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Review

Cytokine Signaling in Skeletal Muscle Wasting

Jin Zhou,[1,6] Bin Liu,[2,6] Chun Liang,[3,6] Yangxin Li,[4,*] and Yao-Hua Song[5,*]

Skeletal muscle wasting occurs in a variety of diseases including diabetes, cancer, Crohn's disease, chronic obstructive pulmonary disease (COPD), disuse, and denervation. Tumor necrosis factor α (TNF-α) is involved in mediating the wasting effect. To date, a causal relationship between TNF-α signaling and muscle wasting has been established in animal models. However, results from clinical trials are conflicting. This is partly due to the fact that other factors such as TNF-like weak inducer of apoptosis (TWEAK) and interleukin 6 (IL-6) are also involved in skeletal muscle wasting. Because muscle wasting is often associated with physical inactivity and reduced food intake, therapeutic interventions will be most effective when multiple approaches are used in conjunction with nutritional support and exercise.

Trends

Muscle wasting is the result of an imbalance between anabolic and catabolic metabolism due to inflammation, physical inactivity, and inadequate nutrition.

TNF-α, IL-6, and TWEAK shift the metabolism balance toward a catabolic process. However, current therapies such as neutralizing antibodies/decoy receptors against TNF-α, IL-6, and nonsteroidal anti-inflammatory drugs had limited success when used alone.

These specific therapies will be more successful when combined with nutritional support, appetite stimulators, and exercise, because combinatorial approaches will not only inhibit protein degradation but also promote protein synthesis.

Clinical trials are warranted and will yield more conclusive results by measuring cytokine levels from each patient prior to treatment.

Inflammatory Cytokines and Cachexia

Cachexia (see Glossary) is characterized by weakness, weight loss, and **muscle atrophy**, due to severe chronic illness, and is often fatal. Cachexia is seen in patients with a variety of serious illnesses, including cancer, **chronic obstructive pulmonary disease** (**COPD**), acquired immune deficiency syndrome (AIDs), multiple sclerosis, congestive heart failure, etc. Chronic inflammation is often seen in cachexia of various causes.

TNF-α is an inflammatory cytokine implicated in muscle **wasting** conditions associated with various diseases [1–4] and has been called cachexin, or cachectin, which refers to substances that cause severe body weight loss. TNF-α is produced by different cell types including macrophages, lymphocytes, and skeletal muscle cells, and is involved in both local and systemic inflammation [5]. The cytokine exerts its effect through two receptors, TNFR1 (p55) and TNFR2 (p75). TNFR1 is believed to mediate the muscle wasting effect, whereas TNFR2 is protective [6–9] (see Box 1 for details).

TWEAK is small pleiotropic cytokine and member of the TNF-α superfamily with multiple biological functions, including stimulation of apoptosis, and induction of inflammatory cytokines. TWEAK is also involved in muscle injury and atrophy and has been shown to play a role in muscle wasting [10]. The cytokine signals through the fibroblast growth factor-inducible 14 (Fn14) receptor and activates nuclear factor (NF)-κB (see Box 2 for details). Finally, interleukins IL-6 and IL-1β have also been implicated in muscle wasting [2,11].

In this review, we will discuss the role of these cytokines in the development of cachexia, and highlight current and emerging treatment options to prevent muscle atrophy.

TNF-α in Conditions Promoting Muscle Wasting

Inflammatory cytokines such as TNF-α, IL-1β, and IL-6 are involved in mediating the wasting effect in cachectic patients. With regard to TNF-α, systemic TNF-α infusion in healthy volunteers

[1]Department of General Surgery, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu, 215006, P.R. China
[2]Cardiovascular Disease Center, The First Hospital of Ji Lin University, Changchun, Jilin, 130021, P.R. China
[3]Department of Cardiology, ChangZheng Hospital, Second Military Medical University, Shanghai, 200003, P.R. China
[4]Department of Cardiovascular Surgery and Institute of Cardiovascular Science, First Affiliated Hospital of Soochow University, Suzhou, Jiangsu 215123, P.R. China
[5]Cyrus Tang Hematology Center, Jiangsu Institute of Hematology, First Affiliated Hospital, Collaborative Innovation Center of Hematology, Soochow University, Suzhou, P.R. China
[6]These authors contributed equally to this work

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Box 1. TNF-α Receptor Signaling

TNFR1 belongs to the death receptor family of proteins that contain death domains, which can induce apoptosis via the caspase pathway. Upon TNF-α binding to TNFR1, TNFRSF1A-associated via death domain (TRADD) is recruited to TNFR1. TRADD then recruits Fas-associated protein with death domain (FADD) that triggers the caspase cascade to induce apoptosis. TNFR2 does not contain a death domain, and therefore is not able to induce apoptosis through caspase-dependent mechanisms. Instead, TNFR2 promotes survival via phosphorylation of Etk and subsequent activation of Akt (Figure I) [7,8].

