Chapter 29
Muscle Atrophy: Present and Future

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Abstract Muscle atrophy is the loss of muscle mass and strength, and it occurs in many diseases, such as cancer, AIDS (acquired immunodeficiency syndrome), congestive heart failure, COPD (chronic obstructive pulmonary disease), renal failure, and severe burns. Muscle atrophy accompanied by cachexia worsens patient's life quality and increases morbidity and mortality. To date there is no effective treatment on that. Here we summarize the diagnosis methods and cellular mechanisms of muscle atrophy. We also discuss the current strategies in muscle atrophy treatment and highlight the potential treatment strategies to resist muscle atrophy.

Keywords Muscle atrophy · Present · Future

29.1 Introduction

Muscle atrophy results from a variety of common diseases, including cancer, AIDS (acquired immunodeficiency syndrome), congestive heart failure, COPD (chronic obstructive pulmonary disease), renal failure, and severe burns [1, 2]. Muscle atrophy is a complex and highly regulated phenomenon. It is characterized by a decrease in muscle fiber cross-sectional area, myonuclear number, protein content, muscle strength, an increase in fatigability, and resistance to insulin [3, 4]. It is also associated with an increased risk of morbidity and mortality.

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Despite decades of research, no effective treatments have been proven to prevent muscle mass loss. Here we will provide a brief overview of researches in the field of muscle atrophy. We will discuss about the new progress in the field as well as its limitations and highlight the future direction of muscle atrophy therapy.

29.2 Diagnosis Methods

Diagnosis is important for clinical management of muscle atrophy. Skeletal muscle mass index (SMI) is the most common indicator to diagnose muscle atrophy. It can be measured by image or laboratory functional test. Dual-energy X-ray absorptiometry (DXA), magnetic resonance imaging (MRI), and computerized tomography (CT) are used in SMI detection. Also, anthropometry (which means by directly measuring the muscle mass) and bioelectrical impedance analysis (BIA) are useful tools in muscle atrophy diagnosis [5, 6]. Lab tests mainly focus on detecting creatinine and urea. Levels of these two chemicals correlate with muscle injury and muscle loss [7, 8]. Strength of handgrip and exercise capacity reveal muscular function. Finally, muscle biopsies could directly show evidence of muscle atrophy but are seldom used due to its invasiveness.

Several technical improvements have been made in lab testing for muscle atrophy. Transcript profiling showed a subset of universal upregulated genes in rat muscle atrophy model, such as muscle RING finger 1 (MuRF1) and muscle atrophy F-box (MAFbx). Especially the latter one could be potential therapeutic target for muscle atrophy [2].

Current tests to evaluate muscle atrophy are time-consuming, invasive (as biopsy is the only confirmatory test), and complicated. However, the biggest disadvantage is that no tests could detect atrophy at the early stage.

Noncoding RNAs (ncRNAs) are a group of RNAs that is not translated into proteins. They function as gene regulators and are widely detected in tissue or in peripheral blood. Noncoding RNAs include microRNAs (miRNAs), long noncoding RNAs (lncRNAs), circular RNAs (circRNAs), etc. Previous studies have found several miRNAs could be candidate serum markers for muscle atrophy. Muscle-specific miRNAs have been proven to regulate muscle metabolism under different conditions [9]. In aging-related muscle atrophy, Let-7 family members including Let-7b and Let-7e were found to be increased compared to young individuals. Meanwhile the expression of cell cycle regulators was significantly downregulated [10]. A study discovered that miR-431 influenced muscle mass through promoting myoblast differentiation and modulating TGF-β downstream effectors [11]. miRNAs are also reported to involve in other muscle wasting conditions, such as regular catabolism, dexamethasone-induced atrophy, denervation injury, and even cancer [12]. Functional miRNAs in muscle atrophy mainly include miR-23a/206/499, miR-1, miR-133, miR-23a, miR-206, miR-27, miR-628, and miR-21 [13–15]. Among them, miR-29b was found to be commonly upregulated in different muscle wasting conditions, including denervation-induced, dexamethasone-induced,

fasting-induced, cancer cachexia-induced, aging-induced, and immobilization-induced muscle atrophy. Moreover, the expression of miR-29b is positively correlated with the degree of denervation-muscle atrophy [16]. Thus, ncRNAs might also be used to diagnose muscle atrophy.

