



Strategies and potential therapeutic agents to counter skeletal muscle atrophy

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Contributions: (I) Conception and design: H Sun, Z Huang; (II) Administrative support: H Sun; (III) Provision of study materials or patients: Z Huang, W Ma; (IV) Collection and assembly of data: Z Huang, J Zhu, W Ma; (V) Data analysis and interpretation: Z Huang, W Ma, H Sun; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Skeletal muscle atrophy is common in various clinical problems. It increases the risk of complications as well as puts a huge economic burden on patients. Numerous diseases or pathologies are able to render the loss of muscle mass, such as diabetes, sepsis, burn injury, carcinoma. Long-time cast immobilization caused by bone fracture may induce bedsores and even severe infections. Indeed, muscle atrophy can occur as either the result of unloading or directly by some particular disease. Unfortunately, to date there are no effective therapies available for completely recovering the attenuated muscle force. Emerging evidence implicates that molecular mechanism related to proteolysis and protein synthesis may genuinely take control of muscle mass. Therefore, investigate these molecular pathways may be helpful to develop a novel strategy for muscle mass loss intervention. The purpose of the present review is to concentrate on potential therapeutic strategies and mechanisms involved in muscle atrophy.

Keywords: Muscle atrophy; phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR); myostatin; myogenin; ubiquitin-proteasome system (UPS)

Received: 30 April 2018; Accepted: 10 May 2018; Published: 22 May 2018.

doi: 10.21037/biotarget.2018.05.02

View this article at: <http://dx.doi.org/10.21037/biotarget.2018.05.02>

Background

Muscle tissues along with bones consist of basic effector of motor system. Once receive nervous impulse, muscle will contract with diverse strength and duration. Notably, muscles are also important place for energy consuming and nutrition metabolism and most amino acids are preserved in muscles. The loss of skeletal muscle mass may happen when disuse or its activity is lower than normal, especially for those who are required to immobilization (1,2). When faced with catabolic condition such as cachexia, muscles will be consumed for energy thus tends to atrophy. As for patients who suffered from disease like malignant tumor or sepsis, muscle mass is also a sensitive indicator for prognosis which predict

morbidity and mortality (3). Therefore, keeping muscle mass is fundamental of normal function and crucial for health maintenance. However, preventing skeletal muscle from wasting remains an unresolved challenge today.

It is acknowledged that muscle mass depends on protein turnover and cell turnover. The former is a more popular research topic because a kind of key cell, satellite cell, which regulates muscle cell turnover is more controversial for its role in muscle mass maintenance (4). Breakdown of balance between protein synthesis and proteolysis is considered the main cause for muscle atrophy, the process in which is thought to be regulated by multiple signal transduction pathways (5,6). Clarifying these cell signals pathways and revealing the underlying mechanism for muscle atrophy may pave the way for effective therapies.

Probable mechanism underlying muscle atrophy and potential molecular interference therapy

Recently, by virtue of gene expression screening, a subset of genes have been identified associated with muscle wasting process, which are called atrophy-related genes or atrogenes (7). More and more evidence implies particular cell signaling pathway regulate atrophy process.

Medication targeting phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) and FoxO signaling

Classic cellular signaling pathway PI3K/AKT/mTOR takes control of the rate of muscle protein synthesis in multiple organs including muscle. It is proved that muscle atrophy condition for example immobilization, denervation accelerates muscle protein degradation via AKT/mTOR (8). The mTOR pathway is required for cell growth and takes part in the regulation of various physiological and pathological pathways such as cell differentiation, proliferation, and apoptosis (9). However, it is interesting that blocking mTORC1 activity with rapamycin does not lead to an increase in muscle loss, therefore simply promoting protein synthesis by activating mTOR seems produce much less effect than expected (10). I have to mention FoxO family, a group of transcription factors that control protein degradation, is also controlled at least partly by AKT pathway. In fact, activation of FoxO transcription factors and atrogen-1 (an important E3 ubiquitin ligase which will be introduced later) usually accompany with inhibition of the PI3K/AKT pathway, while IGF-1 treatment or AKT overexpression inhibits FoxO and atrogen-1 expression (11).

