaptive and innate immune responses, vasculature development, survival of keratinocytes, hematopoietic cells, and hepatocytes, and morphogenesis, growth, and maintenance of cartilage (56–60). Since TAK1 is an upstream activator of NF-κB and p38 MAPK that are implicated in muscle wasting (19, 61, 62), it was speculated that targeted inactivation of TAK1 would improve skeletal muscle mass. However, germline muscle-specific inactivation of TAK1 in mice using myoblast- or myofiber-specific Cre lines were unsuccessful because the pups did not survive beyond 24–48h after birth. Importantly, tamoxifen-inducible inactivation of TAK1 in post-natal mice led to severe muscle wasting and development of kyphosis. This effect was more pronounced when TAK1 was inactivated at a young age (6-week) than in adult (4-month old) mice. Genome-wide transcriptome analysis also showed a remarkable reduction in the gene expression of many growth factors as well as thick and thin filament proteins in *Tak1*-deficient skeletal muscle suggesting that TAK1 is required for growth and maintenance of skeletal muscle mass in adults (63). Further validation of the growth-promoting role of TAK1 came from the findings that mechanical overload increases the phosphorylation of TAK1 within its activation domain along with other positive regulators of muscle mass (63, 64). TAK1 is required for post-natal muscle growth

because inducible inactivation of TAK1 blunts overload-induced myofiber hypertrophy in adult mice (63).

More recent studies have shown that forced activation of TAK1 through intramuscular co-injection of TAK1- and TAB1-expressing adeno-associated viruses (AAVs) causes a significant increase in myofiber cross-sectional area. Intriguingly, the phosphorylation of NF-κB subunit p65, p38 MAPK, and ERK 1/2 is considerably increased in TAK1and TAB1-overexpressing skeletal muscle. While TAK1 has been implicated in tissue inflammation and fibrosis (35, 65, 66), there was no sign of fibrosis or any other overt phenotype in TAK1 and TAB1-expressing skeletal muscle. This could be attributed to the fact that the TAK1 was activated in skeletal muscle that was devoid of any inflammation or injury. In fact, there are reports suggesting that NF-κB or p38 MAPK signaling promotes muscle growth and homeostasis in physiological conditions (67, 68).

TAK1 regulates protein synthesis.

Skeletal muscle growth requires a net increase in protein synthesis that is governed by the translation efficiency (amount of protein synthesis per unit RNA) and translation capacity (the total ribosomal content) within muscle fibers (69–72). Translation is initiated by binding of eukaryotic initiating factor eIF4E to the 5’ Cap of mRNA strand. The interaction between eIF4E and mRNA leads to the recruitment of eIF4G, eIF4A, and eIF4B factors to form eIF4F, the translation preinitiation complex, which recruit the 40S subunit of ribosome to the mRNA strand. The 40S subunit also contain the eIF2-GTP-Met-tRNA complex. Together, this group of proteins form the 43S initiation complex, which is the rate-limiting step for initiation of cap-dependent translation (73). One of the potential mechanisms by which TAK1 improves skeletal muscle growth is through augmenting protein synthesis. Inactivation of TAK1 represses whereas forced activation of TAK1 augments protein synthesis in skeletal muscle of mice and in cultured primary myotubes (63, 64). Inactivation of TAK1 does not appear to influence translational capacity because the markers of ribosomal biogenesis are increased in *Tak1*-deficient skeletal muscle, which could be a compensatory mechanism to mitigate repression in the rate of protein synthesis (63).

Until recently, mTOR, which forms two different protein complexes, the rapamycin-sensitive mTORC1, when bound to Raptor, and the rapamycin-insensitive mTORC2, when bound to Rictor was believed to be the primary mechanism of protein synthesis and muscle growth (16, 74, 75). Activated mTORC1 phosphorylates eIF4E-binding protein 1 (4E-BP1), leading to its release from the inhibitory complex with the translation initiation factor eIF4E, allowing eIF4E to associate with eIF4G and thereby promoting eIF4F complex formation and cap-dependent initiation of translation (2, 16). Furthermore, mTORC1 phosphorylates p70 ribosomal protein S6 (rpS6) kinase beta-1 (S6K1), which stimulates protein synthesis through phosphorylating rpS6 protein, a component of the 40S ribosomal subunit (16). S6K1 also causes inhibitory phosphorylation of eukaryotic elongation factor 2 (eEF2) kinase (eEF2K) that results in repression of eEF2 phosphorylation, allowing protein translation elongation. S6K1 also phosphorylates eIF4B and eIF4G to elicit protein translation. Growth factors and resistance exercise activate rapamycin-sensitive mTORC1 signaling, which leads to translation initiation resulting in a net increase in protein synthesis in skeletal muscle

(74, 76, 77). Indeed, forced activation of mTORC1 is sufficient to induce phosphorylation of S6K1 and stimulation of protein synthesis in skeletal muscle with normal activity (78, 79). Intriguingly, a few recent studies have provided evidence that muscle protein synthesis especially that occurs at late time points in response to a bout of resistance exercise is largely rapamycin-insensitive (80, 81). Inhibition of mTORC1 through inducible deletion of raptor in skeletal muscle does not prevent the increase in protein synthesis that occurs in response passive stretch or chronic mechanical overload suggesting that mTORC1-independent mechanisms also contribute to protein synthesis in response to mechanical stimulus (82).

