Published in final edited form as:
Curr Opin Clin Nutr Metab Care. 2013 May ; 16(3): 243–250. doi:10.1097/MCO.0b013e328360272d.

Mechanisms for fiber-type specificity of skeletal muscle atrophy

Yichen Wang[a] and **Jeffrey E. Pessin**[a,b]

[a]Department of Molecular Pharmacology, Albert Einstein College of Medicine, Diabetes Research and Training Center, Bronx, New York, USA

[b]Department of Medicine, Albert Einstein College of Medicine, Diabetes Research and Training Center, Bronx, New York, USA

Abstract

Purpose of review—There are a variety of pathophysiologic conditions that are known to induce skeletal muscle atrophy. However, muscle wasting can occur through multiple distinct signaling pathways with differential sensitivity between selective skeletal muscle fiber subtypes. This review summarizes some of the underlying molecular mechanisms responsible for fiber-specific muscle mass regulation.

Recent findings—Peroxisome proliferator-activated receptor gamma coactivator 1-alpha protects slow-twitch oxidative fibers from denervation/immobilization (disuse)-induced muscle atrophies. Nutrient-related muscle atrophies, such as those induced by cancer cachexia, sepsis, chronic heart failure, or diabetes, are largely restricted to fast-twitch glycolytic fibers, of which the underlying mechanism is usually related to abnormality of protein degradation, including proteasomal and lysosomal pathways. In contrast, nuclear factor kappaB activation apparently serves a dual function by inducing both fast-twitch fiber atrophy and slow-twitch fiber degeneration.

Summary—Fast-twitch glycolytic fibers are more vulnerable than slow-twitch oxidative fibers under a variety of atrophic conditions related to signaling transduction of Forkhead box O family, autophagy inhibition, transforming growth factor beta family, and nuclear factor-kappaB. The resistance of oxidative fibers may result from the protection of peroxisome proliferator-activated receptor gamma coactivator 1-alpha.

Keywords

fiber-specific atrophy; signaling; skeletal muscle

Correspondence to: Jeffrey E. Pessin, PhD, Judy R. & Alfred A. Rosenberg Professorial, Chair in Diabetes Research, Director, Diabetes Research Center, Departments of Medicine and Molecular Pharmacology, Albert Einstein College of Medicine, 1301 Morris Park Avenue, Bronx, NY 10461, USA., Tel: +1 718 678 1029; fax: +1 718 678 1020; jeffrey.pessin@einstein.yu.edu.

Conflicts of interest
There are no conflicts of interest.

INTRODUCTION

In mammals, skeletal muscle accounts for more than 40% of the mass of a given individual and provides critical functions in metabolism, energy expenditure, physical strength, and locomotor activity. Skeletal muscle is composed of distinct muscle fiber subtypes defined by myosin heavy chain (MyHC) isoforms and metabolic activity. Skeletal muscle fibers are characterized as one type of slow-twitch fiber (type I) and three types of fast-twitch fibers (type IIa, type IIx/d, and type IIb), of which type I and type IIa fibers are oxidative, whereas type IIx and type IIb fibers are primarily glycolytic, although the fiber type specification varies between species (for review see [1▪▪]).

Muscle mass is dependent upon the relative balance of fiber biosynthesis versus fiber degradation. Muscle biosynthesis occurs at the level of satellite cell myogenesis, fusion with existing fibers, and increased fiber macromolecular synthesis. Decreased muscle mass or atrophy typically results from perturbation of protein degradation induced by a variety of pathophysiologic states such as disuse, unloading, denervation, aging, sepsis, cachexia, glucocorticoid treatment, hereditary muscular disorders, diabetes, kidney, and heart failure. Due to distinct physiological character and metabolic activity (Table 1), skeletal muscle fiber subtypes are differentially sensitive to specific pathophysiologic atrophy signals. For example, red, oxidative type I fibers have a higher rate of protein synthesis and degradation and are more resistant to fasting than type II glycolytic fibers. In contrast, type I fibers are more sensitive to inactivity, microgravity, and denervation-induced atrophy [2,3,4▪], whereas type II fibers are more vulnerable to cancer cachexia, diabetes, chronic heart failure, and aging [1▪▪,5]. Even though signaling pathways responsible for muscle atrophy have been recently reviewed [6▪▪,7▪▪,8▪], the basis for the selectivity of fiber-type muscle atrophy remains an important and unresolved issue.

PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR-γ COACTIVATOR-1

Peroxisome proliferator-activated receptor-γ coactivator-1 (PGC1α) is a well described factor required for mitochondrial biogenesis, oxidative metabolism, and slow-twitch fiber formation [6▪▪,9▪,10▪]. PGC1α regulates oxidative type I fiber formation synergistically with calcineurin/nuclear factor of activated T cells (NFAT) pathway, the latter serving as an essential pathway in the maintenance of the slow-twitch fiber oxidative fiber phenotype [11,12].

