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The TWEAK–Fn14 dyad is involved in age-associated pathological changes in skeletal muscle

Marjan M. Tajrishi [a,1], Shuichi Sato [a,1], Jonghyun Shin [a], Timothy S. Zheng [b], Linda C. Burkly [b], Ashok Kumar [a,*]

[a] Department of Anatomical Sciences and Neurobiology, University of Louisville School of Medicine, Louisville, KY 40202, United States
[b] Department of Immunology, Biogen Idec, 14 Cambridge Center, Cambridge, MA 02142, United States

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ABSTRACT

Progressive loss of skeletal muscle mass and strength (sarcopenia) is a major clinical problem in the elderly. Recently, proinflammatory cytokine TWEAK and its receptor Fn14 were identified as key mediators of muscle wasting in various catabolic states. However, the role of the TWEAK–Fn14 pathway in pathological changes in skeletal muscle during aging remains unknown. In this study, we demonstrate that the levels of Fn14 are increased in skeletal muscle of 18-month old (aged) mice compared with adult mice. Genetic ablation of Fn14 significantly increased the levels of specific muscle proteins and blunted the age-associated fiber atrophy in mice. While gene expression of two prominent muscle-specific E3 ubiquitin ligases MAFBx and MuRF1 remained comparable, levels of ubiquitinated proteins and the expression of autophagy-related molecule Atg12 were significantly reduced in Fn14-knockout (KO) mice compared with wild-type mice during aging. Ablation of Fn14 significantly diminished the DNA-binding activity of transcription factor nuclear factor-kappa B (NF-κB), gene expression of various inflammatory molecules, and interstitial fibrosis in skeletal muscle of aged mice. Collectively, our study suggests that the TWEAK–Fn14 signaling axis contributes to age-associated muscle atrophy and fibrosis potentially through its local activation of proteolytic systems and inflammatory pathways.

1. Introduction

Slow and progressive loss of skeletal muscle mass is a devastating consequence of aging leading to both morbidity and mortality in the elderly [1,2]. Although the etiology of sarcopenia is highly complex, many factors such as chronic inflammation, fibrosis, inactivity, declining androgen concentrations, nutritional deficiencies, insulin resistance, mitochondrial dysfunction, and reduction in muscle regenerative capacity have been suggested to contribute to sarcopenia [1–3].

An imbalance in protein turnover is a major factor in the loss of skeletal muscle mass in many catabolic conditions including aging [3,4]. The ubiquitin–proteasome system (UPS) is a highly regulated proteolytic mechanism which plays a critical role in tissue homeostasis through degradation of thousands of misfolded and damaged proteins [5]. The role of UPS in skeletal muscle atrophy is evident by the findings that pharmacological inhibition of proteasome activity or genetic deletion of specific components of UPS leads to sparing of skeletal muscle mass in multiple catabolic conditions [6,7]. In addition, autophagy is an important proteolytic system which is responsible for the degradation of bulk of muscle proteins and dysfunctional organs [8,9]. Although some basal level of autophagy is required for muscle homeostasis, increased activation of autophagy contributes to skeletal muscle atrophy in adult animals [9,10].

Persistent inflammation and increased levels of proinflammatory cytokines have been strongly implicated in age-related loss of skeletal muscle mass [3]. Inflammatory cytokines cause muscle wasting through activation of proteolytic systems, inhibiting anabolic actions of various growth factors, and diminishing skeletal muscle regenerative capacity [3,11]. Recently, TNF-like weak inducer of apoptosis (TWEAK), a proinflammatory cytokine belonging to TNF superfamily, has been identified as an important regulator of skeletal muscle mass [12–14]. While TWEAK is constitutively expressed in many hematopoietic and non-hematopoietic cells including skeletal muscle, its receptor fibroblast growth factor inducible molecule 14 (Fn14) is expressed at relatively low to minimal levels in healthy adult skeletal muscle [12,14,15]. However, specific conditions of atrophy such as inactivity (e.g. denervation, immobilization, and unloading) dramatically increase

* Corresponding author.
E-mail address: ashok.kumar@louisville.edu (A. Kumar).
[1] These authors contributed equally to this study.