TNFR1 and TNFR2 recruit separate downstream adaptor molecules to induce a cellular response, but converge on TNF receptor-associated factor 2 (TRAF2), to activate IKK and NF-κB [77]. TNFR1 recruits TRADD and RIP1 prior to engaging with TRAF2, whereas TNFR2 can interact with TRAF2 directly [7]. TNFR1-triggered NF-κB activation leads to increased expression of muscle RING-finger protein 1 (MuRF1) and subsequent protein degradation through the ubiquitin proteasome pathway. NF-κB activation also inhibits satellite cell activation and differentiation, by promoting DNA methylation of the Notch-1 promoter [78], and by inhibiting MyoD expression [79], respectively. TNFR2 can activate the alternative NF-κB pathway through NIK [77] and its impact on myogenesis remains to be identified. In addition to TRAF2, six other TRAFs have been identified so far to transmit signals via the TNFRs. From those, TRAF6 is the only one involved in protein degradation. TRAF6 is an E3 ubiquitin ligase and a critical autophagy regulator [80]. TRAF6 mRNA levels are significantly upregulated in skeletal muscles of mice subjected to denervation, cancer cachexia, or diabetes [27]. By contrast, TRAF6 knockout (TRAF6mko, muscle-specific) mice show reduced expression of MuRF1, and atrogin-1, and are resistant to denervation and cancer-induced muscle wasting [27]. In a denervation model, activation of NF-κB in skeletal muscle is inhibited in TRAF6mko mice, compared with TRAF6f/f mice. Because NF-κB activation induces the expression of MuRF1 [27], TRAF6-induced muscle atrophy is likely mediated by the NF-κB/ubiquitin/proteasome pathway. However, the upstream signaling molecules that regulate TRAF6 remain unknown. Recent studies suggest that the CD40–TRAF6 interaction leads to obesity-associated insulin resistance [81], which is a condition that induces muscle wasting.

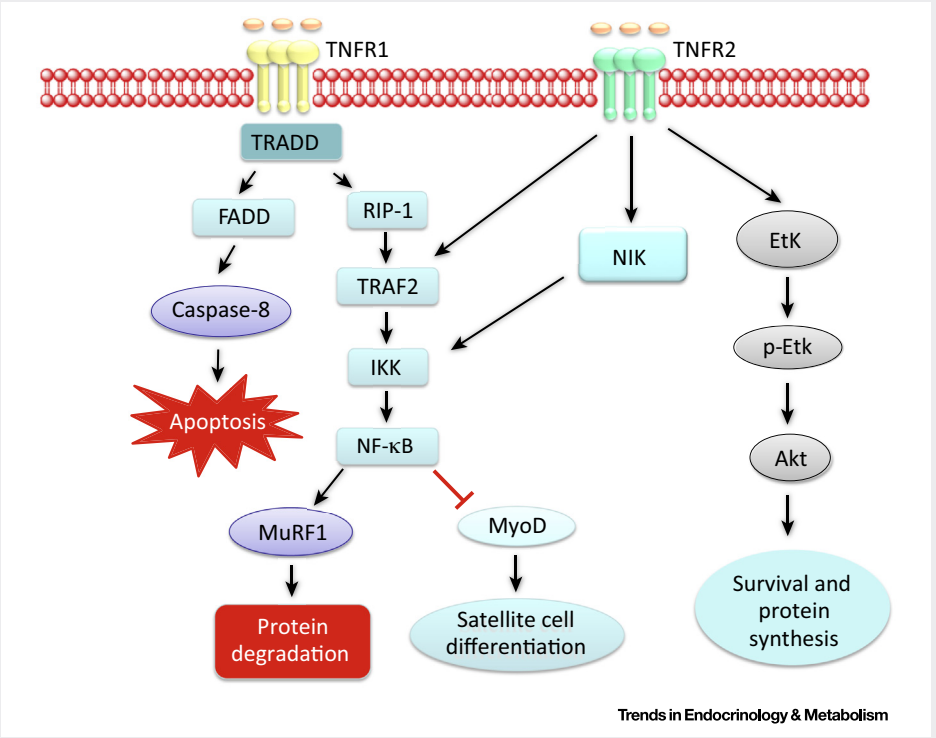

Figure I. TNF-α Signaling Pathway. TNF-α can bind to TNFR1 and TNFR2. TNFR1 activation can induce apoptosis via the TRADD/FADD/Caspase 8 pathway, or activate NF-κB via RIP1/TRAF2/IKK. NF-κB activation results in inhibition of myogenic differentiation and protein degradation. Stimulation of TNFR2 can also lead to NF-κB activation via TFAF2 or NIK. Alternatively, TNFR2 signaling could promote survival and protein synthesis through the Etk/Akt pathway. Abbreviations: TNF-α, tumor necrosis factor α; TRADD, TNFRSF1A-associated via death domain; FADD, Fas-associated protein with death domain; RIP1, receptor-interacting protein 1; TRAF2, TNF receptor-associated factor 2; IKK, IκB kinase; NIK, NF-κB-inducing kinase; Etk, epithelial/endothelial tyrosine kinase.

*Correspondence:
yangxin_li@yahoo.com (Y. Li) and
yaohua_song1@yahoo.com
(Y.-H. Song).