Medication targeting myostatin and myogenin

Myostatin, as a member of the transforming growth factor- β superfamily, is a potent negative regulator of skeletal muscle growth. Myostatin inactivation can lead to skeletal muscle hypertrophy, while overexpression often causes muscle atrophy, the mechanism of which may be attributed to inhibition of myoblast proliferation as well as differentiation. Myostatin can also promote protein synthesis by suppressing the AKT pathway as well as increasing the activity of the ubiquitin-proteasome system (UPS) (12). Indeed, glucocorticoid-induced skeletal muscle atrophy is associated with upregulation of myostatin

gene expression, while genetic deletion of myostatin can effectively prevent muscle atrophy not only in skeletal muscle but also heart itself (13,14).

The transcription factor myogenin, an essential regulator of muscle development, is highly up-regulated in denervated muscles. Evidence show deletion of myogenin is able to resistant to atrophy, which may be associated with MuRF1, atrogen-1 and HDAC (15).

Medication targeting UPS

Pathologic states or loss of nerve connection will render muscle lose its weight mainly through proteolysis which involves three classic pathways, ubiquitin-dependent system, autophagy-lysosome pathway, calpain-dependent pathway. Here we mainly discuss the UPS, because it may be the most important pathway that accelerates protein degradation during muscle atrophy.

Ubiquitination along with de-ubiquitination enzymes have been implicated with muscle wasting. There are two well-known muscle-specific ubiquitin ligases, atrogen-1 (also known as MAFbx) and muscle ring finger 1 (MuRF1). Atrogen-1 contains a functional F-box domain that binds to components of SCF-type Ub-protein ligases (E3s) and it often increases before atrophy occurs (16). Atrogen-1 will be activated by overexpression of Foxo3 thus lead to severely atrophy of muscle, while silencing FoxO is able to protect muscle under atrophy induction condition (11). Both MyoD, a transcription factor that is associated with protein synthesis, and eIF3f are regulated by atrogen-1.

Other newly found medications such as pyropia yezoensis peptide PYP1-5, conessine, astragalus polysaccharide, sulforaphane were all to different degrees have a protective role in muscle atrophy by regulating expression of atrogen-1 or /and MuRF-1 (17-20).

TRAF6, another E3 ubiquitin ligase, plays a crucial role in muscle atrophy. Adequate amount of polyubiquitylated proteins is dependent on existing of TRAF6 (21). Knocking out TRAF6 can have a protective effect on mice that are exposed under starvation or denervation. The underlying mechanisms are still not fully understood, but it has been shown that activation of JNK, AMPK, FoxO3, also NF- κ B is required for TRAF6-mediated ubiquitylation. Therefore, inhibition of TRAF6 may be an effective method to preserve muscle mass (6).

USP19, the most studied deubiquitinating enzyme, is upregulated in muscle under different catabolic conditions. However, the USP19 not only promote protein degradation

but also regulate protein synthesis, so the therapy targeting ubiquitination and deubiquitination remains to be explored (22).

Medication targeting IGF1 signaling

However, skeletal muscle atrophy may partly result from insulin resistance, as insulin can promote muscle protein synthesis. A report involving 4 patients with chronic obstructive pulmonary disease who receive long-term corticosteroids (ICS) treatment found an excessive dynamic collapse of the posterior wall during bronchoscopy. It was exactly considered to be caused by the atrophy of the smooth muscles of the tracheobronchial wall (23). Notably, glucocorticoid treatment can often lead to muscle wasting. It has been found fluctuation of glucocorticoid levels will have an influence on expression of atrogin-1 and MuRF1. Similar outcomes were observed in myotubes treated with dexamethasone(Dex), followed by increasing atrogin-1 and MuRF1 mRNA (24). Therefore, keeping low-level of glucocorticoid by a glucocorticoid receptor antagonist may prevent muscle loss. Due to glucocorticoid receptor β is able to cause glucocorticoid resistance, overexpressing GR β is demonstrated to play a protective role in glucocorticoid-induced catabolic atrophy (25). An interesting phenomenon is that immobilization can also result in muscle insulin resistance(MIR), especially when immobilization for a long time (26). It has been proposed that MIR may interfere phosphorylation of some key proteins involved in muscle glucose uptake. Kimball *et al.* demonstrate that insulin stimulates protein synthesis in skeletal muscle by enhancing the association of eIF-4E and eIF-4G (27). IGF-1 may be a good target for preventing muscle atrophy as it decreases proteolysis and atrogin-1 mRNA expression via activating PI3K-AKT pathway (24). A well-known transcription factor controlled by glucocorticoid receptor KLF15 (Krüppel-like factor 15) was demonstrated regulated by BCAA and mediated by PI3K/AKT pathway (28). The glucocorticoid-KLF15-BCAA pathway as a novel therapeutic target for muscular atrophy show us bright prospects, while improving MIR situation may also be a prospective way to prevent muscle (29).

