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TWEAK and TRAF6 regulate skeletal muscle atrophy

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Abstract

Purpose of review—The purpose of this review is to discuss the roles and mechanisms of action of TWEAK and TRAF6 in skeletal muscle atrophy.

Recent findings—Proinflammatory cytokines are known to mediate muscle atrophy in many chronic disease states. However, their role in the loss of skeletal muscle mass in disuse conditions has just begun to be elucidated. Further, the initial signaling events leading to the activation of various catabolic pathways in skeletal muscle under different atrophic conditions are also less well understood. The TWEAK-Fn14 system has now been identified as a novel inducer of skeletal muscle wasting. Adult skeletal muscles express minimal levels of Fn14, the bona fide TWEAK receptor. Specific conditions of atrophy such as denervation, immobilization, or unloading rapidly induce the expression of Fn14 leading to TWEAK-induced activation of various proteolytic pathways in skeletal muscle. Recent studies have also demonstrated that the expression and activity of TRAF6 are increased in distinct models of muscle atrophy. Muscle-specific ablation of TRAF6 inhibits the induction of atrophy program in response to starvation, denervation, or cancer cachexia. Moreover, TWEAK also appears to activate some catabolic signaling through TRAF6-dependent mechanisms.

Summary—Recent findings have uncovered TWEAK and TRAF6 as novel regulators of skeletal muscle atrophy. These proteins should potentially be used as molecular targets for prevention and/or treatment of muscular atrophy in future therapies.

Keywords

Skeletal muscle atrophy; TWEAK; TRAF6; disuse; Denervation; Cachexia; NF-kappa B; ubiquitin-proteasome pathway; MuRF1

Introduction

Skeletal muscle atrophy is a debilitating consequence of many conditions including aging, denervation, immobilization, chronic disease states, and high dose glucocorticoid therapy (1, 2). Muscle atrophy is characterized by reduction in muscle mass, fiber cross-section area, protein content, and power output. In general, activation of signaling proteins such as c-Jun-N-terminal kinase (JNK), p38 mitogen-activated protein kinase (MAPK), 5' adenosine monophosphate-activated protein kinase (AMPK), and I kappa B kinase (IKK) causes the downstream activation of transcription factors such as nuclear factor-κB (NF-κB), activator protein-1, members of Foxo family, activating transcription factor 4, and p53 which induce muscle atrophy through augmenting the activity of proteolytic systems (3–7). In contrast, the activation of phosphatidylinositol-3 kinase (PI3K)/Akt signaling pathway prevents muscle

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atrophy through inhibiting the activity of Foxo transcription factors and augmenting protein synthesis (3, 7). Further, the ubiquitin-proteasome system (UPS) has now emerged as a major proteolytic system involved in myofibril proteolysis in a variety of catabolic conditions (2, 3). Although their relative contribution may depend on the type of stimuli, accumulating evidence suggests that some proteolytic systems such as autophagy, calpains, and caspases also contribute to the turnover of muscle proteins in catabolic states (5, 8, 9).

Whereas major progress has been made towards understanding the intracellular mechanisms of muscle wasting, the triggers and upstream signaling events involved in the induction of atrophy program remain poorly understood. Inflammatory cytokines have been suggested as local catabolic mediators at advanced stages of chronic diseases leading to the syndrome of cachexia (2, 10). However, what trigger muscle proteolysis in disuse conditions remains unclear. Recently, TWEAK cytokine and its receptor Fn14 have been identified as critical regulator of skeletal muscle mass (11, 12). Moreover, it has now been found that the activation of TRAF6 is one of the initial signaling events that lead to the activation of various downstream signaling pathways in skeletal muscle in response to catabolic stimuli including TWEAK (13). In this article, we have summarized the current knowledge about the roles and the mechanisms of action of TWEAK and TRAF6 in skeletal muscle atrophy.