Protein synthesis in mammalian cells is also regulated through the activation of ERK1/2 and p38 MAPK, which function through phosphorylation and activation of the p90 ribosomal S6 kinases (RSKs) and the MAPK-interacting kinases (MNKs) (73). MNK1a and MNK2a are recruited to eIF4E through eIF4G to phosphorylate eIF4E at Ser209 residue, which may be important for stability of eIF4E-cap interaction and stimulating translation of select mRNAs (73, 83). Intriguingly, while protein synthesis was not measured, no significant difference in muscle hypertrophy was observed between wild type and nonphosphorylatable eIF4E (S209A) knock-in mice indicating that phosphorylation of eIF4E at Ser209 may be dispensable for skeletal muscle hypertrophy in response to mechanical overload (84). ERK1/2 also directly interact and phosphorylate RSKs. In turn, RSKs phosphorylate rpS6 thus providing an mTOR/S6K-independent involvement connecting ERK1/2 signaling to the regulation of mRNA translation (73). RSKs also directly regulate phosphorylation of eIF4B and eEF2K to enhance protein translation (85). Finally, RSK-mediated phosphorylation and inhibition of GSK3β on Ser9 activates eIF2B, an important regulator of protein synthesis (73, 86)

Signaling mechanisms by which TAK1 improves protein synthesis remain enigmatic. While no obvious difference was observed in normal muscle, phosphorylation of mTOR and 4E-BP1 protein was reduced in plantaris muscle in response to 14d of mechanical overload in *Tak1*-knockout mice (63). Intriguingly, forced activation of TAK1 through overexpression of TAK1 and TAB1 does not affect the phosphorylation of mTOR or S6K1 yet induces rpS6 phosphorylation and augments protein synthesis in skeletal muscle. Additionally, TAK1 increases the phosphorylation of ERK1/2, p38 MAPK, MNK1, eIF4E, and RSK1 protein in skeletal muscle. Similarly, overexpression of TAK1 and TAB1 stimulates phosphorylation of ERK1/2, MNK1, p90RSK, eIF4E, and rpS6 and protein synthesis without affecting the phosphorylation of mTOR in cultured primary myotubes (64). These observations suggest that TAK1-mediated signaling might be enhancing protein synthesis through the activation of MAPKs and independent of mTORC1-mediated signaling. Alternatively, it is also possible that TAK1 signaling co-operates with mTORC1 to stimulate protein synthesis in skeletal muscle. Indeed, under certain conditions, ERK1/2 is known to activate mTORC1 complex by phosphorylating and inactivating TSC2 (FIGURE 2). Further investigations are needed to determine whether TAK1 signaling contributes to protein synthesis when mTORC1-rpS6 axis is repressed. Moreover, whether forced activation of TAK1 is sufficient to induce protein synthesis and muscle hypertrophy in muscle-specific raptor-knockout mice needs to be investigated. Similarly, it will be interesting to determine whether the

activation of mTORC1 signaling improves protein synthesis and inhibits atrophy in adult muscle-specific *Tak1*-knockout mice.

While these initial studies have demonstrated that TAK1 mediates protein synthesis, it remains to be investigated whether it contributes to early or late stages of protein synthesis in skeletal muscle following mechanical overload. It is also important to determine whether TAK1 stimulates general translation or regulates selective proteins in skeletal muscle. In addition, signaling mechanisms through which TAK1 stimulates protein synthesis in skeletal muscle needs further investigation. Identification of TAK1 interacting proteins and TAK1-regulated phosphoproteome by quantitative mass spectrometry will help elucidating potential mechanisms through which TAK1 promotes skeletal muscle homeostasis and growth.

TAK1 maintains redox homeostasis and mitochondrial health.

Skeletal muscle produces several reactive oxygen species (ROS), which are balanced by antioxidant mechanisms. However, an exorbitant production of oxidant species and/or suppression of antioxidant species disrupts redox homeostasis, which results in oxidative stress. While ROS act as signaling molecules in physiological processes, such as regeneration, repair, and promote mitochondrial biogenesis following exercise, elevated levels of ROS cause tissue injury due to oxidative damage (26, 87). Indeed, oxidative stress activates various proteolytic systems, which results in muscle weakness and atrophy (1, 8, 88). Accumulating evidence also suggests that mitochondria play a key role in the maintenance of skeletal muscle mass, contractile properties, and metabolic function. Disruption in mitochondrial dynamics (e.g. mitochondrial biogenesis, fusion, fission, or mitophagy) or reduction in mitochondrial oxidative phosphorylation capacity has been found to be a major driver of skeletal muscle wasting in many conditions (27).