Several lines of evidence support a role for PGC1α as a positive effector of oxidative skeletal muscle fiber development [6▪▪,13]. PGC1α also plays an important role in the control of various signaling pathways involved in skeletal muscle wasting [6▪▪]. Overexpression of PGC1α by the muscle creatine kinase (MCK) promoter in transgenic mice had no significant effect on muscle mass at young age but prevented muscle mass wasting in aged mice by inhibiting protein degradation [14]. However, in contrast, other studies of muscle-specific PGC1α overexpression observed muscle atrophy starting at 25 weeks of age [15]. In this model, PGC1α overexpression was equally driven in both slow and fast-twitch muscle depots by the human skeletal actin (HSA) promoter. These transgenic

mice have darker-colored muscle fibers, reduced body weight, increased energy expenditure, and muscle atrophy more pronounced in type IIb fibers. Although the basis for these different effects on muscle mass and function remain unknown, one likely explanation is the relative expression levels of PGC1α in these mouse models. The MCK-PGC1α drives PGC1α protein levels similar to endogenous physiological levels present in type I fibers. In contrast, the HSA-PGC1α transgenic mice display more than 10-fold greater levels of PGC1α protein expression. High levels of PGC1α may have negative consequences on macroautophagy due to suppression of FoxO3, since FoxO3 appears to primarily function in muscle degeneration through macroautophagy. In a genetic macroautophagy-deficient model, skeletal muscle atrophy was primarily restricted to type IIb fibers [16▪]. Thus, it appears that a physiological level of PGC1α protects fibers against atrophy, but excessive PGC1α levels will lead to muscle atrophy, especially for type IIb fibers. The latter scenario was also recently observed in another animal model of above 10-fold PGC1α overexpression [17▪].

FORKHEAD BOX O FAMILY

Forkhead box O (FoxO) transcription factors mediate nutrient and metabolic homeostasis by executing the signals from AKT (also known as protein kinase B, PKB), AMP-activated protein kinase, c-Jun N-terminal kinase, p38, and p300 [7▪▪]. FoxO1 and FoxO3 activity is dependent on nuclear localization and they negatively regulate skeletal muscle mass regulation through ubiquitin/proteasome and autophagy/lysosome systems [7▪▪,18]. Their expression is up-regulated under pathophysiologic catabolic conditions, such as denervation/immobilization, fasting, sepsis, and cancer cachexia, whereas inhibited by resistance training [19,20,21▪].

FoxO1-related muscle atrophy primarily affects fast-twitch fibers. The type II fiber preference of FoxO1 may come from its regulation of muscle RING-finger protein-1 (MuRF1) [21▪], since MuRF1 is enriched and primarily induced after denervation in type II fibers, and muscle atrophy is reduced in MuRF1 knockout mice [22]. However, there are contradictory opinions about fiber type-specific control of FoxO1 [23,24]. Endurance training decreases FoxO1 transcriptional activity with a fast-to-slow twitch fiber transition that correspondingly leads to more oxidative genes expression, such as *TnI* slow and *myoglobin* [23]. Muscle-specific FoxO1 transgenic mice have more dramatic muscle atrophy in type I fibers than in type II fibers [25]. This may be due to enhanced type I muscle structural protein degradation through FoxO1-mediated lysosomal degradation mediated by cathepsin L [25] and inhibition of calcineurin/NFAT pathway [23]. Further studies are required to clarify the fiber specificity of FoxO1-induced atrophy.

FoxO3 participates in protein degradation, primarily in a macroautophagy-lysosomal pathway [26▪]. So far, few reports focus on fiber-specific regulation of FoxO3, but FoxO3 may regulate glycolytic fiber atrophy more than oxidative fibers, since PGC1α can suppress FoxO3-induced atrogin expression and PGC1α is much more abundant in oxidative fibers [14]. The apparent role of PGC1α at high expression levels that inhibits FoxO and induces skeletal muscle atrophy in contrast to activation of FoxO that also induces skeletal muscle wasting, underscores an important but poorly understood paradox in that genetic

manipulations that result in either enhanced macroautophagy or inhibition of macroautophagy both result in similar skeletal muscle atrophy and wasting phenotypes.

MACROAUTOPHAGY REGULATION

Macroautophagy (hereafter autophagy) is a cell-survival mechanism which degrades sequestered organelles and long-lived proteins through the lysosome [6▪▪]. In normal muscle, low-protein diets up-regulate autophagy that leads to the loss of muscle mass at least partially through lysosomal degradation [27]. Intriguingly, under other circumstances decreased autophagy can also lead to muscle atrophy. For example, the *Col6a1*-deficient mice display reduced autophagy flux and muscle wasting and in this animal model reactivation of autophagy is protective against muscle mass loss [28].