The TWEAK-Fn14 System

TWEAK is a multifunctional protein and a member of the TNF super family (TNFSF) cytokines (14, 15). TWEAK is initially synthesized as a 249-amino-acid protein comprising a C-terminal extracellular domain, a transmembrane domain, and an N-terminal intracellular domain. TWEAK is proteolytically cleaved at its C-terminal domain to its active soluble form which trimerizes and signals as a homotrimer molecule (14). Although the regulation of their relative abundance in specific conditions is not yet understood, TWEAK is fully functional in both membrane-bound and soluble forms (14). TWEAK binds to Fn14 (fibroblast growth factor-inducible 14) receptor which is a type I transmembrane protein and is a member of TNF receptor super family (TNFRSF) (14). Fn14 was first recognized by differential display technique and later identified as an exclusive TWEAK receptor. The TWEAK-Fn14 axis regulates various physiological responses including cell survival, proliferation, differentiation, angiogenesis, migration, and apoptosis (14). However, aberrant expression of TWEAK and/or Fn14 has been found to be linked with deleterious pathogenic effects in autoimmune disorders, renal damage and dysfunction, neuronal anomalies, several types of cancer, and cardiac dysfunction and failure (14, 15). It has been proposed that TWEAK causes Fn14 trimerization, interaction with TRAF2/cIAP1 (cellular inhibitor of apoptosis protein 1) complex to Fn14 cytoplasmic domain, and subsequent activation of several signaling proteins including TRAF6, transforming growth factor-β activated kinase1, IKK, and MAPK leading to the activation of various transcription factors followed by gene expression (11, 16, 17). Mice null for TWEAK or Fn14 are viable and exhibit no developmental defects suggesting that their deficiency is compensated by other factors present during development (2, 15, 18).

TWEAK-Fn14 System in Muscle Atrophy

Elevated levels of classical inflammatory cytokines such as TNF-α, interleukin (IL)-1β, IL-6, and interferon (IFN)-γ have been implicated in muscle wasting in various chronic disease states (10). However, therapeutic strategies targeting these multifunctional cytokines have been proven inefficient in prevention of muscle loss in some conditions which indicates the involvement of other mediators of skeletal muscle wasting. Few years back, we directed our studies to identify additional mediators of muscle wasting. Our initial experiments demonstrated that TWEAK has major effects on muscle cell cultures. Both

C2C12 and mouse primary myoblasts express Fn14 receptor on their cell surface (18–20). TWEAK induced the proliferation of myoblasts and inhibited their differentiation into myotubes in cultures. Furthermore, TWEAK was found to activate NF-κB and MAPK signaling pathways and reduced the levels of MyoD in cultured myoblasts (19, 20). Around the same time, another group also published an article demonstrating similar effects of TWEAK on cultured myoblasts (18). These reports established that cells of myogenic lineage respond to TWEAK.

The effects of TWEAK on differentiated myotubes were also investigated in our laboratory. Addition of soluble TWEAK protein caused a significant reduction in myotube size and induced the activation of various catabolic pathways (12). Specific muscle proteins such as myosin heavy chain (MyHC), which undergo rapid proteolysis in catabolic states, were reduced in myotubes treated with TWEAK (12). It has been consistently observed that expression of two muscle-specific E3 ubiquitin ligases, muscle RING-finger 1 (MuRF1) and muscleatrophy F-box (MAFBx; also known as Atrogin-1) is increased in diverse conditions of muscle atrophy (3, 7). A previous study has shown that MuRF1 mediates the degradation of MyHC in response to atrophic stimuli (21). One of the important mechanisms by which TWEAK induces muscle atrophy is through augmenting the expression of MuRF1 and activation of UPS. TWEAK induced the expression of MuRF1 and stimulated the conjugation of ubiquitin (Ub) with MyHC in C2C12 myotubes (12). The role of MuRF1 and UPS in TWEAK-induced atrophy has been validated by the findings that knockdown of MuRF1 using siRNA technique or treatment with proteasome inhibitors improved myotube diameter and levels of MyHC in TWEAK-treated cultures (22). Transcription factor NF-κB is activated in skeletal muscle in response to a number of catabolic stimuli including TWEAK and mediates atrophy. NF-κB induces muscle atrophy primarily through augmenting the expression of proinflammatory cytokines and chemokines and components of UPS including MuRF1 (1, 23). Our studies have suggested that TWEAK causes the activation of NF-κB which leads to the increased expression of MuRF1 and degradation of muscle proteins including MyHC (12, 24).