Exosome was also shown to play important roles in muscle atrophy. Exosomes are vesicles measuring from 30 to 100 μm and able to carry many factors (RNA and protein) in the blood. They mediate cell–cell and tissue–tissue communication in an autocrine, paracrine, or endocrine manner [17]. Exosomes are nature reservoirs for signal factors, and they are detectable in the peripheral blood, which makes them ideal disease markers. In dexamethasone-induced muscle atrophy model, miR-23a is reported to participate in muscle atrophy through calcineurin/NFAT pathway. Dexamethasone increases concentration of miR-23a in the exosomes while it does not affect the number of exosomes [18]. Other studies showed a connection between exosomes secretion and malignancy-related muscle loss. Exosomes secreted by cancer cells carried miRNAs that function as apoptosis factors. miRNAs like miR-21, miR-182, and some other miRNAs from heart shock family were found to induce apoptosis in myocytes [19, 20]. Other noncoding RNAs, such as lncRNAs and circRNAs, were also reported to be contained in exosomes and contribute to various processes [21].

29.3 Pathways Regulating Muscle Atrophy

The major process during muscle atrophy is myofiber reduction, which is the result of excessive protein degradation. Current theory for these degradation pathways was the ubiquitin–proteasome system and the autophagy–lysosome pathway. Studies have been carried out to explore the regulating factors of these two pathways. Both of them could be triggered by stimulation like chronic inflammation and acute metabolic changes.

Ubiquitin–proteasome system (UPS) could degrade sarcomeric proteins in response to catabolic stimulate. UPS works through a series of enzymatic reactions involving activating (E1), conjugating (E2), and ligating (E3) enzymes [22]. Among them, atrogin-1/MAFbx (muscle atrophy F-box) and muscle RING finger 1 (MuRF1) are the main E3 ubiquitin ligases that play important roles in muscle atrophy. Genetic deficiency of either of these two genes showed a significant resistance to atrophy [2]. Likewise, their expressions were elevated in almost all types of muscle atrophy [23]. Other E3 ligating enzymes, such as Trim32 [24], TRAF6, ZNF216, USP14, and USP19 [25], were identified to function in muscle atrophy.

IGF1-PI3K-AKT pathway is the dominant pathway that mediates protein degradation. Catabolic signals inhibit this pathway by reducing the protein phosphorylation levels and then promote the proteolysis and depress protein synthesis. In addition, IGF1–PI3K–AKT–mTOR pathway and IGF1–PI3K–AKT–FoxO pathway also regulate the autophagy–lysosome systems [26–29].

Chronic inflammation influences myocyte metabolism through the interactions between different cytokines. Studies have found that interleukin 6 (IL-6) deficiency is associated with muscle atrophy [30, 31]. On the other hand, IL-6 induces myocyte proliferation through STAT3 signaling pathway, which occurs exclusively in the nuclei of satellite cells [32]. Other inflammatory pathway like IKKbeta/NF-kappaB/MuRF1 pathway was also found to regulate muscle atrophy [33].

Another way to disturb muscle volume is to inhibit muscle growth. Myostatin is the major autocrine inhibitor of muscle growth. It binds to the activin A receptor type IIB (ActRIIB) in skeletal muscle cells and activates transcription factors SMAD2 and SMAD3, thus suppressing muscle growth [34–37].

Catecholamine axis also contributes to the balance of muscle atrophy and growth. Deficiency of β2-adrenoceptors worsens skeletal muscle atrophy in patients with heart failure [38]. In cardiac muscle, sympathetic neurons control cardiomyocyte size by a β2-AR-dependent mechanism [39]. Further study showed this could be a result of its suppression effects on atrogin-1/MAFbx, which has been known as a muscle-specific ubiquitin ligase [40, 41].

Noncoding RNAs like miR-1, miR-1331a/b, miR-206, miR-146a, miR-221, miR-499, miR-208b, miR-486, and miR-29b, several long noncoding RNAs, and circRNAs are reported to contribute to muscle atrophy as well [42–44]. The fruitful achievements in the nucleic acid studies have led us to understand disease in a new way.