Previous studies have demonstrated that inactivation of TAK1 triggers ROS production leading to inflammation and injury in kidney and intestinal epithelial tissues. Moreover, deletion of TAK1 also causes oxidative stress in keratinocytes and satellite stem cells (31, 89–91). Inactivation of TAK1 also disrupts redox balance leading to the accumulation of reactive ROS and irreversibly oxidized (carbonylated) proteins in skeletal muscle (63, 92). The role of oxidative stress in muscle weakness and atrophy is supported by the findings that Trolox, a water-soluble antioxidant, improves muscle mass and contractile function in muscle-specific *Tak1*-knockout mice (92). TAK1 inactivation also increases the proportion of type IIA (oxidative fast-type) myofibers and mitochondrial content in skeletal muscle of adult mice. This increase in mitochondria content may be attributed to enhanced mitochondrial biogenesis because *Tak1*-deficient skeletal muscle demonstrates increased activation AMPK and higher levels of PGC-1α, which are known to promote mitochondrial biogenesis (63). Intriguingly, mitochondria in *Tak1*-deficient skeletal muscle are enlarged and found to contain lipid-like inclusions or vacuolations. Moreover, mitochondrial oxidative capacity in considerably reduced suggesting accumulation of dysfunctional mitochondria in *Tak1*-deficient skeletal muscle (63). It is notable that aggregates of mitochondria with vacuolation is characteristic of skeletal muscle and motor neurons of the SOD1 mutant mouse model of amyotrophic lateral sclerosis, where oxidative

stress has been implicated to play a major role in disease progression (93). Enlarged mitochondria have been consistently observed in the skeletal muscle of the elderly (3, 94). While mitochondria are one of the important sources for ROS production, elevated oxidative stress causes mitochondrial dysfunction in many cells and tissues, including skeletal muscle. Indeed, mitigation of oxidative stress using Trolox improves mitochondrial oxidative phosphorylation capacity in skeletal muscle of *Tak1*-knockout mice (92).

Nuclear factor erythroid 2 (NF-E2)-related factor 2 (Nrf2) transcription factor regulates the antioxidant capacity to maintain redox homeostasis in mammalian cells (95). In normal conditions, Nrf2 is sequestered in the cytosol by KEAP1 (Kelch-like ECH-associated protein 1). KEAP1 also induces the degradation of Nrf2. Following oxidative stress, KEAP1 undergoes thiol modification that triggers disengagement and subsequent nuclear translocation of Nrf2, which increases expression of Antioxidant Response Element (ARE) genes to boost cellular antioxidant capacity (95). It has been reported that TAK1 induces the phosphorylation of p62/Sequestosome-1 (SQSTM1) that enhances p62/SQSTM1 and Keap1 interaction and subsequent KEAP1 degradation (91). Although exact mechanisms remain unknown, it is apparent that inactivation of TAK1 dysregulates the Nrf2/KEAP1 signaling axis resulting in increased KEAP1 protein levels, Nrf2 sequestration in cytoplasm, and consequent oxidative stress and muscle atrophy (92).

TAK1 regulation of neuromuscular junctions (NMJs).

NMJ is a cholinergic synapse that is formed by motor nerve terminals, postjunctional sarcolemma region expressing acetylcholine receptors (AChRs), and terminal Schwann cells that cover the nerve-muscle contact. Acetylcholine produced by nerve terminals binds with AChRs on sarcolemma at NMJs to initiate voluntary muscle contraction (96). NMJ integrity is critical for the maintenance of skeletal muscle mass and health (97). Reduction in nerve terminal area and post-synaptic morphological changes have been consistently observed in the elderly and various muscle wasting conditions, including cancer. These pronounced changes in NMJ morphology lead to muscle wasting and frailty (17, 98, 99).

Many features, such as myofiber atrophy, development of kyphosis, and accumulation of enlarged and dysfunctional mitochondria observed in skeletal muscle-specific *Tak1*-knockout mice suggest that inactivation of TAK1 accelerates an aging phenotype (63). Interestingly, inducible inactivation of TAK1 in skeletal muscle of adult mice also results in derangement of NMJ at the post-synaptic region. The agrin-LRP4-MuSK signaling along with other accessory molecules support the accumulation, patterning, and formation of NMJs. During development, a specific Agrin isoform is secreted from the innervating nerve, which interacts with muscle-specific receptor tyrosine kinase (MuSK) in the developing myofiber. Agrin activates MuSK via co-receptor Low-density lipoprotein receptor-related protein 4 (Lrp4), Downstream of kinases-7 (Dok-7), and Rapasyn mediates AChR accumulation and clustering. Once the synaptic contacts during development are established, the transcription of AChRs genes is restricted to the synaptic regions of muscle fibers and is actively repressed. However, nerve damage, sarcopenia and denervation causes disorganization of the NMJs and increases turnover of AChRs. The bHLH transcription factor myogenin binds to conserved sequence of AChR and MuSK promoter and triggers

