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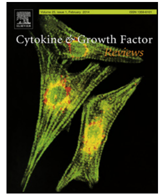

Mini review

The TWEAK-Fn14 pathway: A potent regulator of skeletal muscle biology in health and disease

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ABSTRACT

TNF-like weak inducer of apoptosis (TWEAK), a TNF superfamily ligand, and its bona fide receptor, the TNF receptor superfamily member fibroblast growth factor-inducible 14 (Fn14), represent a pivotal axis for shaping both physiological and pathological tissue responses to acute or chronic injury and disease. In recent years significant advances have been made in delineating the prominent role of TWEAK-Fn14 dyad in regulating skeletal muscle mass and metabolism. Also emerging from the broad study of tissue injury in skeletal muscle and other organs is the role of the TWEAK-Fn14 pathway in promoting fibrosis. This review article highlights recent advancements toward understanding how the TWEAK-Fn14 pathway regulates the response to various skeletal muscle insults and, more broadly, engages multiple mechanisms to drive tissue fibrosis.

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1. Introduction

Skeletal muscle comprises approximately 40% of total body mass which provides structural support, enables the body to maintain posture, and ensures basic functions such as locomotion, respiration, energy storage, and whole body metabolism. Skeletal muscle also demonstrates high level of plasticity in response to various physiological stressors such as weight bearing and exercise. In response to environmental demands, skeletal muscle remodels by activating multiple signaling pathways to reprogram gene expression to sustain muscle mass, energy metabolism, and performance. By contrast, chronic diseases or prolonged inactivity leads to loss of skeletal muscle mass and function commonly known as skeletal muscle atrophy or wasting [1]. Furthermore, degeneration of myofibers and their eventual replacement by fibrotic tissues are the major pathological features in many genetic muscle disorders such as muscular dystrophy [2].

TNF-like weak inducer of apoptosis (TWEAK), a TNF superfamily ligand, and its only known signaling receptor, the TNF receptor superfamily member fibroblast growth factor inducible 14 (Fn14), have emerged as a pivotal axis for shaping tissue responses to acute and chronic injury and disease [3]. Usually dormant due to the relatively low levels of Fn14 expressed in normal healthy tissues, the TWEAK-Fn14 axis is activated as a consequence of the highly induced local expression of Fn14 in injured and diseased tissues. Fn14 can be induced in various architectural tissue cell types, including epithelial, vascular, and other mesenchymal and stromal cell types in response to growth factors and proinflammatory cytokines as well as profibrotic cytokines [4]. Fn14 can also be expressed in tissue progenitor cells. The ligand TWEAK, which is constitutively and fairly ubiquitously expressed in all types of leukocytes and some non-hematopoietic cell types, is initially synthesized as a Type II transmembrane protein, but then secreted as a soluble cytokine due to efficient furin-mediated cleavage [4]. Thus, the TWEAK-Fn14 axis becomes specifically engaged in contexts of tissue injury and disease, triggering the activation of various downstream signaling pathways and thereby shapes the tissue response to injury through the induction of cellular responses including proinflammatory and proangiogenic responses, and the regulation of cell survival, migration and differentiation, and progenitor cell fate.

Significant advances have now been made in delineating the prominent role of the TWEAK-Fn14 axis in regulating skeletal muscle biology, with respect to mature muscle fiber atrophy,

Abbreviations: ALS, autophagy-lysosomal system; α-SMA, α-smooth muscle actin; Dnmt, DNA methyltransferase; ECM, extracellular matrix; Fn14, fibroblast growth factor-inducible 14; HDAC, histone deacetylase; IBM, inclusion-body myositis; KO, knockout; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1α; MEF2c, myocyte-specific enhancer factor 2C; MMP, matrix metalloproteinase; MyHC, myosin heavy chain; miR, microRNA; NF-κB, nuclear factor-kappa B; PA, plasminogen activator; SP1, specificity protein 1; Tg, transgenic; TIMP, tissue inhibitors of metalloproteinase; TWEAK, TNF-like weak inducer of apoptosis; UPS, ubiquitin-proteasome system.

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mitochondrial function, and muscle regeneration through its control of myoblast proliferation and differentiation [5]. Also emerging from the studies of skeletal muscle injury is the role of the TWEAK-Fn14 pathway in driving a number of skeletal muscle pathologies including tissue fibrosis. In this focused review, we continue to explore the paradigm and mechanisms of how the TWEAK-Fn14 pathway shapes tissue response in contexts of health, injury and disease [5,6]. Firstly, we review recent advances in our understanding of TWEAK-Fn14 pathway-mediated tissue responses to skeletal muscle injury and atrophic stimuli, including differential utilization and regulation of multiple signaling pathways. Secondly, we discuss the evidence for an emerging role for the TWEAK-Fn14 axis in promoting fibrosis as a pathological outcome of tissue injury and disease, highlighting multiple underlying mechanisms.

2. TWEAK-Fn14: a key regulator of skeletal muscle biology

Emerging evidence suggests that TWEAK-Fn14 signaling axis is a major regulator of skeletal muscle atrophy, regeneration, and metabolic function. In the following sections, we discuss the role of TWEAK-Fn14 system in skeletal muscle health and disease.