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the expression of Fn14 in skeletal muscle leading to the engagement of the TWEAK–Fn14 signaling axis, activation of proteolytic systems, and eventually fiber atrophy [16]. Interestingly, there are several similarities between muscle atrophy in response to inactivity and the normal aging process. Cellular and molecular mechanisms that are commonly associated with inactivity also increase with advanced age [17]. However, it remains unknown whether TWEAK–Fn14 dyad is involved in age-associated pathological changes in skeletal muscle.

In the present study, using wild-type (WT) and Fn14-knockout (KO) mice, we have investigated the role and mechanisms of action of TWEAK–Fn14 system in skeletal muscle during aging. Our results demonstrate that age-associated muscle fiber atrophy, activation of proinflammatory transcription factor NF-κB, gene expression of several inflammatory molecules, and fibrosis are significantly reduced in skeletal muscle of Fn14-KO mice compared with WT mice.

2. Materials and methods

2.1. Mice

Fn14-KO mice have been previously described [18]. All experimental protocols with mice were approved in advance by the Institutional Animal Care and Use Committee (IACUC) of the University of Louisville.

2.2. Histology and morphometric analysis

For the assessment of tissue morphology, 10 μm thick transverse sections of individual hind limb muscle were stained with the Hematoxylin and Eosin (H&E) and examined under Nikon Eclipse TE 2000-U microscope (Nikon). Fiber cross-sectional area was analyzed in H&E-stained muscle sections using Nikon NIS Elements BR 3.00 software (Nikon). For each muscle, the distribution of fiber cross-sectional area (CSA) was calculated by analyzing 200–250 myofibers as described [16,19]. The amount of fibrosis in TA muscle sections was determined using Masson's Trichrome staining kit according to a protocol suggested by the manufacturer (American Master Tech). Fibrotic area in muscle sections was quantified using Nikon NIS Elements BR 3.00 software.

2.3. RNA isolation and quantitative real-time PCR (QRT-PCR)

RNA isolation and QRT-PCR were performed using a method as described [19,20].

2.4. Western blotting

Levels of different proteins in skeletal muscle were determined by performing immunoblotting as described previously [21].

2.5. Electrophoretic mobility shift assay (EMSA)

DNA-binding activity of NF-κB was measured by performing EMSA following a method as described [19].

2.6. Statistical analysis

Results are expressed as mean ± standard deviation (SD). Statistical analyses used two-tailed *t*-test to compare quantitative data populations with normal distribution and equal variance. A value of $p < 0.05$ was considered statistically significant unless otherwise specified.

3. Results

3.1. Genetic ablation of Fn14 attenuates age-associated skeletal muscle atrophy in mice

We first investigated whether the levels of TWEAK or Fn14 change with age. Tibial anterior (TA) and gastrocnemius (GA) muscle were isolated from 3-month (adult) and 18-month (aged but not senescent) wild-type (WT) mice and processed for QRT-PCR analysis to measure mRNA levels of TWEAK and Fn14. Transcript levels of Fn14 were significantly increased in both TA and GA muscle of 18-month old mice compared with 3-month old mice (Fig. 1A). By contrast, there was no significant difference in the mRNA levels of TWEAK in skeletal muscle of 3- and 18-month old mice (data not shown). To delineate the role of TWEAK–Fn14 signaling in age-associated skeletal muscle atrophy, we compared fiber cross-sectional area (CSA) in hind limb muscle from 3-month and 18-month old WT and Fn14-KO mice by performing H&E-staining and morphometric analysis. There was a significant decrease in fiber CSA in TA muscle of 18-month old WT mice compared with 3-month old WT mice. In contrast, no age-associated decrease in mean fiber CSA in TA muscle was noticeable in Fn14-KO mice (Fig. 1B and C).