Other important mechanisms

Previous studies have shown that miRNAs play a crucial role in protein synthesis and degradation of muscle. MiRNAs, also known as microRNAs, belong to small non-coding RNAs, take part in diverse biological and pathological processes. Recently, some new identified

muscle-specific miRNAs such as miR-1, miR-133 were reported to play important roles in the control of muscle growth and differentiation (30). Newly identified miRNA, miR-23a, which binds to both atrogin-1 and MuRF1 thus functions a protective role in muscles. Animal experiments in which miR-23a transgenic mice were confirmed resistant to dexamethasone- induce muscle atrophy (31). Recently, miR-351 is demonstrated to inhibit denervation-induced atrophy of TA muscles following sciatic nerve transection, protein expression levels of TRAF6, MuRF1 and Atrogin1 in the TA muscles were all to some degree suppressed (32).

Tumor necrosis factor-like weak inducer of apoptosis (TWEAK) has been shown to regulate many cellular responses including proliferation, differentiation, apoptosis, and inflammation. Atrophic stimulus such as denervation, immobilization, starvation, can also activate the TWEAK/Fn14 signaling pathway which participates in proteolytic process of muscle and thus finally lead to muscle atrophy (33).

Oxidative stress may another cause for muscle atrophy. It is observed reactive oxygen can directly lead to DNA fragmentation and protein oxidation, thus muscle cells may apoptosis. Furthermore, once proteins are carbonylated, they are more easily hydrolyzed in order to protect cell function (34). We will introduce some antioxidants drugs in the following passage.

Collectively, targeting related signaling pathway has been shown promise for the prevention or reversal of muscle atrophy. However, targeting one single signaling pathway does not generate a cheerful result since different pathway crosstalk like a complicated network and influence each other at different levels. More concentration needs to be focused on further investigation in these signal pathways.

Exercise

Long-term physical inactivity can cause the atrophy of skeletal muscle. Exercise is an effective and convenient countermeasure to restore or maintain the function of skeletal-muscular system. Especially in elderly people, exercise can effectively maintain or prevent muscle mass loss (35). Endurance exercise training has been proved to improve oxidative, metabolic situation, and heat stress on skeletal muscle. A variety of cellular signaling pathways are detected to be activated and followed by increased expression of proteins related to muscle protection (36). Exercise has already been introduced to prevent muscle atrophy. From a systematically review on patients with spinal cord injury, early exercise on muscle is thought to

be of positive effects (37). Physical training has also been proved safe and effective in multiple disease including spinobulbar muscular atrophy (38), Duchenne muscular dystrophy (DMD), diabetes caused muscle atrophy (39), and patients who are receiving hemodialysis (40). Even in motor neuron disorders such as amyotrophic lateral sclerosis (ALS), although there are some controversial judgements about physical training, improvements in function have also been observed via reasonable exercise (38). Since high level of reactive oxygen species (ROS) may have many deleterious effects and thus lead to muscle atrophy, exercise used to be thought as a harmful behavior especially for those who are suffering from muscle wasting. However, accumulative evidence show ROS produced during exercise also have positive effects by influencing cellular processes that produce antioxidants (41). Considering about the phenomenon that mitochondrial dysfunction has been proved associated with protein degradation through increased levels of ROS which binds mtDNA and can be reversed by mitochondrial transcription factor A (MTFA). Interestingly, a synergistic effect in protecting muscle function can be accomplished by combination of exercise and TFAM. The intrinsic mechanism may lie on exercise can stimulate some cell signaling pathway that finally activate transcription of TFAM and mitochondrial biogenesis (42). Moreover, it is important to take proper type of exercise since different kinds of exercise do not share the same role. It seems that resistance exercise such as flywheel, vascular occlusion, dynamic, isometric, and eccentric exercise obtain the optimal outcomes to counter muscle atrophy (43). Indeed, muscle specific miRNAs, like myomiRs, controlling muscle development, are regulated by endurance exercise (44). Compared with traditional strengthening programs which emphasize enhancing muscle strength, eccentric strength and muscle velocity enhancement can improve muscle atrophy of elders more effectively (45). Additionally, the effect of exercise on muscles differs depending on the type of muscles. During a trial in which 25 male volunteers stay in bed for 90 days, a high-intensity concentric-eccentric (flywheel) resistance exercise reduce atrophy in the vasti, adductor magnus and ankle dorsiflexors/toe flexors but not the hamstrings, medial thigh muscles or peroneals and dorsiflexor muscles (46).