transcription of these genes following denervation or synaptic blockade (99). Interestingly, myogenin also mediates the denervation-induced muscle atrophy through augmenting gene expression of MAFbx and MuRF1 (100). Disruption of NMJs in *Tak1*-knockout is also evidenced by increased levels of myogenin, HDAC4, AChRs, Agrin, MuSK, Dok7, and FoxOs which are hallmarks of denervated muscle (64). Although molecular underpinnings remain less understood, retrograde signaling has been speculated to influence NMJ dynamics. Earlier studies have shown that inhibition of protein synthesis in pre-synaptic muscle causes pre-synaptic NMJ anomaly (101). While mTOR plays a critical role in preserving NMJ structure and innervation, sustained activation of mTORC1 triggers NMJ instability characterized by axon thinning and sprouting, reduced postsynaptic AChR density, and fragmentation of postsynaptic structure that could be attributed to the suppression of autophagy and dysfunctional mitochondria (102, 103). Similar to mTORC1, inactivation of TAK1 also inhibits protein synthesis and leads to the accumulation of large dysfunctional mitochondria. However, TAK inactivation leads to stimulation of the UPS and autophagy in skeletal muscle. Even though long-term effects of inhibition of TAK1 have not been yet investigated, forced activation or inhibition of TAK1 does not cause myopathy in adult mice (63, 64).

Oxidative stress observed during aging or neurodegenerative disorder has been linked with mitochondrial dysfunction and impairment of autophagy flux leading to NMJ instability and muscle atrophy reminiscent of denervation (99). As mentioned above, inactivation of TAK1 causes oxidative stress in skeletal muscle both in vivo and in vitro. Therefore, it is possible that increased oxidative stress in *Tak1*-deficient muscle is one of the reasons for degeneration of NMJs. Indeed, inhibition of oxidative stress through chronic administration of Trolox improves skeletal muscle mass and contractile function in muscle-specific *Tak1*-knockout mice (92). It will be interesting to determine whether inhibition of oxidative stress improves NMJ stability in *Tak1*-knockout mice. Collectively, these initial studies support an important role of TAK1 signaling in maintaining NMJs (FIGURE 3).

TAK1 inhibits catabolic signaling in skeletal muscle.

Loss of muscle mass involves accelerated degradation of myofibril proteins (1, 5, 8). Since TAK1 regulates multiple signaling pathways, overstimulation of TAK1 that occurs in response to proinflammatory cytokines or tumor-derived factors may be responsible for muscle wasting in some conditions (19, 104, 105). However, studies using genetic mouse models suggest that physiological levels of TAK1 prevent proteolysis in skeletal muscle. Activity of 20S proteasome and levels of multiple components of the UPS and autophagy are increased in skeletal muscle of *Tak1*-knockout mice. Inactivation of TAK1 reduces the levels of phosphorylated p38MAPK but does not affect activation of canonical NF-κB signaling in skeletal muscle. Intriguingly, TAK1 inactivation causes noticeable activation of non-canonical NF-κB signaling in skeletal muscle in vivo and in vitro (63). Non-canonical NF-κB signaling has been found to be associated with mitochondrial biogenesis as well as muscle atrophy during disuse (19, 106, 107). While *Tak1*-deficient skeletal muscle shows increased mitochondrial content and concomitant atrophy, it remains unknown whether some of these effects are mediated by non-canonical NF-κB signaling.

TAK1 also regulates the activation of other pathways involved in muscle proteolysis. As discussed above, targeted inactivation of TAK1 leads to NMJ instability and denervation. FoxO transcription factors, which induces the gene expression of various E3 ubiquitin ligases, are some of the most important mediators of muscle wasting (2, 15). Furthermore, HDAC4 and myogenin constitute another major signaling axis triggering muscle proteolysis, especially in denervated muscle (1, 8). Consistent with denervation phenotype, *Tak1*-deficient skeletal muscle shows elevated levels of FoxO3a, FoxO4, HDAC4, and myogenin protein along with increased gene expression of E3 ubiquitin ligases: MAFbx, MuRF1 and MUSA1 (64).

Another potential mechanism through which TAK1 regulates skeletal muscle mass is through coordinating the activation of TGFβ- and bone morphogenetic protein (BMP)-signaling pathways, which have opposite effects on the regulation of muscle mass. TGF-β subfamily of ligands (e.g. Activin, myostatin, and TGF-β) activate Smad2/3 transcription factors, which stimulate muscle wasting through augmenting the gene expression of MAFbx and MuRF1, and repressing protein synthesis (1, 18, 108). Indeed, blockade of Smad2/3-mediated signaling prevents skeletal muscle wasting in diverse catabolic conditions as well as in genetic muscle disorders (109, 110). In contrast, BMP ligands activate Smad1/5/8 signaling axis that positively regulates skeletal muscle mass (18, 110–112). Forced activation of this pathway is sufficient to induce skeletal muscle growth and to attenuate denervation-induced muscle atrophy (18, 110, 111). Therefore, a delicate balance between Smad2/3 and Smad1/5/8 signaling is essential for the maintenance skeletal muscle mass. Intriguingly, inactivation of TAK1 leads to a remarkable increase in the gene expression of various BMP and TGFβ family ligands and receptors and increased phosphorylation of Smad2 as well as Smad1/5/8 in skeletal muscle of mice (64). It is possible that TAK1 directly activates Smad1/5/8 to prevent excessive loss of muscle mass, especially in response to denervation. TAK1 makes a complex with Smad1 in denervated muscle and inactivation of TAK1 exacerbates proteolysis and denervation-induced muscle atrophy. Indeed, recombinant BMP7 or BMP13 protein requires TAK1 to induce Smad1/5/8 phosphorylation in cultured myotubes (64). However, it remains unknown whether TAK1 directly phosphorylates Smad2/3 in denervated muscle. Moreover, the role of TAK1 in spatial distribution (cytoplasmic vs. nuclear) of Smad2/3 in atrophying skeletal muscle warrants further investigations.