Muscle atrophy in response to different catabolic stimuli involves degradation of several contractile proteins [23,29]. To further understand the role of TWEAK–Fn14 system in muscle atrophy during aging, we quantified levels of a few muscle proteins. There was no difference in the protein levels of myosin heavy chain (MyHC), troponin, and sarcomeric α-actin between WT and Fn14-KO at the age of 3-month (data not shown). However, at the age of 18-month, protein levels of MyHC, troponin, and sarcomeric α-actin were significantly higher in skeletal muscle of Fn14-KO mice compared with corresponding WT mice (Fig. 1D and E). Altogether, these results suggest that ablation of Fn14 inhibits age-associated muscle atrophy in mice.

3.2. Role of TWEAK–Fn14 axis in regulation of UPS and autophagy in aging skeletal muscle

To understand whether TWEAK–Fn14 system regulates the activity of UPS in skeletal muscle during aging, we studied conjugation of ubiquitin to muscle proteins. Protein extracts prepared from skeletal muscle of WT and Fn14-KO were immunoblotted using ubiquitin antibody. The level of ubiquitinated protein in skeletal muscle was minimal at the age of 3-month and there was no significant difference between WT and Fn14-KO mice (data not shown). Aging increased the conjugation of ubiquitin to muscle proteins in skeletal muscle. Importantly, levels of ubiquitinated protein were considerably reduced in skeletal muscle of 18-month old Fn14-KO mice compared with age-matched WT mice (Fig. 2A).

In UPS, E3 ubiquitin ligase targets specific protein substrates for degradation by the proteasome [5]. Although hundreds of E3s have been identified in mammalian cells, the activation of UPS under multiple atrophy conditions involves increased expression of two muscle-specific E3 ligases, MAFBx and MuRF1 [11]. We investigated whether TWEAK–Fn14 signaling affects the expression of MAFBx and MuRF1 in skeletal muscle of mice during aging. Consistent with a published report [22], we did not find any significant increase in the mRNA levels of MAFBx or MuRF1 in skeletal muscle of 18-month old WT or Fn14-KO mice compared with their corresponding 3-month old mice (data not shown). While there was a trend of decrease in mRNA levels of MAFBx and MuRF1 in skeletal muscle of 18-month old Fn14-KO mice compared with age-matched WT mice, no significant difference was observed (Fig. 2B).