Even with these accomplishments, challenges still exist in the muscle atrophy field. First, functional noncoding RNAs are still to be studied. Second, epigenetic genes involving a serious of histone and DNA modifying enzymes have emerged as novel targets for the therapeutics purpose. They are widely studied in various fields, but little is known in muscle atrophy [45]. Third, current studies are mainly focused on the muscle cell itself, neglecting the cross talk between muscle cells and other factors, such as extracellular matrix, stem cells, and immune cells. Muscle atrophy always represents as a complication, which means it happens along with other diseases. For example, in cancer-induced muscle atrophy, cancer cells release exosomes which specifically interfere muscle cell growth. While under the condition of inflammation, muscle cells are influenced by inflammatory factors. Also, the biological process of muscle atrophy varies in different external conditions. For example, autophagy was considered as defense mechanism in fasting-induced muscle atrophy, but it causes damages in other scenarios [25, 46, 47]. Understanding this difference may be important for treatment of muscle atrophy. Finally, almost all previous study has stayed at the animal level. Translational research and clinical research need to be carried out in the future.

29.4 Therapeutic Approaches and Limits

Although a lot of basic research has been invested to treat muscle atrophy, there are no efficient drugs for neither prevention nor treatment of muscle atrophy [5]. Current standard treatments for muscle atrophy are nutritional supplement, physiologic therapy, and drug treatment.

29.4.1 Nutrition Treatment

Nutrition supplement provides energy for muscle activity directly and helps to maintain muscle mass. Increased consumption of calorie and protein could bring beneficial effects. In severely ill patients or those who suffer from muscle atrophy, some trials have shown that nutrition treatment improved life quality and long-term survival [48, 49]. In fact, many nutritional components were found to be beneficial to muscle atrophy (Table 29.1). But the effects might be only limited within patients who have primary muscle wasting [50].

29.4.2 Exercise Training

Physical therapy has been well studied to be effective in maintaining muscle strength [64, 65]. Exercise has also been considered as an effective way to promote muscle hypertrophy and muscle regeneration [66, 67]. In heart failure-induced muscle atrophy, aerobic exercise alleviates the process by reducing inflammatory reactions and decreasing ubiquitin-proteasome activities [68, 69]. Malignancy-related muscle

Table 29.1 Nutrition treatment used in muscle atrophy

Component	Muscle atrophy type	References
Protein	Sarcopenia	[51]
	Heart failure	[52]
Essential amino acid	Sarcopenia	[53]
	Heart failure	[52]
β-Hydroxy β-methylbutyrate (HMB)	Cancer	[54]
	AIDS	[55]
	Chronic obstructive pulmonary disease	[56, 57]
	Sarcopenia	[58]
	Immobilization	[59]
Vitamin D	Sarcopenia	[60]
	Cancer cachexia	[61]
Allopurinol	Sarcopenia	[62]
	Unloading	[63]

atrophy could also benefit from exercise therapy. Apart from suppressing inflammation, exercise promotes the mitochondrial biogenesis via peroxisome proliferator-activated receptor (PPAR)-γ coactivator-1α (PGC-1α) pathway [70–74]. In addition, exercise training inhibits myocyte autophagy [73]. Unfortunately, exercise therapy cannot be applied to everybody. It has limited effects on patients who are immobilized on the bed or patients who have nerve injury. Moreover, certain patients with severe muscle atrophy cannot tolerate exercise therapy.

29.4.3 Drug Treatment

Based on the prior studies, current drug treatment for muscle wasting mainly focused on improving appetite, modulating inflammation, and interfering with anabolic and catabolic reactions. Table 29.2 summarized the candidate medications and its therapeutic targets. However, no medications have been approved to be effective in clinical trials so far.

29.5 New Therapeutic Strategy

Due to the advance of new technologies and theories, novel treatment strategies have sprung up.

29.5.1 Noncoding RNAs

With the development of next-generation deep sequencing, the research on gene regulation transfers from genome to transcriptome. Researches on RNA field have been developed unprecedentedly. Unlike protein-coding genes, noncoding RNAs are the ones which lack the ability to code protein. They were once considered as "evolutionary junk," until later on it was discovered that these group of RNAs had tremendous effects on regulating gene expression. Current well-defined noncoding RNAs include ribosomal RNAs (rRNAs), transfer RNAs (tRNAs), long noncoding RNAs (lncRNAs), microRNAs (miRNAs), circular RNAs (circRNAs), and other small RNA-related molecules. Great achievements have been made in exploring the functions of these RNAs. Some of the noncoding RNAs have already been studied in clinical trials. For instance, liposomal miR-34 mimic was used to repress oncogene expression, and its ability to shrink tumor size has been proved [102]. On the other hand, miRNA antagomirs, such as anti-microRNA oligonucleotides (AMOs) and N,N-diethyl-4-(4-nitronaphthalen-1-ylazo)-phenylamine ("ZEN"), are used to downregulate certain miRNAs [103, 104]. The use of antisense RNA in long noncoding RNA interference has showed a significant value in