TAK1 signaling in Muscular Dystrophy.

Muscular dystrophy is a group of genetic neuromuscular disorders that involves severe muscle wasting. Duchenne muscular dystrophy (DMD) is one of the most prevalent forms of muscular dystrophies that results from total or partial deficiency of dystrophin protein (113). Pathogenesis of DMD also involves aberrant activation of multiple signaling pathways, such as NF-κB and MAPKs, which exacerbates muscle injury, inflammation, and fibrosis (114–117). Indeed, targeted inhibition of NF-κB in myofibers or macrophages improves dystrophic phenotype in mdx mouse model of DMD (118).

A recent study has demonstrated that TAK1 is highly activated in skeletal muscle of DMD patients and in dystrophic muscle of mdx mice and that inhibition of TAK1 improves

dystrophic phenotype in mdx mice (66). Consistent with this published report (66), we also found that targeted inducible inactivation of TAK1 in young mdx mice reduces skeletal muscle injury and accumulation of macrophages. Interestingly, TAK1 inactivation in adult mdx mice show modest improvement in histopathology (119). However, similar to wild-type mice (63, 92), inducible muscle-specific inactivation of TAK1 also decreases myofiber size and contractile function in dystrophic muscle of both young and adult mdx mice. More importantly, forced activation of TAK1 in skeletal muscle after peak necrotic phase induces myofiber growth without having any deleterious effect on muscle histopathology in mdx mice (119). It is apparent that AAV-TAK1 shRNA causes only a small reduction in levels of TAK1 in skeletal muscle (66). By contrast, genetic approaches lead to a drastic reduction in the levels of TAK1 protein in dystrophic muscle of mdx mice (119). The published study also demonstrate that inhibition of TAK1 ameliorates fibrosis in mdx mice (66). However, we did not find any difference in the level of fibrosis after myofiber-specific ablation of TAK1 in mdx mice. It is noteworthy that due to robust muscle regenerative program, fibrosis is observed in skeletal muscle of older mdx mice (120). In addition, pharmacological or shRNA-mediated approach can inhibit TAK1 in multiple cell types that can lead to the discrepant phenotype. Certainly, more investigations are needed to understand the role of TAK1 in pathogenesis of DMD and other types of muscular dystrophy. Moreover, it will be important to determine how TAK1 regulates muscle pathogenesis in other muscular disorders and inflammatory myositis.

Concluding remarks.

Substantial progress has been made towards understanding the molecular and signaling mechanisms that regulate skeletal muscle mass in health and disease. However, there is still no efficient drug to counter the loss of muscle mass. The accumulating evidence suggests that TAK1 is an important regulator of skeletal muscle mass. While inducing protein synthesis, TAK1 inhibits catabolic signaling and proteolytic systems in skeletal muscle (FIGURE 3). Remarkably, forced activation of TAK1 does not produce any overt phenotype in skeletal muscle suggesting that stimulation of TAK1-mediated signaling can be used as therapeutic approach to counteract muscle wasting.

Although initial studies demonstrate that TAK1 promotes gain of skeletal muscle mass, several questions need to be answered before considering TAK1 as a potential therapeutic target for muscle disorders. For example, almost all the studies regarding the role of TAK1 in skeletal muscle are short-term. It will be important to investigate how prolonged inhibition or activation of TAK1 influence skeletal muscle mass in mice. While TAK1 activity is reduced in skeletal muscle following denervation, it remains to be investigated whether repression of TAK1 activity is a common denominator of muscle wasting in all catabolic conditions. Future studies will also investigate whether forced activation of TAK1 can prevent muscle wasting in other conditions, such as aging, cancer-induced cachexia, and neuromuscular disorders.

How mechanical overload and potentially other anabolic stimuli activate TAK1 in skeletal muscle needs to be investigated. Even though TAK1 appears to regulate activation of multiple signaling pathways, the proteins that are directly phosphorylated by TAK1 in

skeletal muscle remains unknown. Future studies should focus on identifying TAK1 interacting proteins and its phosphorylation targets. Furthermore, it will be important to determine whether TAK1 regulates muscle mass in conjunction with other anabolic signaling pathways, such as mTORC1. Nevertheless, recent studies have provided robust evidence that TAK1 is an important regulator of skeletal muscle mass and health.