The integrative regulation of autophagy initiation, cargo selection, trafficking, and lysosome fusion is a very complex process and the readers are referred to several reviews on this subject [6▪▪,29]. Skeletal muscle deletion of an autophagy-essential gene, *Atg7*, resulted in muscle atrophy concomitant with increased expression of atrogins [30]. Since autophagy is considered a major cellular degradative system, one would have predicted that the genetic inhibition of autophagy would result in muscle hypertrophy and not the counter-intuitive atrophy/wasting phenotype observed, again highlighting the requirement of autophagy function in normal muscle homeostasis. Although the fiber-type specificity was not examined in the ATG7 muscle knockout mice, analysis of muscle specific ATG5 knockout mice also demonstrates reduced autophagy selectively displaying an atrophy phenotype primarily in fast-twitch glycolytic fibers [31].

Pompe's disease is a glycogen storage disease caused by defects in lysosomal GAA (acid α-glycosidase). GAA breaks down glucose polymers (glycogen) and when defective glucooligosaccharides accumulate in the lysosome resulting in lysosome swelling and neutralization of the lysosome pH, which is normally acidic [32▪]. This defect in lysosome function results in a late block in autophagy by preventing autophagosome-lysosome fusion and cargo degradation steps, resulting in the accumulation of large amounts of autophagic vacuoles. Partial GAA enzyme deficiency occurs in late-onset patients leading to progress skeletal muscle weakness whereas near complete loss of GAA activity results in an infantile form that is lethal due to cardiorespiratory failure [33▪]. GAA knockout mice that mimic the human late-onset form display dramatic size reduction in type II fibers with less affect on type I fibers. This occurs despite the lysosomal defect and inhibition of autophagy in both fiber types. Deletion of the *Atg5* gene in GAA knockout mice results in an additive defect in autophagy, which gives rise to more severe muscle wasting than either the GAA or ATG5 single knockout mice. This greater autophagy inhibition resulted in massive autophagy vacuole build-up, accumulation of ubiquitinated protein in fast-twitch fibers, but no obvious effect on slow-twitch fibers. The selective muscle wasting of type II fibers that occurs by autophagy inhibition has been observed in other mouse models such as the Fyn-overexpressing transgenic mice [16▪].

TRANSFORMING GROWTH FACTOR BETA FAMILY

The signaling transduction of transforming growth factor beta (TGFβ) superfamily is executed by components of ligands, receptors, and intracellular mediators and readers may refer to reviews for more details about that of $TGF\beta_1$, myostatin, and activins [6▪▪,34,35▪].

Postnatal treatment of wild-type mice with $TGF\beta_1$ resulted in decreased cross-sectional area of extensor digitorum longus (EDL) type II fibers, that was correlated with increased atrogin1 expression suggesting a potential role for $TGF\beta_1$ signaling in muscle atrophy [36]. In this regard, Marfan's syndrome (MFS) is an autosomal-dominant systemic disease caused by mutation of *FBN1* gene coding fibrillin-1, a connective tissue protein that normally binds $TGF\beta_1$ [37▪]. Additionally, enhanced $TGF\beta_1$ signaling has been observed in dystophin-deficient mice and inhibition of TFGβ signaling improves myopathies associated with congenital muscular dystrophy [38].

In addition to $TGF\beta_1$, myostatin (GDF-8) binds to the type IIB activin receptor (ActRIIB) and negatively regulates muscle mass [35▪]. Myostatin is upregulated in cachexia of aging and in states of muscle paralysis [39▪▪,40]. Both skeletal muscle-specific and systematic overexpression of myostatin in mice display similar phenotypes of muscle atrophy with greater sensitivity of glycolytic type II fibers than oxidative type I fibers [39▪▪]. In contrast, loss-of-function mutations in myostatin lead to increased muscle mass in several species. For example, embryonic and fetal muscle development in myostatin knockout mice ($MSTN^{-/-}$) is markedly increased with a 2–3-fold enhancement in muscle mass resulting from both hypertrophy and fiber hyperplasia, with a proportionally larger increase in glycolytic type II fast-twitch fibers [41]. Adult $MSTN^{-/-}$ mice display decreased type I fibers with increased type II fibers and a greater shift to type IIb fibers in EDL muscle [42]. The different sensitivity between fiber types may be partly related to the level of myostatin and its receptor, since myostatin has higher mRNA level in fast-twitch muscles [20] and EDL muscle has twice the amount of ActRIIB than that of the soleus muscle [43]. Myostatin/ActRIIB activates SMAD2/3 signaling and importantly SMAD2/3 inhibition completely desensitizes ActRIIB-induced muscle atrophy [44]. Inhibition of myostatin by a dominant negative ActRIIB promotes muscle hypertrophy independent of muscle satellite cell recruitment consistent with a direct signaling effect on muscle catabolism [44].

NUCLEAR FACTOR κB PATHWAY

The nuclear factor κB (NF-κB) regulation of muscle atrophy is predominantly executed by promoting proteasome-mediated degradation [45]. Activation of NF-κB has been detected in both physiological and pathological atrophic conditions such as denervation, unloading, aging, cancer, sepsis, diabetes, and which atrophy can be reversed by pharmacologic or genetic NF-κB inhibition [46▪].