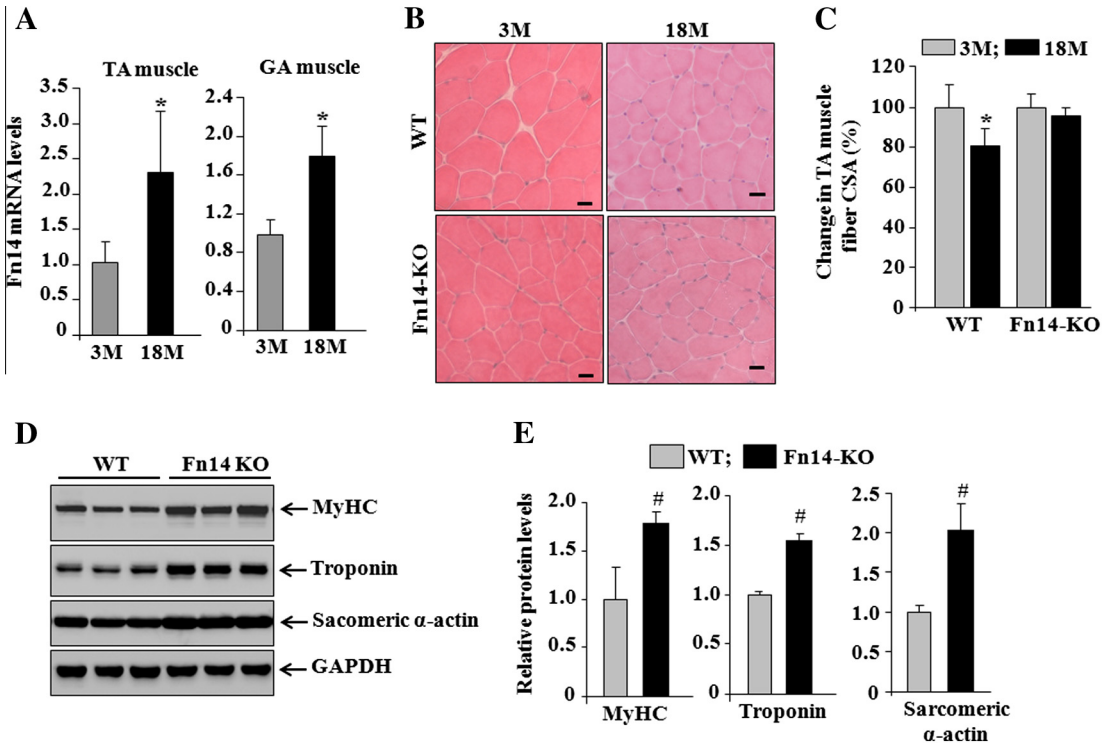

Fig. 1. Ablation of Fn14 inhibits age-associated skeletal muscle atrophy in mice. (A) Relative mRNA levels of Fn14 in TA and GA muscle of 3-month (3 M) and 18-month (18 M) old wild type (WT) mice. $N = 4$ in each group. (B) Representative photomicrographs of H&E-stained transverse sections of TA muscle of 3 and 18-month old WT and Fn14 KO mice. Scale bar: 20 μm. (C) Quantification of percentage change in average fiber CSA in TA muscle of 18-month old WT and Fn14-KO mice compared with corresponding 3-month old mice. $N = 5$–6 in each group. (D) Representative immunoblots for MyHC, troponin, sarcomeric α-actin, and GAPDH in GA muscle of 18-month old WT and Fn14-KO mice. (E) Fold change in protein levels of MyHC, troponin and sarcomeric α-actin in GA muscle of 18-month old WT and Fn14-KO mice. $N = 3$ in each group. Error bars represent SD. $^{*}p < 0.05$ values significantly different from corresponding 3-month old WT mice. $^{\#}p < 0.05$, values significantly different from corresponding WT mice.