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ABBREVIATIONS:

AChR	Acetylcholine receptor
AMPK	AMP-activated protein kinase
BMP	Bone morphogenetic protein
DMD	Duchenne muscular dystrophy
eEF	Eukaryotic elongation factor
4E-BP1	eIF4E-binding protein 1
eIF	Eukaryotic initiation factor
MNK	MAPK-interacting kinase
mTORC1	mTOR complex 1
NMJ	Neuromuscular junction
ROS	Reactive oxygen species
RSK	p90 ribosomal S6 kinase
rpS6	Ribosomal protein S6
S6K1	Ribosomal protein S6 kinase 1
TGF-β	Transforming growth factor β
TAK1	TGF-β-activated kinase 1
TAB	TAK1-binding protein
UPS	Ubiquitin-proteasome system

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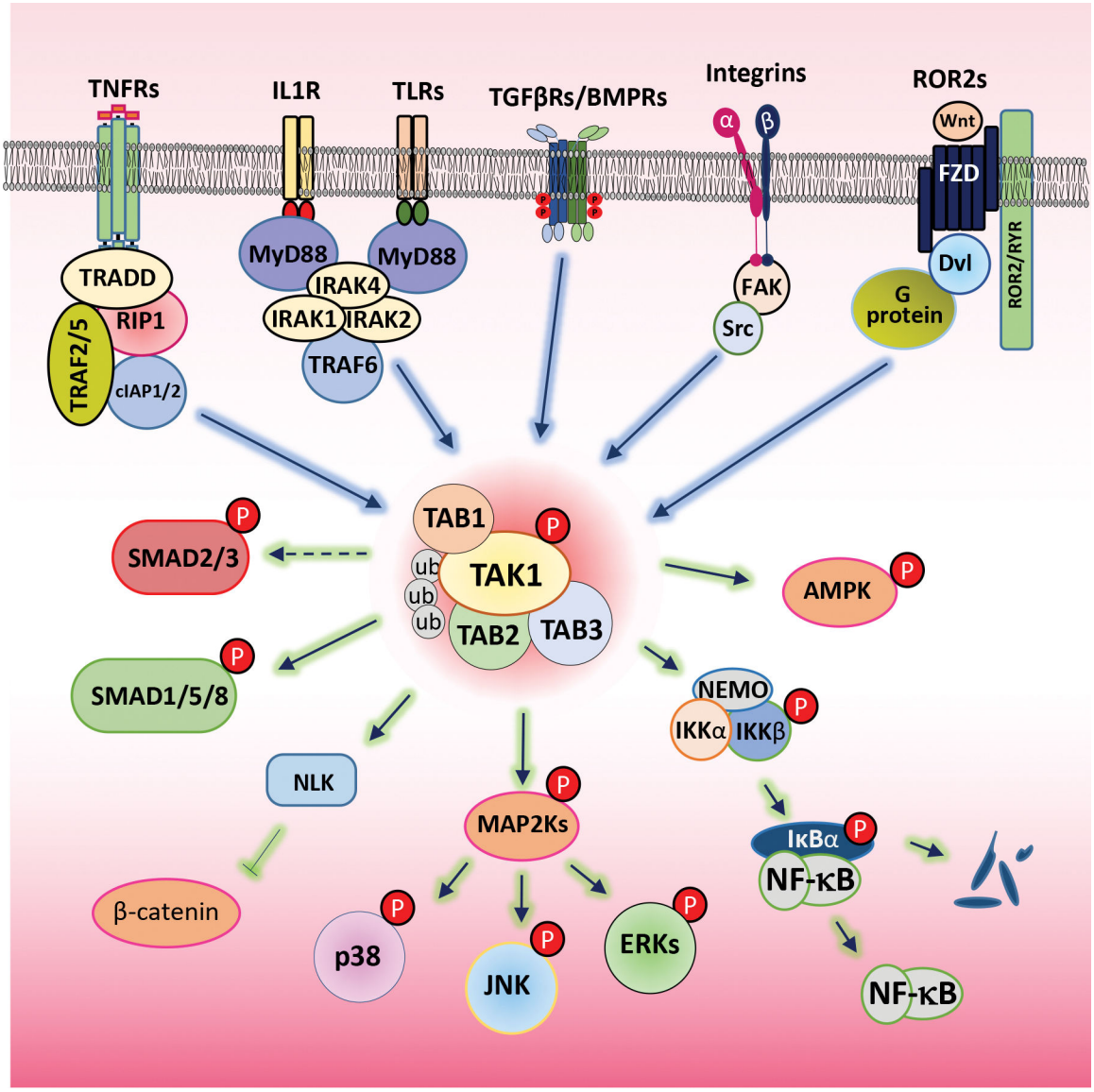

FIGURE 1: A schematic representation of various signaling pathways regulated by TAK1.

Stimulation of TNF receptors (TNFRs), IL-1β receptor (IL1R), Toll-like receptors (TLRs), Transforming growth factor-β receptors (TGF-βRs), or Bone morphogenetic protein receptors (BMPRs) leads to recruitment of various adaptor proteins to their cytoplasmic domains. This results in activation of TAK1. Signaling from integrin receptors or tyrosine kinase (RYK)-like orphan receptor 2 (ROR2) also activates TAK1 in some cell types. Once activated, TAK1 triggers phosphorylation and activation of multiple downstream targets leading to the activation ERKs, JNK, p38 MAPKs, and canonical NF-κB signaling. TAK1 causes phosphorylation of SMAD1/5/8 and potentially SMAD2/3 as well. Additionally, TAK1 through NEMO-like kinase (NLK) antagonizes β-catenin signaling in some cell types. AMPK, AMP-activated protein kinase; cIAP, cellular inhibitor of apoptosis protein; FAK, focal adhesion kinase; IKK, IκB kinase; IRAK, Interleukin-1 receptor-associated kinases; MAP2K, Mitogen-activated protein kinase kinase; MyD88, Myeloid differentiation

primary response 88; NEMO, NF-κB essential modulator; RIP1, Receptor-interacting protein 1; TRADD, Tumor necrosis factor receptor 1-associated death domain protein; TRAF, TNF receptor-associated factor; Ub, ubiquitin.