Close scrutiny of the NF-κB skeletal muscle literature suggests that fast fibers are predominantly affected. For example, overexpression of muscle-specific IκB kinase β leads to severe decrease of muscle weight and fiber cross-sectional area in fast fiber-dominant muscles, but not soleus muscle [45]. This atrophy is largely due to enhanced proteasome-mediated degradation through induction of MuRF1, and crossing with *MuRF1* knockout

(*MuRF1*$^{-/-}$) mice can block this effect [45]. Disuse/immobilization leads to fatigue intolerance and a greater extent of atrophy in fast fibers than slow fibers, which process is accompanied with NF-κB activation [47], and knocking out of NF-κB (*NFkB*$^{-/-}$ mice) inhibits muscle atrophy in fast fibers more robustly than in slow fibers [47].

The effect of NF-κB in muscle atrophy has also been examined by disrupting its upstream regulators. TWEAK (tumor necrosis factor-like weak inducer of apoptosis) and its receptor Fn14 (fibro-blast growth factor-inducible receptor 14) mediate NF-κB activity through TRAF6 (tumor necrosis factor α receptor adaptor protein 6) and negatively regulate skeletal muscle mass [46▪]. Muscle specific overexpression of TWEAK (MCK-TWEAK transgenic mice) causes 36% reduction of fiber cross-sectional area in fast-twitch fibers but only 7.2% in slow-twitch fibers, indicating its fast fiber preference, and this is related to accelerated muscle-specific protein degradation through MuRF1 but not Atrogin1 [48]. Similarly increased tumor necrosis factor α (TNFα) has been correlated with sarcopenia, which show a greater atrophy in superficial vastus lateralis (SVL, predominantly type IIa and type IIb fibers) muscles than soleus muscle, and TNFα-induced NF-κB activation has been detected in aged SVL but not in aged soleus muscle [49]. Interestingly, denervation and immobilization-induced slow-to-fast fiber transition is prevented in multiple mouse models of NF-κB inhibition [47,48]. These data indicate that in addition to the role of NF-κB activation in fast-twitch fiber atrophy, NF-κB signaling may also function in the loss of slow-twitch fibers [9▪].

CONCLUSION

In general, disuse-related skeletal muscle atrophy that typically occurs during denervation, immobilization is primarily oxidative fiber-related, whereas nutrient-related atrophy such as cancer/aging cachexia, sepsis, and diabetes are more directed to glycolytic fiber wasting. At the molecular level, fiber-specific atrophy appears to be attributed to different signaling pathways, and most of them are relevant to abnormality of protein degradation (Fig. 1 and Table 2). PGC1α protects slow-twitch oxidative fibers from atrophy. On the contrary, FoxO family, TGFβ family, autophagy inhibition, and NF-κB signaling tend to primarily affect fast-twitch glycolytic fibers, although the specificity of these signals are still under debate. Further study is necessary to molecularly distinguish the relative signaling events and mechanisms accounting for the skeletal muscle atrophy in general and specifically the events accounting for fiber type selectively. Understanding these detailed issues will provide important insight in developing therapeutic approaches that can be used to prevent skeletal muscle atrophy under specific degenerative conditions.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

▪ of special interest

▪▪ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 352).

1▪▪. Schiaffino S, Reggiani C. Fiber types in mammalian skeletal muscles. Physiol Rev. 2011; 91:1447–1531. A comprehensive review about fiber-type specification and characterization. [PubMed: 22013216]

2. Macpherson PC, Wang X, Goldman D. Myogenin regulates denervation-dependent muscle atrophy in mouse soleus muscle. J Cell Biochem. 2011; 112:2149–2159. [PubMed: 21465538]

3. von Walden F, Jakobsson F, Edstrom L, et al. Altered autophagy gene expression and persistent atrophy suggest impaired remodeling in chronic hemiplegic human skeletal muscle. Muscle Nerve. 2012; 46:785–792. [PubMed: 22996233]

4▪. Sandona D, Desaphy JF, Camerino GM, et al. Adaptation of mouse skeletal muscle to long-term microgravity in the MDS mission. PLoS One. 2012; 7:e33232. Uploading induces skeletal muscle atrophy and slow-to-fast fiber conversion. [PubMed: 22470446]

5. Picard M, Ritchie D, Thomas MM, et al. Alterations in intrinsic mitochondrial function with aging are fiber type-specific and do not explain differential atrophy between muscles. Aging Cell. 2011; 10:1047–1055. [PubMed: 21933339]

6▪▪. Wing SS, Lecker SH, Jagoe RT. Proteolysis inillness-associated skeletal muscle atrophy: from pathways to networks. Crit Rev Clin Lab Sci. 2011; 48:49–70. A review discusses skeletal muscle atrophy from proteolysis mechanisms. [PubMed: 21699435]

7▪▪. Goodman CA, Mayhew DL, Hornberger TA. Recent progress toward understanding the molecular mechanisms that regulate skeletal muscle mass. Cell Signal. 2011; 23:1896–1906. A review discusses skeletal muscle regulation on a signaling basis. [PubMed: 21821120]