In a more recent report, it was shown that TWEAK can also induce the expression of the components of autophagy-lysosomal system (ALS) and activates caspases (especially caspase 3) in cultured myotubes suggesting that other proteolytic systems may also contribute to TWEAK-induced myotube atrophy (22). The PI3K/Akt is a major signaling pathway involved in anabolic response in skeletal muscle (3). The activation of PI3K/Akt is also known to inhibit muscle atrophy through suppressing the activity of Foxo1 and Foxo3a transcription factors (3, 7). Interestingly, TWEAK inhibits the activity of PI3K/Akt signaling pathway which further bolsters the robust catabolic action of TWEAK on cultured myotubes (12).

The *in vivo* effects of TWEAK on skeletal muscle have been assessed by chronic administration of soluble TWEAK protein in mice as well as through generation of muscle-specific TWEAK-transgenic (Tg) mice. Treatment of wild-type mice with TWEAK caused a significant reduction in body weight, skeletal muscle mass, and fiber cross-sectional area compared to untreated littermates (12). Furthermore, muscle creatine kinase promoter-driven transgenic overexpression of full-length TWEAK cDNA also showed profound loss of skeletal muscle mass and neonatal lethality in mice (12). Founder TWEAK-Tg mice were smaller in size and exhibited impaired breathing and locomotion due to profound muscle loss (12). A comparatively lower expression of TWEAK (only 4–6 folds higher than littermate wild-type mice) made TWEAK-Tg mice viable but still caused muscle atrophy, slow-to-fast type fiber transformation, and interstitial fibrosis at around six months of age (11). Muscle-specific transgenic overexpression of TWEAK or systemic treatment with TWEAK protein led to the activation of NF-κB transcription factor, expression of MuRF1,

and ubiquitination of MyHC in skeletal muscle (11, 12). Collectively, these observations led us to conclude that similar to cultured myotubes, increased levels of TWEAK cause muscle-wasting *in vivo* through activation of NF-κB and enhancing the expression of the components of UPS such as MuRF1 (Figure 1).

Involvement of TWEAK-Fn14 system in physiological atrophy has also now been identified (11). The expression of Fn14 (but not TWEAK) is regulated in skeletal muscle in conditions of atrophy and hypertrophy (11). Transcript and protein levels of Fn14 are induced in skeletal muscle of mice in conditions of denervation or immobilization (11). Recently, Wu et al (25) have reported that the expression of Fn14 is significantly increased in gastrocnemius muscle of mice subjected to hind limb suspension (another model of disuse atrophy) which further affirms that the expression of Fn14 goes up in multiple conditions of disuse. In contrast, hypertrophy stimuli such as recovery after cast immobilization or exercise reduced even the basal mRNA levels of Fn14 in skeletal muscle (11).

The role of TWEAK-Fn14 system in disuse atrophy was confirmed by the observations that denervation-induced loss of skeletal muscle mass and function was significantly inhibited in TWEAK-KO mice (11). Conversely, TWEAK-Tg mice in which TWEAK was overexpressed specifically in skeletal muscle showed increased atrophy and fibrosis compared to corresponding littermates upon denervation (11). Consistent with *in vitro* studies, the activation of NF-κB and expression of MuRF1 were noticeably inhibited in denervated skeletal muscle of TWEAK-KO and enhanced in TWEAK-Tg mice compared to corresponding control mice (11). While in cultured myotubes, TWEAK inhibits the phosphorylation of Akt (12), there was no major difference in level of phosphorylation of Akt in denervated muscle of wild-type, TWEAK-Tg and TWEAK-KO mice suggesting the presence of some antagonizing factors of the inhibitory effect of TWEAK on PI3K/Akt pathway in denervated skeletal muscle (11). Furthermore, while the denervation led to increased expression of several autophagy-related genes (such as LC3B, Beclin1, Atg5, Atg12, and Gabarapl1) in skeletal muscle, this induction was comparable between denervated muscle of wild-type, TWEAK-Tg, and TWEAK-KO mice (11). It is noteworthy that all the effects of TWEAK on various signaling pathways or proteolytic systems in cultured myotubes are not recapitulated in denervated muscle. We believe that the denervated muscle contains certain factors which neutralize some of the effects of TWEAK on specific pathways. However, it is likely that TWEAK also mediates muscle atrophy in many yet to be identified conditions and in those conditions TWEAK may modulate the activity the pathways that are affected in TWEAK-treated cultured myotubes but not in denervated muscles.