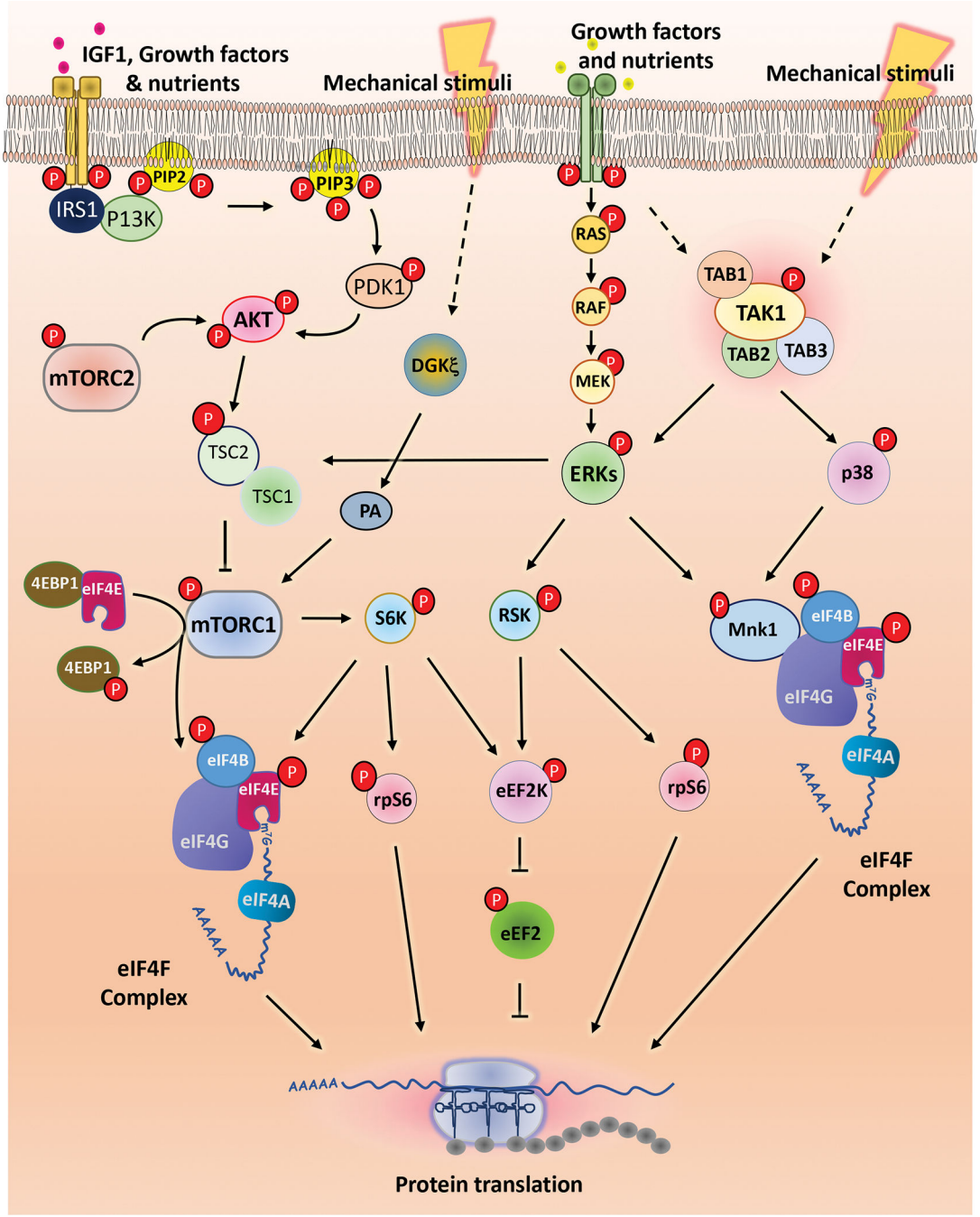

FIGURE 2: Potential mechanisms of action of TAK1 in protein synthesis in skeletal muscle.