8▪. Fearon KC, Glass DJ, Guttridge DC. Cancer cachexia: mediators, signaling, and metabolic pathways. Cell Metab. 2012; 16:153–166. Mechanisms underlying muscle atrophy related with cancer cachexia. [PubMed: 22795476]

9▪. Kang C, Li Ji L. Role of PGC-1alpha signaling in skeletal muscle health and disease. Ann N Y Acad Sci. 2012; 1271:110–117. A review introduces PGC1α role in mitochondrial function and skeletal muscle atrophy. [PubMed: 23050972]

10▪. Tonkin J, Villarroya F, Puri PL, et al. SIRT1 signaling as potential modulator of skeletal muscle diseases. Curr Opin Pharmacol. 2012; 12:372–376. A review introduces SIRT1 regulates muscle atrophy through PGC1α and NF-κB. [PubMed: 22401932]

11. Tavi P, Westerblad H. The role of in vivo Ca(2)(+) signals acting on Ca(2)(+)-calmodulin-dependent proteins for skeletal muscle plasticity. J Physiol. 2011; 589 (Pt 21):5021–5031. [PubMed: 21911615]

12. Sakuma K, Yamaguchi A. The functional role of calcineurin in hypertrophy, regeneration, and disorders of skeletal muscle. J Biomed Biotechnol. 2010 Epub ahead of print. 10.1155/2010/721219

13. Takikita S, Schreiner C, Baum R, et al. Fiber type conversion by PGC-1alpha activates lysosomal and autophagosomal biogenesis in both unaffected and Pompe skeletal muscle. PLoS One. 2010; 5:e15239. [PubMed: 21179212]

14. Sandri M, Lin J, Handschin C, et al. PGC-1alpha protects skeletal muscle from atrophy by suppressing FoxO3 action and atrophy-specific gene transcription. Proc Natl Acad Sci U S A. 2006; 103:16260–16265. [PubMed: 17053067]

15. Miura S, Tomitsuka E, Kamei Y, et al. Overexpression of peroxisome proliferator-activated receptor gamma co-activator-1alpha leads to muscle atrophy with depletion of ATP. Am J Pathol. 2006; 169:1129–1139. [PubMed: 17003473]

16▪. Yamada E, Bastie CC, Koga H, et al. Mouse skeletal muscle fiber-type specific macroautophagy and muscle wasting are regulated by a Fyn/STAT3/ Vps34 signaling pathway. Cell Rep. 2012; 1:557–569. Autophagy inhibition induces type II fiber atrophy in skeletal muscle. [PubMed: 22745922]

17▪. Selsby JT, Morine KJ, Pendrak K, et al. Rescue of dystrophic skeletal muscle by PGC-1alpha involves a fast to slow fiber type shift in the mdx mouse. PLoS One. 2012; 7:e30063. PGC1α overexpression causes transition towards slow fiber type. [PubMed: 22253880]