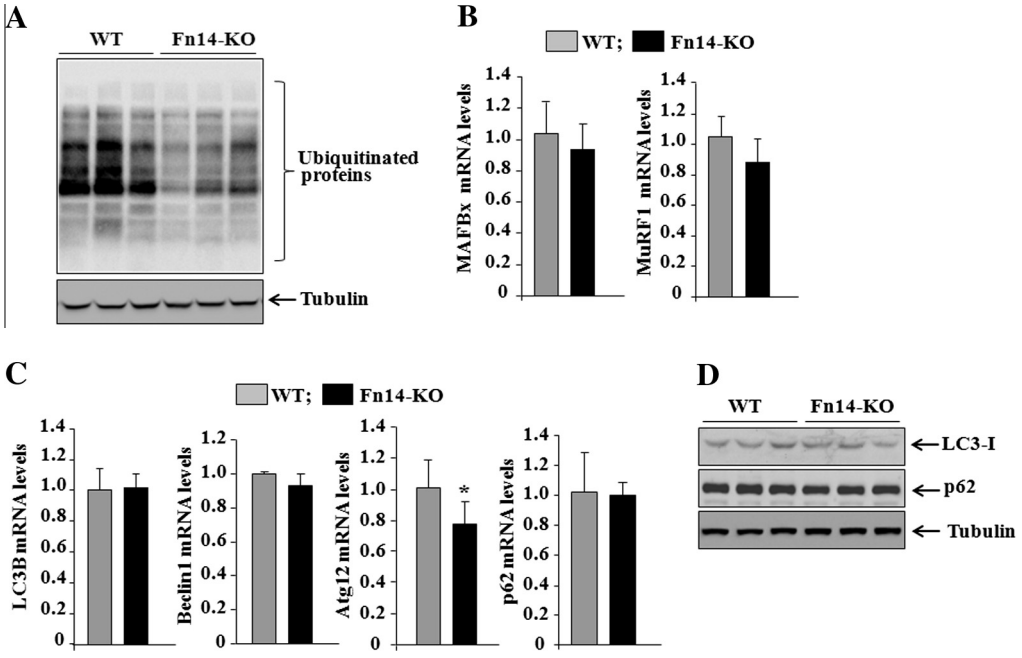

Fig. 2. Role of Fn14 in activation of UPS and autophagy in skeletal muscle during aging. (A) Muscle extracts prepared from 18-month old WT and Fn14-KO mice were used for Western blotting using ubiquitin (Ub) antibody. A representative immunoblot presented here demonstrates that the level of uniquitinated proteins is considerably reduced in Fn14-KO mice compared with age-matched WT mice. (B) Transcript levels of MAFBx and MuRF1 in TA muscle of 18-month old WT and Fn14-KO mice assayed by performing QRT-PCR assay. (C) Transcript levels of autophagy-related molecules LC3, Beclin1, Atg12, and p62 in TA muscle of 18-month old WT and Fn14-KO mice. (D) Immunoblots presented here demonstrate that levels of LC3 and p62 protein remain comparable in skeletal muscle of WT and Fn14-KO mice. Error bars represent SD. $^{*}p < 0.05$, values significantly different from WT mice.

Autophagy is another prominent mechanism for degradation of muscle proteins in atrophy conditions [23]. We compared gene expression of some proteins involved in autophagy pathway. Aging significantly ($p < 0.05$) increased the transcript levels of LC3 (~1.6-fold), Beclin1 (~1.3-fold), Atg12 (~1.5-fold), and p62 (~1.7-fold). However, transcript levels of LC3, Beclin1, and p62 in skeletal muscle remained comparable between 18-month old WT and Fn14-KO mice (Fig. 2C). In contrast, mRNA levels of Atg12 were found to be significantly reduced in 18-month old Fn14-KO mice compared with age-matched WT mice (Fig. 2C). During autophagy, LC3-I is converted to LC3-II through lipidation that allows for LC3 to become associated with autophagic vesicles. Furthermore, p62 is a bona fide substrate of autophagy and its levels are reduced on activation of autophagy [9]. To further understand whether TWEAK–Fn14 system affects autophagy in aged muscle, we measured protein levels of LC3I and II and p62. LC3II was undetectable in skeletal muscle of either WT or Fn14-KO mice. Moreover, there was no significant difference in the levels of LC3I and p62 proteins in skeletal muscle of 18-month old WT and Fn14-KO mice suggesting that autophagy pathway is not affected by TWEAK–Fn14 system during aging (Fig. 2D).

3.3. Genetic ablation of Fn14 reduces NF-κB activity and gene expression of inflammatory molecules in skeletal muscle during aging

We next investigated whether ablation of Fn14 affects the DNA-binding activity of NF-κB in skeletal muscle of mice during aging. NF-κB activity was almost undetectable in skeletal muscle of 3-month old mice and there was no apparent difference between WT and Fn14-KO mice (data not shown). Consistent with published reports [11], activation of NF-κB was markedly increased in skeletal muscle of 18-month old WT mice. Importantly, the DNA-binding activity of NF-κB was found to be significantly reduced in skeletal muscle of 18-month old Fn14-KO mice compared with age-matched WT mice (Fig. 3A and B).

A wide range of inflammatory molecules have been suggested to contribute to sarcopenia [24]. We next studied the mRNA levels of a few inflammatory molecules in skeletal muscle of 18-month old WT and Fn14-KO mice by performing QRT-PCR assay. Results showed that whereas levels of TNF-α remained comparable between WT and Fn14-KO mice, the mRNA levels of TNF receptor (TNFR) I and TNFRII were significantly reduced in Fn14-KO mice compared with WT mice. Furthermore, mRNA levels of IL-1β and matrix metalloproteinase-9 (MMP-9) were found to be significantly reduced in skeletal muscle of 18-month old Fn14-KO mice compared with age-matched WT mice. There was also a trend of reduced expression of CCL2 in Fn14-KO mice though it was not significantly different from WT mice (Fig. 3C).