Nutritional strategies to counteract muscle atrophy

Although exercise may be the best way to recover muscle

mass, it is not always applicable. In the particular situation, we need other effective approaches to intervene muscle loss. For example, nutritional strategies may be a good choice as it limits muscle wasting and even promotes recovery of muscle atrophy (47). Long time immobilization can often lead to a decrease in responsiveness of muscle protein synthesis to amino acids. Under the condition defined as anabolic resistance, anabolic response of skeletal muscle to amino acids is not sensitive, which makes a normal diet unable to provide sufficient proteins for muscle synthesis (48). As to handle this dilemma, increasing supplementation of protein or amino acid in addition to a normal diet may overcome anabolic resistance and improve the N balance. Supplementations of both essential amino acid (EAA) and branched-chain amino acids can stimulate muscle protein synthesis and reduce muscle protein breakdown. The underlying mechanism of which remains elucidated while it may be explained partly by fact that leucine signal can activate the mTOR pathway and transcription (47). For example, free leucine, which is also called 'nutrient signal', is beneficial for stimulating protein synthesis and preventing protein decrease. It is detected that the mTOR pathway is activated by that and eIF4E-binding protein 1 is further phosphorylated (49). However, it is interesting to realize the supplement of sufficient nutrition does not always produce benign outcomes, because it may increase proteasome and some UPS components. Researchers demonstrate that energy intake in excess of requirements could accelerate loss of muscle mass, which may be partly explained by activated inflammation system and antioxidant defense (50). Therefore, the key point of the optimal strategy may be the proper amount of energy intake. Indeed, dietary restriction is an effective intervention to cope with immobilization-induced atrophy (51). Supplementation of adequate dietary protein (>1.5 g/kg per day) in combination with exercise training can improve muscle mass more apparently than taking just single measure alone (52).

Anti-inflammation, antioxidant and free radical scavengers

The exhaustive mechanism for muscle mass loss is very complicated and associated with a lot of physiopathological changes, but protein degradation exceed synthesis can play the central role. Evidence show local inflammation and oxidative stress should be responsible for the unbalance of protein metabolism as well. Since inflammation can directly induce muscle atrophy, anti-inflammation treatment may

be an effective countermeasure to reduce noxious micro-environment. For example, elimination inflammatory cytokines such as IL-1 β , IL-6 can block pathways which initiate proteolysis in muscle and eventually prevent atrophy (53). Indeed, classic immunity related JAK/STAT3 pathway take part in process of atrophy inflammation, as it is found strongly activated by IL-6 and inhibition of which lead to cease of muscle wasting (54). It is reported that fish oil can alleviate muscle atrophy, due to its rich content of long-chain n-3 fatty acids (DHA and EPA) that is crucial for protein anabolism (55). N-3 fatty acids, as an anti-inflammation nutrient, enhance insulin-sensitive protein anabolism through the Akt/mTOR/S6K1 pathway (56). A recent research found that S-allyl cysteine (SAC), an active component of garlic, has an anti-atrophic role in TNF α induced muscle atrophy model by regulating multiple proteolytic systems. Furthermore, suppressing of inflammatory molecules such as TNF α , IL-6, IL-1 β , TNF-like weak inducer of apoptosis (TWEAK), fibroblast growth factor-inducible 14 (Fn14) and NO $_x$ were all detected, and these molecules were known as contributors of atrophy (57). Similar results have been obtained with antioxidant treatment (58). Antioxidant can reduce oxidative stress in cells, while stress situation will aggravate muscle protein hydrolyzation. For example, Resveratrol, a well-known antioxidant, was proved to help contain muscle loss, which may function by the decrease of glutathione (59). Other antioxidants such as vitamin E, soya protein have also been studied and proved beneficial for limitation of muscle wasting. Surprisingly, chromium can improve skeletal muscle atrophy via controlling the UPS and AKT pathway (60). Free radical scavengers may be a hopeful treatment to prevent muscle atrophy. In a randomized pilot study in hemiparetic stroke patients, researchers found those receiving edaravone for a comparative long time can walk faster than the control group, and their femoral muscle atrophy was also significantly milder, which demonstrate long-term administration of free radical scavenger may prevent muscle atrophy thereby improving locomotor function (61).