Although it is increasingly clear that the expression of Fn14 is a rate-limiting step in TWEAK-induced muscle atrophy, it remains unknown how the expression of Fn14 gets upregulated in settings of muscle atrophy. *In silico* analysis has demonstrated consensus binding sites for several transcription factors (including NF-κB, AP-1, SP-1, and MyoD) in the promoter regions of both human and mouse Fn14 gene (26). More recently, Wu et al reported that unloading-induced upregulation of Fn14 is significantly inhibited in *Nfkb1*-knockout mice supporting a role of NF-κB in the increased expression of Fn14 in disuse conditions (25). It is worth mentioning that while TWEAK-Fn14 dyad is an important regulator of skeletal muscle wasting, there are conditions where this ligand-receptor dyad may not have any role in muscle atrophy. For example, the mRNA levels of TWEAK or Fn14 were not affected under the conditions of high dose of glucocorticoids which is also known to cause severe muscle-wasting (11).

TWEAK inhibits Skeletal Muscle Regeneration

Although muscle atrophy is primarily caused by enhanced protein degradation, impairment in the process of muscle regeneration is also a critical determinant of skeletal muscle-wasting in chronic diseases (1). Coincidently, TWEAK also attenuates regeneration and growth of myofibers after injury. The expression levels of both TWEAK and Fn14 are increased in skeletal muscle following injury caused by intramuscular injection of cardiotoxin (27). Histological and morphometric analyses showed that diameter of regenerating myofibers was larger in TWEAK-KO and smaller in TWEAK-Tg mice compared to corresponding age-matched wild-type mice (27). Furthermore, TWEAK was found to exacerbate inflammatory response in injured myofibers leading to their diminished regeneration and growth (27). The levels of activation of NF-κB, expression of inflammatory cytokines and matrix-degrading enzymes, and accumulation of interstitial fibrosis were significantly reduced in regenerating myofibers of TWEAK-KO and augmented in those of TWEAK-Tg mice in comparison to wild-type mice (27). Although the underpinning mechanisms by which TWEAK regulates skeletal muscle regeneration remain enigmatic, it is possible that TWEAK in association with other inflammatory cytokines blocks the fusion of satellite cells resulting in reduced differentiation and growth of myofibers which is consistent with the effects on myoblasts where TWEAK was found to inhibit their differentiation into myotubes (18, 19). Furthermore, TWEAK may directly act on regenerating myofibers leading to activation of various proteolytic systems similar to that observed in cultured myotubes or denervated skeletal muscle (11, 12).

TRAF6: An unconventional E3 Ubiquitin ligase

TRAF6 belongs to a family of conserved intracellular adaptor proteins containing seven members. TRAFs are involved in transduction of signals from cytosolic domain of TNF receptor super family, the Epstein–Barr virus protein LMP1, the interleukin-1 receptor (IL-1R), and transforming growth factor-β (TGF-β) receptor (28). All TRAFs comprise a conserved C-terminal domain, the TRAF domain (which further consists a more divergent N-proximal domain known as TRAF-N and a highly conserved C-proximal sub-domain known as TRAF-C) and an N-terminal zinc-binding RING-domain (28). While the TRAF domain is responsible for homo-and hetrodimerization of the TRAF proteins and their direct and indirect interactions with associated surface receptors, the N-terminal domain (except in TRAF1) has been shown to be crucial for the activation of downstream signaling cascades (28, 29). TRAF proteins exhibit specificity for receptors, heterodimerization partners, adaptor molecules, and downstream signal transducers with which they interact, and this specificity originates from their structural differences (28, 29). Distinct from other TRAF proteins, TRAF2 and TRAF6 have been shown to have E3 ubiquitin ligase activity (30). Furthermore, TRAF2 and TRAF6, in association with dimeric ubiquitin-conjugating enzyme Ubc13/Uev1A, catalyze formation of unique lysine (Lys)-63-linked poly-Ub chains, rather than the conventional Lys-48-linked poly-Ub chains that target proteins for degradation (31–33). TRAF6 is also distinct as it undergoes auto-ubiquitination which results in the activation of several downstream kinases (34) and there are reported differences between receptor recognition by TRAF2 and TRAF6 (35).