18. McCarthy JJ, Esser KA. Anabolic and catabolic pathways regulating skeletal muscle mass. Curr Opin Clin Nutr Metab Care. 2010; 13:230–235. [PubMed: 20154608]
19. Bae SK, Cha HN, Ju TJ, et al. Deficiency of inducible nitric oxide synthase attenuates immobilization-induced skeletal muscle atrophy in mice. J Appl Physiol. 2012; 113:114–123. [PubMed: 22518831]
20. Yamazaki Y, Kamei Y, Sugita S, et al. The cathepsin L gene is a direct target of FOXO1 in skeletal muscle. Biochem J. 2010; 427:171–178. [PubMed: 20088826]
21▪. Reed SA, Sandesara PB, Senf SM, et al. Inhibition of FoxO transcriptional activity prevents muscle fiber atrophy during cachexia and induces hypertrophy. FASEB J. 2012; 26:987–1000. FoxO participates in skeletal atrophy induced by cancer cachexia and sepsis. [PubMed: 22102632]
22. Moriscot AS, Baptista IL, Bogomolovas J, et al. MuRF1 is a muscle fiber-type II associated factor and together with MuRF2 regulates type-II fiber trophicity and maintenance. J Struct Biol. 2010; 170:344–353. [PubMed: 20149877]
23. Yuan Y, Shi XE, Liu YG, et al. FoxO1 regulates muscle fiber-type specification and inhibits calcineurin signaling during C2C12 myoblast differentiation. Mol Cell Biochem. 2011; 348:77–87. [PubMed: 21080037]
24. Kitamura T, Kitamura YI, Funahashi Y, et al. A Foxo/Notch pathway controls myogenic differentiation and fiber type specification. J Clin Invest. 2007; 117:2477–2485. [PubMed: 17717603]
25. Kamei Y, Miura S, Suzuki M, et al. Skeletal muscle FOXO1 (FKHR) transgenic mice have less skeletal muscle mass, down-regulated Type I (slow twitch/red muscle) fiber genes, and impaired glycemic control. J Biol Chem. 2004; 279:41114–41123. [PubMed: 15272020]
26▪. Braun T, Gautel M. Transcriptional mechanisms regulating skeletal muscle differentiation, growth and homeostasis. Nat Rev Mol Cell Biol. 2011; 12:349–361. FoxOs are transcription factors regulating postnatal control of muscle mass. [PubMed: 21602905]
27. She P, Zhang Z, Marchionini D, et al. Molecular characterization of skeletal muscle atrophy in the R6/2 mouse model of Huntington's disease. Am J Physiol Endocrinol Metab. 2011; 301:E49–E61. [PubMed: 21505144]
28. Grumati P, Coletto L, Sabatelli P, et al. Autophagy is defective in collagen VI muscular dystrophies, and its reactivation rescues myofiber degeneration. Nat Med. 2010; 16:1313–1320. [PubMed: 21037586]
29. Singh R, Cuervo AM. Autophagy in the cellular energetic balance. Cell Metab. 2011; 13:495–504. [PubMed: 21531332]
30. Masiero E, Agatea L, Mammucari C, et al. Autophagy is required to maintain muscle mass. Cell Metab. 2009; 10:507–515. [PubMed: 19945408]
31. Raben N, Hill V, Shea L, et al. Suppression of autophagy in skeletal muscle uncovers the accumulation of ubiquitinated proteins and their potential role in muscle damage in Pompe disease. Hum Mol Genet. 2008; 17:3897–3908. [PubMed: 18782848]
32▪. Raben N, Wong A, Ralston E, et al. Autophagy and mitochondria in Pompe disease: nothing is so new as what has long been forgotten. Am J Med Genet C Semin Med Genet. 2012; 160:13–21. The role of macroautophagy playing in POMPE disease. [PubMed: 22253254]
33▪. Nascimbeni AC, Fanin M, Masiero E, et al. Impaired autophagy contributes to muscle atrophy in glycogen storage disease type II patients. Autophagy. 2012; 8:1697– 1700. Autophagy defect induces muscle atrophy in patients of pompe disease. [PubMed: 22940840]
34. Katsuno M, Adachi H, Banno H, et al. Transforming growth factor-beta signaling in motor neuron diseases. Curr Mol Med. 2011; 11:48–56. [PubMed: 21189118]
35▪. Huang Z, Chen X, Chen D. Myostatin: a novel insight into its role in metabolism, signal pathways, and expression regulation. Cell Signal. 2011; 23:1441–1446. A review about myostatin signaling and function. [PubMed: 21609762]
36. Mendias CL, Gumucio JP, Davis ME, et al. Transforming growth factor-beta induces skeletal muscle atrophy and fibrosis through the induction of atrogin-1 and scleraxis. Muscle Nerve. 2012; 45:55–59. [PubMed: 22190307]

37▪. Akhurst RJ, Hata A. Targeting the TGFbeta signalling pathway in disease. Nat Rev Drug Discov. 2012; 11:790–811. A general introduction about TGFbeta family signaling and function. [PubMed: 23000686]

38. MacDonald EM, Cohn RD. TGFbeta signaling: its role in fibrosis formation and myopathies. Curr Opin Rheumatol. 2012; 24:628–634. [PubMed: 22918531]

39▪▪. Elkina Y, von Haehling S, Anker SD, et al. The role of myostatin in muscle wasting: an overview. J Cachexia Sarcopenia Muscle. 2011; 2:143–151. A review focusing on myostatin fitting in signaling pathway map to regulate muscle mass. [PubMed: 21966641]

40. Ryan AS, Ivey FM, Prior S, et al. Skeletal muscle hypertrophy and muscle myostatin reduction after resistive training in stroke survivors. Stroke. 2011; 42:416–420. [PubMed: 21164115]

41. Girgenrath S, Song K, Whittemore LA. Loss of myostatin expression alters fiber-type distribution and expression of myosin heavy chain isoforms in slow-and fast-type skeletal muscle. Muscle Nerve. 2005; 31:34–40. [PubMed: 15468312]

42. Morine KJ, Bish LT, Pendrak K, et al. Systemic myostatin inhibition via liver-targeted gene transfer in normal and dystrophic mice. PLoS One. 2010; 5:e9176. [PubMed: 20161803]

43. Mendias CL, Marcin JE, Calerdon DR, et al. Contractile properties of EDL and soleus muscles of myostatin-deficient mice. J Appl Physiol. 2006; 101:898–905. [PubMed: 16709649]

44. Sartori R, Milan G, Patron M, et al. Smad2 and 3 transcription factors control muscle mass in adulthood. Am J Physiol Cell Physiol. 2009; 296:C1248–C1257. [PubMed: 19357234]

45. Cai D, Frantz JD, Tawa NE Jr, et al. IKKbeta/NF-kappaB activation causes severe muscle wasting in mice. Cell. 2004; 119:285–298. [PubMed: 15479644]

46▪. Kumar A, Bhatnagar S, Paul PK. TWEAK and TRAF6 regulate skeletal muscle atrophy. Curr Opin Clin Nutr Metab Care. 2012; 15:233–239. A review introduces TWEAK/TRAF regulation on NF-κB and muscle atrophy. [PubMed: 22366923]