Emerging new and novel countermeasures

A series of unbiased genome-wide mRNA expression analyses show us some potential transcriptional factors play crucial roles in regulating expression of atrophy-related genes. For example, two transcription factors ATF4 and p53 have been demonstrated that play essential roles in atrophy

of immobilized skeletal muscle. Both ATF4 mKO mice and p53 mKO mice show resistant to immobilization-induced skeletal muscle atrophy. Furthermore, *in vivo* plasmid transfection to force expression of ATF4 and/or p53 in skeletal muscle fibers of wild-type, apparent muscle fiber atrophy is observed even in the absence of immobilization, which means down regulation of ATF4 and/or p53 may develop into a potential therapeutic treatment to muscle atrophy caused by other multiple inducement (62). Apart from finding out defective genes, then overexpress or silence specific genes expression, regulating target genes precisely depending on different time points may be more effective. Antisense oligonucleotide (ASO) technologies, which function by specifically interfering translation of targeted mRNA thus inhibit *de novo* synthesis of protein, seems a more effective intervention (63). Histone deacetylases (HDACs) has been found participating in various muscle atrophy including denervation and disuse recently, therefore targeting HDACs may another potential strategy for muscle atrophy patients (64).

Bone marrow stromal cells (MSCs) are well-known popular topic and have been widely investigated due to its therapeutic potential in regenerated medicine for various types of disease and multiple organ injury as well as failure. MSCs from adult bone marrow can differentiate into multiple type cells including skeletal muscle cells and cardiac muscle cells (65). It has been reported that MSCs can be induced to myofibers and thus contribute to functional recovery of muscle tissue (66). Other researchers found that MSCs injected during hind limb immobilization can effectively maintain satellite cell pools and prevent apoptosis after atrophy. Skeletal muscle protein synthesis was detected reinforced and the regulation of protein might also be related to the AKT pathway (67). The transplantation of rMSCs significantly preserved the function of denervated gastrocnemius muscle, which may correlate with the preservation of post-junctional folds at the neuromuscular junction of the denervated muscle (65).

Conclusions

Muscle atrophy is a formidable challenge which can be caused in a variety of conditions. The explicit mechanism responsible for muscle mass loss remains puzzled, but the imbalance between protein synthesis and proteolysis is probably the most important key point. A lot of therapeutic methods have been developed to control or prolong the period of muscle wasting. However, to date, there is

still no effective countermeasure to entirely reverse the deteriorating muscles. Perhaps a combination of multiple treatments might have a synergistic effect and produce more satisfactory outcomes. With the development of molecular biology, the changes of cell signal transduction pathway during atrophy will be further elucidated. Understanding these molecular pathways is also a prerequisite for the development of potential therapeutic methods.

Acknowledgements

Funding: This study was supported by National Natural Science Foundation of China (Grant No. 81671230, 81301628), the 973 Program (Grant No. 2014CB542202 and 2014CB542203), a project funded by Jiangsu Provincial Key Medical Center, the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD), China Postdoctoral Science Foundation (Grant No. 2016M591894), Jiangsu Postdoctoral Science Foundation (Grant No. 1601040A), Fund of Doctoral Start-up of Nantong University (Grant No. 15B18, 17ZZ040), Jiangsu College Students Innovation and Entrepreneurship Training Program (Grant No. 201710304029Z).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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doi: 10.21037/biotarget.2018.05.02

Cite this article as: Huang Z, Zhu J, Ma W, Sun H. Strategies and potential therapeutic agents to counter skeletal muscle atrophy. *Biotarget* 2018;2:8.