Several recent studies have cumulatively suggested that TRAF6 is the most unique of mammalian TRAFs, not only due to its gene structure and homology but also due to its capability to mediate signals stemming from various receptor families. TRAF6 is indispensable for the activation of signaling pathways downstream of TNF-related activation-induced cytokine (TRANCE)- Receptor Activator of Nuclear Factor κB (RANK) axis, CD40 signaling, and IL-1R/toll like receptor (TLR) axis (36) causing the activation of NF-κB, p38MAPK, PI3K/Akt, JNK, and AMPK (13, 32, 37, 38). In addition, TRAF6 also

interacts with p62/SQSTM1-LC3 and Beclin-1 which are involved in induction of autophagy and protein degradation (39). More recently, TRAF6 has been reported to regulate signaling pathways downstream of TWEAK-Fn14 axis (11). While the pathways regulated through TRAF6 are reported to be involved in atrophic and hypertrophic responses, its direct role in regulation of skeletal muscle mass has been investigated only recently (Figure 1).

TRAF6 in skeletal muscle atrophy

Skeletal muscle atrophy has been explored extensively over the period of last decade. Many of these studies were aimed to unearth the mechanisms that orchestrate catabolic changes in an atrophic program. Expression and activation of E3 ubiquitin ligase MuRF1 and Atrogin-1 has been suggested to be at the distal end of several catabolic pathways and biochemical changes observed in atrophying skeletal muscle. TRAF6, being a different type of E3 ubiquitin-ligase, may not be directly involved in targeting myofibrillar proteins for degradation, however, it can potentially be an upstream regulator for the activation of signaling cascades that eventually lead to loss of muscle proteins in conditions of atrophy. Indeed, TRAF6 is the only TRAF that is regulated during myogenic differentiation (13, 40). The levels of TRAF6 are also significantly induced in skeletal muscle in response to denervation, tumor-induction, or diabetes onset (13). More recent findings in our laboratory have suggested that the levels and autoubiquitination of TRAF6 are also increased in skeletal muscle of mice in response to fasting (41).

We evaluated the role of TRAF6 in skeletal muscle atrophy using muscle-specific TRAF6-knockout ($TRAF6^{mko}$) mice. While previous studies have shown that TRAF6-null mice show significant abnormalities and are perinatal lethal (28), there was no overt phenotype upon depletion of TRAF6 only in skeletal muscle of mice (13). Remarkably, the hallmark signatures of atrophy such as loss of skeletal muscle mass, specific muscle proteins, fiber cross section area, and contractile force production were significantly rescued in $TRAF6^{mko}$ mice compared to littermate control mice in two distinct models of atrophy: denervation and cancer cachexia (13). Skeletal muscle of $TRAF6^{mko}$ mice also demonstrated reduced activation of UPS and expression of MuRF1 and MAFBx compared to control $TRAF6^{f/f}$ mice in atrophic conditions (13). The reduced expression of MuRF1 and MAFBx could be a result of inhibition of catabolic pathways and transcription as muscle specific ablation of TRAF6 was sufficient to inhibit the activation of NF-κB, AMPK, JNK, and p38 MAPK pathways (13). It is already known that TRAF6 interacts with p62/SQSTM1-LC3 and Beclin-1 which are markers of autophagy (42). Recapitulating this in skeletal muscle, we observed not only a significant reduction in the expression of components of ALS but also reduced autophagosome formation and mitochondrial degradation (13) (Figure 1).