47. Hunter RB, Kandarian SC. Disruption of either the Nfkb1 or the Bcl3 gene inhibits skeletal muscle atrophy. J Clin Invest. 2004; 114:1504–1511. [PubMed: 15546001]

48. Mittal A, Bhatnagar S, Kumar A, et al. The TWEAK-Fn14 system is a critical regulator of denervation-induced skeletal muscle atrophy in mice. J Cell Biol. 2010; 188:833–849. [PubMed: 20308426]

49. Phillips T, Leeuwenburgh C. Muscle fiber specific apoptosis and TNF-alpha signaling in sarcopenia are attenuated by life-long calorie restriction. FASEB J. 2005; 19:668–670. [PubMed: 15665035]

50. Lee SJ, Lee YS, Zimmers TA, et al. Regulation of muscle mass by follistatin and activins. Mol Endocrinol. 2010; 24:1998–2008. [PubMed: 20810712]

51. Fukuda T, Ewan L, Bauer M, et al. Dysfunction of endocytic and autophagic pathways in a lysosomal storage disease. Ann Neurol. 2006; 59:700–708. [PubMed: 16532490]

KEY POINTS

- Skeletal muscle type I fiber-specific atrophy and slow-to-fast fiber transition can be induced by denervation and immobilization.
- Skeletal muscle fiber II specific atrophy is typically induced under cachexia, sepsis, diabetes, and chronic heart failure.
- Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α) protects slow, oxidative fibers from atrophy.
- Forkhead box O (FoxO) family, transforming growth factor beta (TGFβ) family, autophagy inhibition, and nuclear factor kappaB (NF-κB) affect fast, glycolytic fibers more than slow, oxidative fibers.

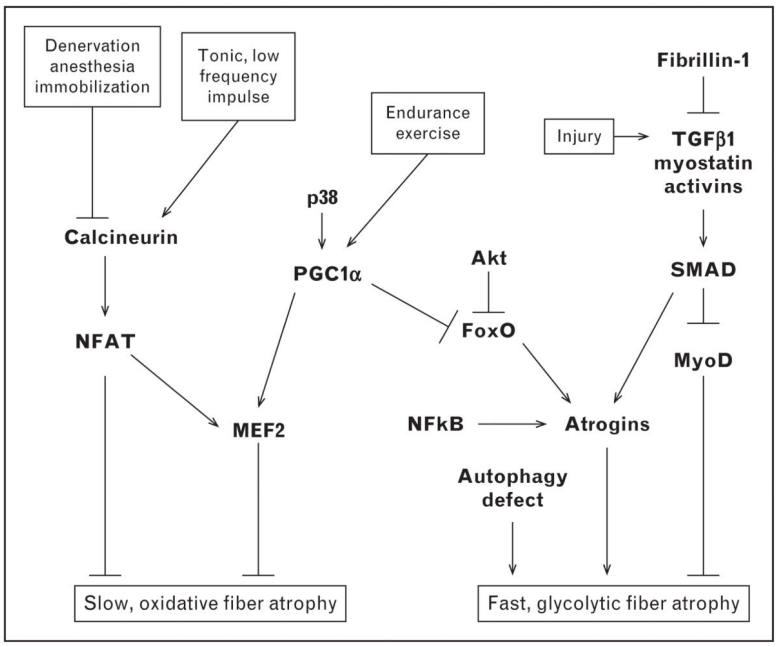

FIGURE 1.
Signaling pathways targeting fiber-specific atrophy in skeletal muscle.

Table 1

Mouse fiber specificity

	Type I	Type II Type IIa	Type IIx/d	Type IIb
Color	Red	Red	White	White
MyHC isoform	MyHCI	MyHCIIa	MyHCIIx/d	MyHCIIb
Contractile speed	Slow	Fast	Fast	Fast
Fatigue resistant	High	High	Low	Low
Metabolism	Oxidative	Oxidative	Glycolytic	Glycolytic
SDH Activity	High	High	Low	Low
Mitochondria and myoglobin content; CS activity	High	High	Low	Low
ATPase activity	Low	Low	High	High
Mitochondrial CK (miCK) and H-LDH	High	High	Low	Low
M-CK; M-LDH	Low	Low	High	High

CK, creatine kinase; CS, citrate synthase; LDH, lactate dehydrogenase; SDH, succinate dehydrogenase.