3.4. Ablation of Fn14 reduces fibrosis and diminishes the expression of collagens in skeletal muscle of mice during aging

Aging leads to excessive extracellular matrix accumulation and fibrosis in skeletal muscle [25]. Since skeletal muscle of Fn14-KO mice showed reduced expression of inflammatory molecules which are generally associated with fibrosis in various organs, we next studied whether there is any difference in the level of fibrosis in skeletal muscle of 18-month old WT and Fn14-KO mice. To assess fibrosis, we performed Trichrome staining on TA muscle sections. Fibrosis was undetectable by Trichrome staining in TA muscle of 3-month old WT or Fn14-KO mice (data not shown). The level of fibrosis was also relatively low at the age of 18 months. However, quantitative analysis revealed that fibrotic area was significantly reduced in skeletal muscle of Fn14-KO mice compared with age-matched WT mice (Fig. 4A and B). To further understand the role of TWEAK–Fn14 axis in fibrosis, we also compared mRNA levels of collagen I (Col1a), III (Col3a) and IV (Col4a), the major collagens in skeletal muscle extracellular matrix [26]. Interestingly, mRNA levels of all these three collagens were found to be significantly reduced in TA muscle of 18-month old Fn14-KO mice compared with age-matched WT mice (Fig. 4C).

4. Discussion

Recent studies have highlighted a pivotal role of the TWEAK–Fn14 axis in skeletal muscle wasting in various catabolic states

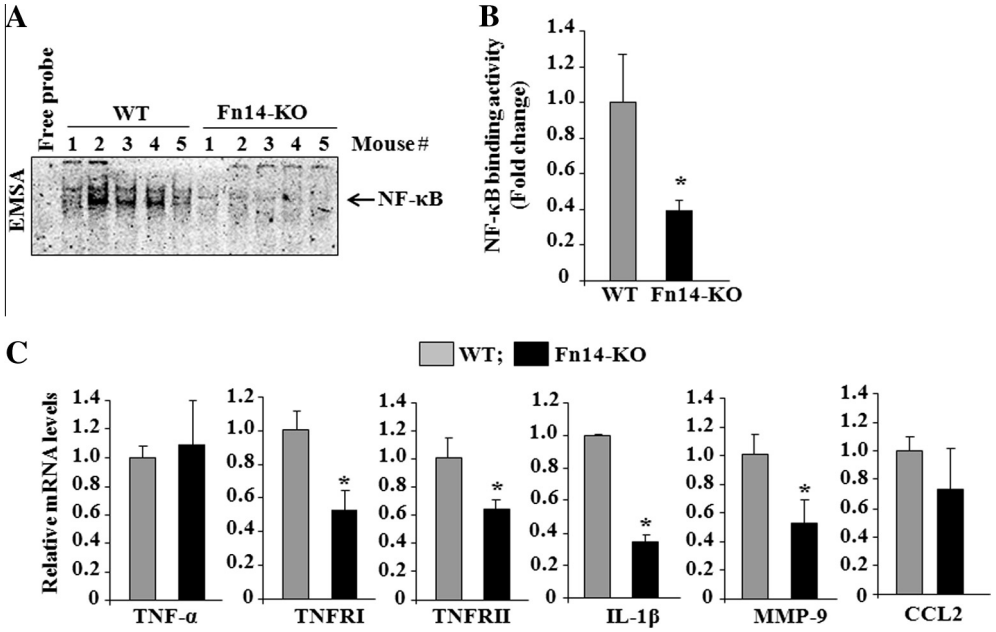

Fig. 3. Role of Fn14 in regulation of inflammatory milieu in aging skeletal muscle. (A) DNA-binding activity of NF-κB in GA muscle of 18-month old WT and Fn14-KO mice measured by performing EMSA. A representative EMSA gel is presented here. (B) Quantification of fold change in DNA-binding activity of NF-κB in GA muscle of 18-month old WT and Fn14-KO mice. Relative mRNA level of (C) TNF-α, TNFRI, TNFRII, IL-1β, MMP-9, and CCL2. Error bars represent SD. $N = 4$ or 5 in each group. $^{*}p < 0.05$, values significantly different from WT mice.