2.1. TWEAK and Fn14 regulate myogenesis

Skeletal muscle formation or myogenesis is a highly regulated process that involves the lineage determination of multipotential mesodermal cells to give rise to myoblasts, exit of these myoblasts from the cell cycle, and their differentiation into muscle fibers. This process is required not only for the embryonic development of skeletal muscle but also for postnatal growth and regeneration of myofibers after injury [7]. Myogenesis is regulated by sequential expression of several myogenic regulatory factors (MRFs), a group of basic helix–loop–helix transcription factors, which include Myf5, MyoD, myogenin, and MRF4. During myogenesis, fusion of myoblasts into multinucleated myotubes is the terminal step of differentiation after which no further mitotic divisions occur within the myotubes or myofibers [8]. The extra nuclei required for muscle growth or repair are provided by satellite cells (i.e. adult muscle stem cells), which are located under the basal lamina of the muscle fiber [7,9].

The TWEAK receptor, Fn14, is constitutively expressed in muscle progenitor cells such as satellite cells and myoblasts [10,11]. Accumulating evidence suggests that TWEAK-Fn14 axis affects multiple steps in the process of myogenesis (Fig. 1). Initial studies demonstrated that addition of exogenous TWEAK to cultured myoblasts augments proliferation but inhibits their differentiation into multinucleated myotubes through suppressing the expression of MyoD and myogenin and reducing the stability of MyoD protein in differentiating myoblasts [11,12]. TWEAK stimulates mitogen-activated protein kinase (MAPK) and canonical and non-canonical nuclear factor-kappa B (NF-κB) signaling pathways in myoblasts [10,12,13]. One of the mechanisms by which TWEAK inhibits myogenesis is through the activation of canonical NF-κB signaling. Activation of canonical NF-κB signaling is also responsible, at least in part, for the enhanced degradation of MyoD in TWEAK-treated myoblasts [12]. Consistent with the inhibitory effects of TWEAK in myogenesis, a recent study has demonstrated that TWEAK is a negative regulator of human mesoangioblast differentiation and TWEAK-Fn14 axis is dysregulated in sporadic inclusion-body myositis (IBM) muscle. Compared to controls, IBM mesoangioblasts have increased levels of Fn14 protein, produce significantly higher amounts of TWEAK in culture medium, and show reduced differentiation capacity. Importantly, inhibition of TWEAK using Fn14-Fc chimera or short interfering RNA technique improved myogenic differentiation in IBM mesoangioblasts, providing initial evidence that dysregulated TWEAK-Fn14 axis interferes with myogenic differentiation in IBM [14].

While the TWEAK-Fn14 axis can promote myoblast proliferation and impede their differentiation, a distinct role of TWEAK and Fn14 in myogenesis is supported by the findings that primary myoblasts from Fn14-knockout (KO), but not TWEAK-KO, mice display reduced proliferative capacity and slightly aberrant myotube formation upon induction of differentiation [11]. Although the exact mechanisms remain poorly understood, knockdown of Fn14 impairs the activation of RhoA GTPase and serum response factor (the positive regulators of myogenesis) in cultured myoblasts, providing a potential mechanism by which Fn14 regulates myogenic differentiation [10,15]. Consistent with published reports suggesting that increased expression of Fn14 alone is sufficient to induce various cellular responses including tumor cell migration and invasion [16–18], these findings imply that Fn14 receptor can signal independently of TWEAK and produce distinct biological responses. While it remains a formal possibility that a yet to be identified ligand other than TWEAK can bind and signal through Fn14, a more intriguing scenario is that it might be evolutionarily advantageous for Fn14 to retain some ability to trigger ligand-independent signaling under certain biological conditions. For example, in settings of acute skeletal muscle injury, the significantly increased Fn14 expression could potentially be conductive to TWEAK-independent signaling, thus 'jumpstart' the proliferation of myogenic progenitors required for repair before abundant TWEAK becomes available from the infiltrating leukocytes. Thus, it is likely that in the absence of TWEAK, Fn14 predominantly activates promyogenic signaling and stimulates myotube formation. However, when the levels of TWEAK are elevated as observed during chronic tissue injury and inflammation, it binds to Fn14 and causes the activation of specific signaling pathways such as MAPKs and canonical NF-κB which promote proliferation but inhibit myogenesis by blocking the withdrawal of myoblasts from the cell cycle and inducing degradation of MyoD protein (Fig. 2).

Recent studies have also highlighted that while relatively high levels (≥100 ng/ml) of TWEAK induce proliferation and inhibit differentiation, low amounts (10 ng/ml) of TWEAK can produce distinct responses in muscle progenitor cells. Myoblast fusion is a critical step during myogenesis. It is now increasingly clear that coordinated interaction between different signaling pathways regulates fusion of myoblasts during myogenesis [8]. Enwere et al. recently reported that non-canonical NF-κB signaling, which gets activated during myogenesis, stimulates myoblast fusion during myogenesis. This study also showed that low levels of TWEAK predominately activate non-canonical arm of NF-κB signaling to promote myoblast fusion [13]. While low levels of exogenous TWEAK may transiently enhance myoblast fusion, it is notable that chronic presence of even low levels of TWEAK can lead to deleterious effects on nascent myotubes. The amount of TWEAK (i.e. 10 ng/ml), which induces myoblast fusion, also causes atrophy and reduces the survival of differentiated myotubes [19]. Furthermore, chronic presence of even low levels of TWEAK, especially in the conditions where the expression of Fn14 is also increased in myogenic cells, may be sufficient to inhibit myogenic differentiation. This possibility is supported by studies in IBM mesoangioblasts which produce relatively low levels (~0.8 ng/ml) of TWEAK; however, neutralization of TWEAK is sufficient to increase myotube formation in IBM mesoangioblast cultures [14]. Similarly, it has been found that neutralization of endogenously produced TWEAK using Fn14-Fc chimera increases myogenic differentiation in C2C12 myoblasts [10] and cultured primary myoblasts from TWEAK-KO mice show increased myotube formation upon induction of differentiation [20].

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