Table 2

Studies focusing on fiber-specific atrophy

Keywords	Models	Results	Primarily affected fiber type	References
Long-term microgravity	Mice exposed under microgravity for 91 days	Long-term exposure of microgravity causes decreased fiber cross-sectional area, more type I MyHC and less type IIA/B MyHC in soleus muscle but not EDL muscle	Slow fibers	[4▪]
PGC1α, GAA	GAA KO mice overexpressing PGC1α in skeletal muscle	PGC1α overexpression in GAA KO mice causes a fast-to-slow fiber switch and prevented autophagic built-up formation in fast fibers, but does not affect muscle strength and fiber size.	Fast-to-slow fiber switch	[13]
PGC1α, FoxO3	MCK-PGC1α transgenic mice	PGC1α expression is dramatically down-regulated in gastrocnemius under atrophic conditions. PGC1α overexpression driven by MCK reduces type II fiber atrophy in TA (tibialis anterior) muscle under denervation and fasting through suppressing FoxO3.	Type IIb fibers	[14]
PGC1α	HSA-PGC1α transgenic mice	Overexpression of PGC1α in skeletal muscle causes muscle atrophy, especially for type IIb-enriched muscles.	Type IIb-rich muscles	[15]
FYN, STAT3, VPS34, autophagy	HSA-Fyn transgenic mice	HSA-Fyn transgenic mice have more severe muscle mass loss in glycolytic fiber-rich muscles	Glycolytic fibers	[16▪]
PGC1α, dystrophin	Dystophin-deficient (*mdx*) mice	PGC1α overexpression causes more slow fibers and decreases muscle mass, which is more severe in type II fiber-rich muscles.	Type II fibers	[17▪]
Cancer cachexia, sepsis, FoxO	Sepsis induced by cecal ligation and puncture (CLP) and cancer cachexia induced by LLC cell injection in C57BL/6 mice	Tumor bearing-induced atrophy affects TA muscle but not soleus muscle, and is prevented by FoxO activity inhibition.	Type II fibers	[21▪]
FoxO1	MLC-FoxO1 transgenic mice	MLC-FoxO1 mice have less body weight, reduced muscle mass with a paler color, decreased number of type I fiber and running activity, less type I muscle structural proteins and more cathepsin L expression.	Type I fibers	[25]
FoxO1, Notch	FoxO1 fl/fl-myogenin-Cre transgenic mice (Myog-Foxo1 mice)	FoxO1 inactivation causes a decrease of type I fiber in soleus but not in type II fiber-rich muscles, along	Slow fibers	[24]

Keywords	Models	Results	Primarily affected fiber type	References
		with decreased type I fiber markers expression and increased type II fiber markers.		
MuRF1/2, myozenin-1, calcineurin	MuRF1 KO mice, MuRF1/MuRF2 double KO mice	Denervation enhances MuRF1 expression primarily in type II fibers. Denervation-induced atrophy is protected on type II fiber-rich TA muscle. Double KO of MuRF1 and MuRF2 causes loss of type II fibers, probably because of loss the inhibition of calcineurin/NFAT through myozenin1/2.	Type II fibers	[22]
Myostatin	*Mstn*$^{-/-}$ mice,	Fiber type transition from slow, oxidative fibers to fast, glycolytic fibers in both soleus and EDL muscles	Fast fibers	[41]
Myostatin, ActRIIB	*Mstn*$^{-/-}$ mice	*MSTN*$^{-/-}$ mice have more gain of muscle mass and fiber number of EDL muscle than those of soleus muscle compared to WT mice.	Fast fibers	[43]
Follistatin, activin, myostatin	*Fst*$^{-}$/$^{+}$ mice	*Fst*$^{-}$/$^{+}$ mice have higher percentage of type I fibers than WT mice	Fast fibers	[50]
GAA, Atg5	AD-GAA KO (HSA-Cre-Atg5 fl/fl, GAA KO) Mice, GAA KO mice	AD-GAA KO mice have a further muscle atrophy than GAA KO. Both GAA KO mice and AD-GAA KO show autophagy malfunction only in fast fibers.	Type II fibers	[31]
GAA, autophagy	GAA KO mice	GAA KO mice show decreased fiber size and more autophagic buildup in type II fibers but no significant change in type I fibers.	Type II fibers	[51]
NF-κB, IKKβ, MuRF1	MCK-MIKK mice (constitutive IκB Kinase β, muscle specific); MCK-MISR (IκBα suppressor, muscle specific)	MCK-MIKK mice have muscle weight loss in all muscles except soleus, and pharmacological inhibition of NFκB or crossing with MCK-MISR mice could reverse this loss.	Type II fibers	[45]
NF-κB	*Nfkb1*$^{-/-}$ mice	In soleus muscle, hind limb unloading causes 17 and 33% cross-sectional reduction of slow and fast fibers, but only 15 and 10% corresponding reduction in *Nfkb1*$^{-/-}$ mice. Moreover, in fast fiber dominant-plantaris muscle, *Nfkb1*$^{-/-}$ mice completely abolished unloading-induced muscle atrophy.	Type II fibers	[47]

Keywords	Models	Results	Primarily affected fiber type	References
TWEAK/Fn14,	MCK-TWEAK transgenic mice	Compared to control, TWEAK transgenic mice show 36% reduction of cross sectional-area in fast fibers but only 7.2% reduction in slow fibers.	Type II fibers	[48]
TNFα, NF-κB, sarcopenia	6-month-old and 26-month-old Fischer 344 rats	SVL muscle show greater muscle weight loss than soleus during aging, which is correlated with TNFα and NF-κB activity increase.	Type II fibers	[49]