Extending this quest further, we investigated role of TRAF6 in starvation-induced skeletal muscle atrophy. To our surprise, we observed that TRAF6 regulates different atrophic programs by employing distinct mechanisms. In addition to UPS and ALS, nutrient deprivation also induced the expression and activation of several components of endoplasmic reticulum (ER) stress and unfolded protein response (UPR) (41). Until very recently, there was no evidence that TRAF6 has any interaction with components of UPR. However, a recently published report suggests such an interaction in macrophages (43). Apparently, many of interactions of TRAF6 remain preserved across the systems. $TRAF6^{mko}$ mice and TRAF6-deficient cells both exhibit significantly reduced activation of ER-stress and UPR markers in response to starvation (41).

It is noteworthy that while depletion of TRAF6 significantly inhibits muscle atrophy and activation of catabolic pathways in response to both cancer cachexia and denervation, the

effect is more pronounced in cancer cachexia (13). Better rescuing effect of inhibition of TRAF6 in cancer cachexia model could be attributed to the fact that muscle wasting in tumor-bearing subjects involves systemic inflammation evident by increased levels of catabolic cytokines and fibrosis (10). A plethora of literature exists suggesting that several proinflammatory cytokines and tumor-derived factors require TRAF6 for downstream activation of NF-κB and MAPK signaling pathways which are also known to mediate skeletal muscle atrophy (29, 44). By contrast, inflammatory response is not very common in denervated skeletal muscle though TWEAK cytokine has now been found to be an important mediator of muscle loss under conditions of denervation (11). However, the denervation-induced muscle loss was also not completely blunted in TWEAK-KO mice (11) suggesting that muscle atrophy in response to denervation involves some other unidentified factor(s) that function independent of TRAF6.

Earlier research has established diversified regulatory roles of TRAF6 in several systems. Our data extends this further to skeletal muscle atrophy and adds novel information by demonstrating that TRAF6 augments skeletal muscle atrophy through activation of several distinct mechanisms (13, 41). Although this information underlines a new potential of TRAF6 as a therapeutic target, the regulation of TRAF6 itself is not yet fully delineated. Future research will unveil the mechanisms leading to increased expression of TRAF6 in atrophying skeletal muscle and how TRAF6 mediates muscle atrophy in response to diverse stimuli.

Conclusions

The understanding of extracellular catabolic cues, intracellular molecular mediators, and signaling mechanisms that modulate skeletal muscle atrophy has taken a quantum leap in recent years. Studies summarized above indicate that TWEAK and TRAF6 play important roles in regulation of skeletal muscle atrophic programs. Since TWEAK is an extracellular protein, TWEAK-dependent signaling can be blocked using a TWEAK neutralizing antibody or soluble Fn14-Fc decoy protein. While the induction of Fn14 and TRAF6 occurs across the spectrum of atrophic responses, the mechanisms which lead to their increased expression are yet to be identified. TRAF6 ablation has been found to inhibit the activation of several catabolic pathways. However, this inhibition is not commensurate with the extent to which its ablation inhibits atrophy in mouse models. Therefore, it necessitates the identification of compensating mechanisms and whether there is a functional redundancy between TRAF6 and other upstream regulators especially in denervated muscle. With these questions answered, TRAF6 could be an important target for pharmacological inhibition of skeletal muscle atrophy.

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Abbreviations

ALS	autophagy lysosomal system
AMPK	5' adenosine monophosphate-activated protein kinase
Fn14	fibroblast growth factor inducible 14
IKK	I kappa B kinase
MAPK	mitogen-activated protein kinase

PI3K	phosphatidylinositol-3 kinase
NF-κB	nuclear factor-kappa B
Tg	transgenic
TLR	toll-like receptor
TNF	tumor necrosis factor
TNFSF	TNF super family
TNFRSF	TNF receptor super family
TRAF	TNF-receptor activated factor 6
TWEAK	TNF-like weak inducer of apoptosis
UPS	ubiquitin-proteasome system

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KEY BULLET POINTS

- The TWEAK-Fn14 system mediates denervation-induced skeletal muscle atrophy
- TWEAK and TRAF6 mediate the activation of NF-κB in skeletal muscle in atrophic conditions
- TWEAK stimulates proliferation of myoblasts but inhibits their differentiation into myotubes
- TRAF6 augments the activation of ubiquitin-proteasome system and autophagy in skeletal muscle in catabolic conditions
- TRAF6 regulates induction of ER-stress and unfolded protein response in skeletal muscle upon starvation