Insulin or IGF-1 stimulates IGF-1 receptor to recruit PI3K. PI3K catalyzes the conversion of phosphatidylinositol (4,5)-bisphosphate (PIP_2) into phosphatidylinositol (3,4,5)-trisphosphate (PIP_3) which binds protein kinase B (AKT). AKT is then phosphorylated by PDK1 at Threonine 308 and the mammalian target of rapamycin complex 2 (mTORC2) at Serine 473 for complete activation. AKT phosphorylates and inhibit TSC2 protein, which leads to the activation of rapamycin-sensitive mTORC1 complex. Mechanical stimuli also leads to endogenous phosphatidic acid (PA) synthesis

via diacylglycerol kinase zeta (DGKξ) which directly activates mTORC1. The mTORC1 stimulates protein synthesis by phosphorylating S6K1 and 4E-BP1 protein. This allows the eIF4E protein to form eIF4F complex formation and bind to the 5'cap structure of mRNA required for translational initiation. eIF4E, eIF4B, rpS6 and eEF2K are downstream substrates of S6K1 and are phosphorylated for translational initiation and elongation. IGF and other growth factors and nutrients can also stimulate activation of Ras/Raf/MEK/ERKs cascade. ERK1/2 phosphorylated and activated p90 ribosomal S6 kinases (RSKs), which contributes to phosphorylation of eEF2K and rpS6 for protein translation. TSC2 protein is also phosphorylated by ERK1/2. Additionally, ERK1/2 and p38 MAPK phosphorylate Mnk1 which in turn induces phosphorylation of eIF4E and eIF4B to initiate protein translation. Activation of TAK1 by growth factors, nutrients, or mechanical stress leads to the phosphorylation of ERK/2 and p38 MAPK which stimulate protein synthesis through the activation of RSKs and Mnk1.

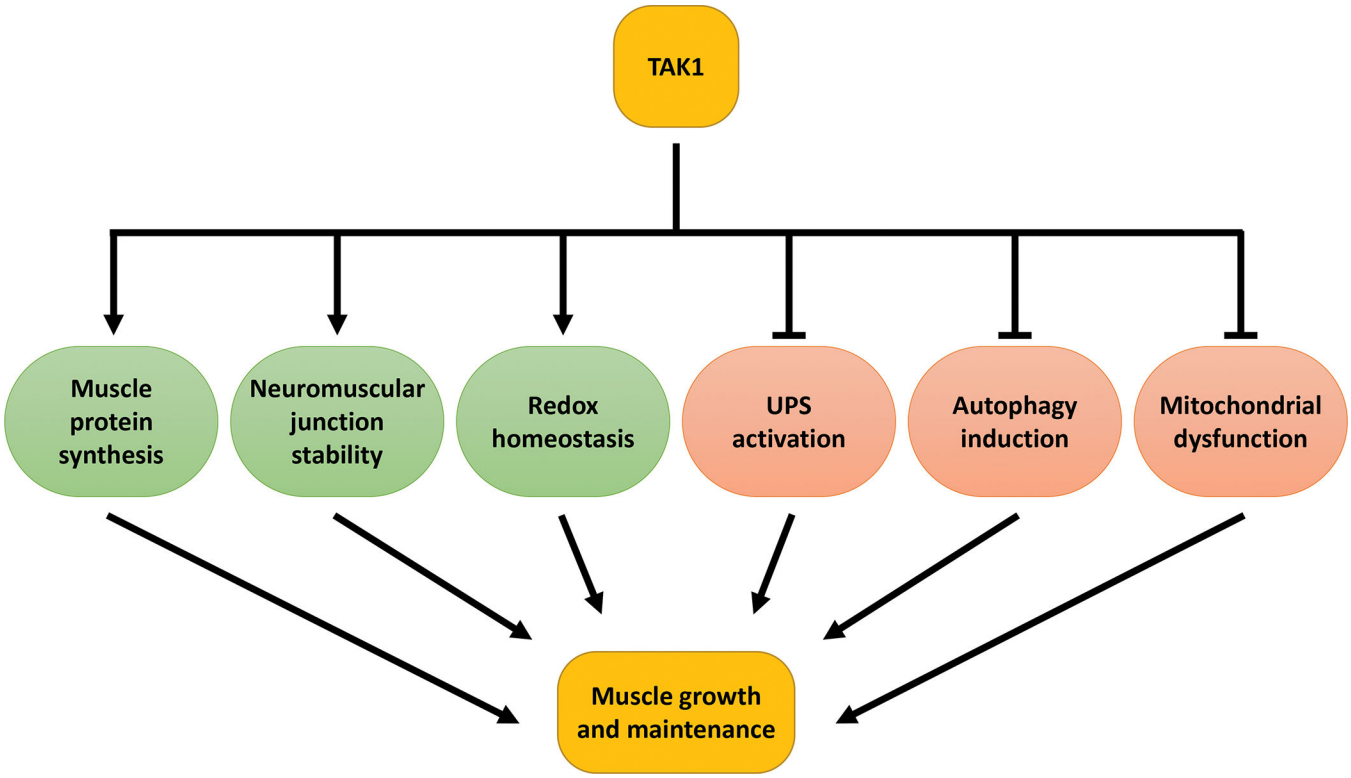

FIGURE 3. Mechanisms of action of TAK1 in skeletal muscle.

TAK1 induces muscle protein synthesis, neuromuscular junction stability, and redox homoeostasis. TAK1 also restricts activation of ubiquitin proteasome system (UPS) and autophagy and prevents mitochondrial dysfunction to maintain skeletal muscle mass and improve muscle growth.