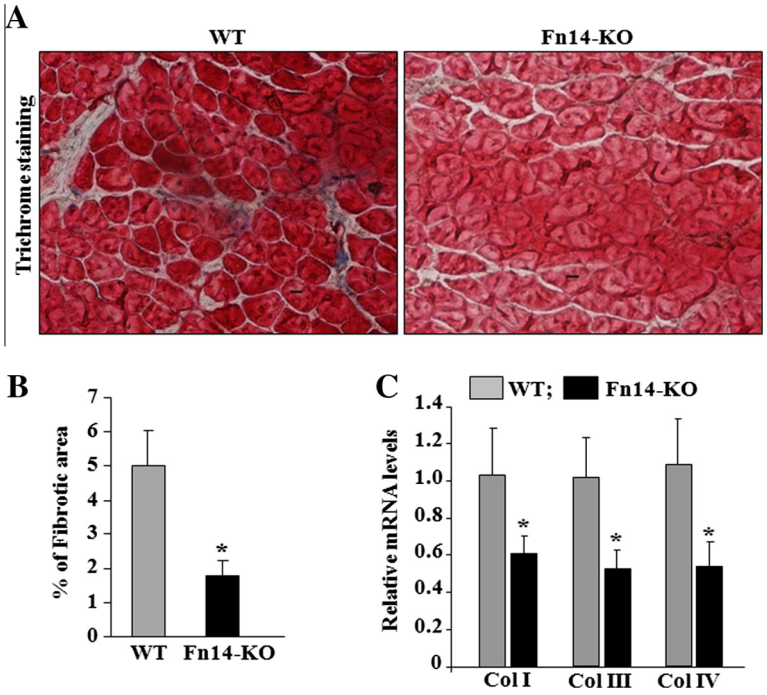

Fig. 4. Role of Fn14 in fibrosis in skeletal muscle of mice during aging. (A) TA muscle sections of 18-months old WT and Fn14-KO mice were used to perform Masson's trichrome staining. Representative photomicrographs are presented here. Scale bars: 20 μm. (B) Quantitative estimation of fibrotic area (blue color) in TA muscle of WT and Fn14-KO mice. (C) Transcript levels of collagen I, III, and IV in TA muscle of 18-month old WT and Fn14-KO mice. $N = 4$ or 5 in each group. Error bars represent SD. $^{*}p < 0.05$, values significantly different from WT mice. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

[14]. In this study, we have investigated whether TWEAK–Fn14 axis has a role in regulation of skeletal muscle mass during aging. Consistent with published reports that skeletal muscle of adult mice express minimal to undetectable levels of Fn14 [16,27], we did not find any histological or biochemical differences in skeletal muscle of 3-month old WT and Fn14-KO mice. However, the expression of Fn14 is significantly increased in skeletal muscle with advancing age and the differences in fiber size and biochemical changes became evident in skeletal muscle of WT and Fn14-KO mice at the age of 18 months.

Since reduced muscle load leads to the activation of various catabolic pathways and proteolytic systems in skeletal muscle, inactivity is considered as one of the important stimuli for the loss of skeletal muscle mass during aging [28]. Our analyses showed that age-associated loss of fiber CSA in TA muscle is blunted in Fn14-KO mice (Fig. 1B and C). Skeletal muscle atrophy during aging involves a modest activation of UPS [8]. Our results demonstrating that overall protein ubiquitinylation is decreased in skeletal muscle of Fn14-KO mice suggest that TWEAK–Fn14 signaling contributes to the activation of UPS during aging (Fig. 2A). Consistent with marked decrease in muscle protein ubiquitinylation, we have also found that the levels of specific muscle proteins are significantly increased skeletal muscle of 18-month old Fn14-KO mice compared with age-matched WT mice (Fig. 1D and E).