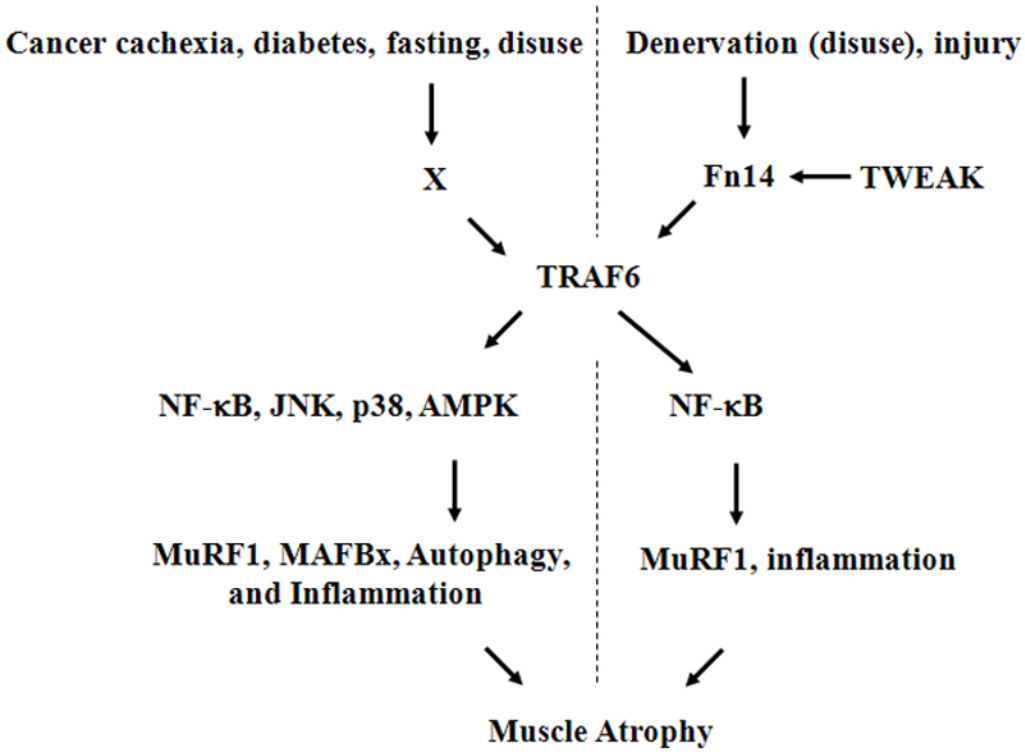

FIGURE 1. Schematic diagram illustrating the mechanisms of action of TWEAK and TRAF6 in skeletal muscle atrophy *in vivo*

Specific conditions of muscle atrophy (e.g. denervation, muscle injury, fasting, tumor growth etc.) and potentially other catabolic stimuli (e.g. inflammatory cytokines) augment the expression and activity of TWEAK-Fn14 dyad and TRAF6 in skeletal muscle tissues. The activation of TRAF6 is central to several catabolic mechanisms. In response to tumor growth, fasting denervation, and diabetes, TRAF6 mediates the activation of NF-κB, AMPK, JNK, and p38MAPK signaling pathways, expression of E3 ubiquitin ligase MuRF1 and MAFBx, and augments autophagy. In response to denervation or muscle injury, interaction of TWEAK with Fn14 induces the activation of NF-κB and expression of inflammatory molecules and MuRF1 through TRAF6-dependent mechanism. Increased activation of catabolic pathways, inflammation, and reduced muscle regeneration eventually lead to the loss of skeletal muscle mass. **TWEAK,** TNF-like weak inducer of apoptosis; **TRAF**, TNF receptor associated factor 6; **NF-κB,** Nuclear factor-kappa B; **JNK**, c-jun N-terminal kinase; **MAPK**, mitogen-activated protein kinase; **AMPK,** 5' adenosine monophosphate-activated protein kinase; **X,** unknown factor/pathway