It has been reported that the induction in the expression of MuRF1 and MAFBx (which label the target proteins for degradation by 26S proteasome) or other components of the UPS is very limited during aging compared with other catabolic stimuli suggesting that these E3 ubiquitin ligases contribute little to the establishment of sarcopenia [29]. While ubiquitinylation of muscle proteins was decreased (Fig. 2A), we did not find any significant difference in the mRNA levels of MAFBx and MuRF1 in the skeletal muscle of WT and Fn14-KO mice at the age of 18 months (Fig. 2B). Coincidently, a recent study has shown that sparing of muscle mass in MuRF1-KO mice in response to denervation is associated with a significant increase in 20S and 26S proteasome subunit activities further highlighting that the age-associated increase in proteolytic activity may not involve the induction of MAFBx and MuRF1 [30]. Our study provides evidence that while the TWEAK–Fn14 axis contributes to the activation of UPS in aged muscle, it does not affect the gene expression of MAFBx and MuRF1 in skeletal muscle.

There are contradictory results and varying interpretations regarding the effects of aging on the activation of autophagy in skeletal muscle. Some studies suggest that autophagy flux is increased during aging and this increase requires a transcriptional regulation to replenish components that are lost [8,31]. Although we found a significant decrease in gene expression of Atg12, the expression levels of LC3, Beclin1, and p62 remained comparable between 18-month old WT and Fn14-KO mice (Fig. 2C). Moreover, comparable protein levels of LC3B and p62 in skeletal muscle of WT and Fn14-KO mice further suggest that TWEAK–Fn14 signaling may not have any impact on the activation of autophagy pathway in aged skeletal muscle.

Chronic low-grade inflammation has been recognized as an important causative factor for sarcopenia [32]. NF-κB is a major proinflammatory transcription factor which not only mediates the effects of inflammatory cytokines but also increases their expression [11]. Although the role of NF-κB in the deterioration of skeletal muscle mass during aging has not been yet investigated using genetic mouse models, our results demonstrate that DNA-binding activity of NF-κB and gene expression of several inflammatory molecules are significantly reduced in skeletal muscle of 18-month old Fn14-KO mice compared with age-matched WT mice (Fig. 3A–C) providing initial evidence that the TWEAK–Fn14 axis mediates the activation of NF-κB in skeletal muscle during aging. Indeed, TWEAK appears to be one of the most important stimuli for the activation of NF-κB in skeletal muscle. Previous studies have shown that the inhibition of TWEAK–Fn14 signaling attenuates the activation of NF-κB in adult skeletal muscle in response to cardiotoxin-mediated injury and upon denervation

[13,16]. Since the activation of NF-κB is sufficient to induce atrophy [33], sparing of myofiber size in 18-month old Fn14-KO mice could be attributed to reduced activation of NF-κB by TWEAK–Fn14 system.

Results from different animal studies and humans have shown that the collagen concentration of intact skeletal muscle increases with age [34]. The TWEAK–Fn14 system has been found to be an important regulator of fibrosis in multiple tissues [13,16]. Accumulating evidence further suggests that the TWEAK–Fn14 axis promotes fibrogenic activities through its direct action on stromal cell types, and thereby causing the accumulation of myofibroblasts, the major collagen-producing cell type in injured and fibrotic tissues [14,35]. The TWEAK–Fn14 pathway has also been shown to regulate collagen gene expression [14]. Direct role of TWEAK in inducing collagen expression has been validated using reporter assays for the Col1a1 and Col1a2 genes [36,37]. Consistent with profibrotic role of TWEAK–Fn14 axis, our results in this study demonstrate that levels of fibrosis and gene expression of collagen I, III, and IV are reduced in skeletal muscle of 18-month old Fn14-KO mice compared with age-matched WT mice (Fig. 4).

In summary, the results of the present study suggest that the TWEAK–Fn14 pathway is involved in multiple age-related pathological changes in skeletal muscle. Blocking TWEAK–Fn14 signaling can be a potential approach to prevent skeletal muscle deterioration in the elderly.

Conflict of interest

None.

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