Table 29.2 Studies of agents with potential efficacy in muscle atrophy

Disease process	Drug/compound	Target	References
Cancer cachexia	Thalidomide	TNF-α	[75]
	ALD-518	IL-6	[76]
	RC-1291	Ghrelin mimetic	[77]
	RC-1291	Ghrelin receptor agonist	[78, 77]
	Celecoxib	COX-2	[79]
	BYM338	Myostatin and the activin type II B receptor (ActRIIB)	[26]
	MG132	Ubiquitin–proteasome system	[80]
	Myostatin-specific antibody	Myostatin	[81, 82]
Heart failure	JA-16	Myostatin	[83]
	Salbutamol	β2-Agonists	[84]
	Clenbuterol	β2-Agonists	[85]
	Testosterone	Testosterone	[86, 87]
	Selective androgen receptor modulators (SARMs)	Hormonal	[88]
	Ghrelin agonist	Ghrelin	[89] [90]
Sarcopenia	Metformin	/	Clinical Trials NCT01804049
	Incretins	Enzyme dipeptidyl peptidase IV	[91]
	Statins	Glucose oxidation	[92]
	Allopurinol	Xanthine oxidase (XO)	[62]
	Formoterol	β2-adrenoceptor	[93]
	Myostatin-specific antibody	Myostatin	[94]
Chronic obstructive pulmonary disease (COPD)	Ghrelin/GH/IGF-axis Ghrelin	Stimulates GH secretion	[95]
	SUN11031	Synthetic ghrelin	[96, 97]
	NAC	ROS scavenger	[98]
	α-lipoic acid	ROS scavenger	[99]
Renal failure	Myostatin-specific peptibody	Myostatin	[100]
	C188-9	STAT3	[101]

treating myocardial hypertrophy and fibrosis [105–107]. Besides, miR-1, miR-133, miR-23a, miR-206, miR-27, miR-628, miR-431, miR-21, and miR-29b are considered to be the therapeutic target for muscle atrophy. miR-29b was an increased miRNA in multiple types of muscle atrophy, and miR-29b inhibition could relieve muscle atrophy [11, 108–113].

29.5.2 Gene Therapy

In the last few years, targeted genome-editing technology has developed. Among them, clustered regularly interspaced short palindromic repeats (CRISPR) are well studied and applied in clinical trials. This is a highly versatile system, which is derived from a prokaryotic adaptive immune system. In bacteria, CRISPR/Cas system captures and avoids the invasion of foreign DNA via RNA-guided DNA cleavage [114]. The recently developed CRISPR–Cas9 system has two biological components: the RNA-guided DNA endonuclease Cas9 and a chimeric single guide RNA (sgRNA) [115–119]. The guide RNA binds Cas9 with one end, and the other end recognizes the target DNA sequence by base pairing. This system has been applied to modify endogenous genes in a wide range of organisms, including bacteria, yeast, plants, fruit flies, zebrafish, frogs, rabbits, mice, rats, pigs, dog, sheep, goat, monkeys, and human cells [120].

This technique can be applied to various research fields. In cancer, CRISPR/cas9 was used to produce the next-generation chimeric antigen receptor T cells (CAR-Ts), which have potential effects in cancer treatment [121, 122]. CRISPR/Cas9 was also used to disturb HIV duplication by targeting LTR sequence [123]. Additionally, CRISPR/Cas9 disrupts rs1421085 of FTO region and thus restores thermogenesis and opposes obesity [124].

CRISPR is widely used in muscle atrophy studies as well. CRISPR was used to knock out myostatin in dog, goat, pig, sheet, and rabbit and thus induce typical muscle hyperplasia or hypertrophy in vivo [125–132]. This highlights the hope in muscle atrophy treatment. Interestingly, CRISPR/Cas9 was used to target myostatin in cancer-related cachexia [133]. Insulin-like growth factor-1 (IGF1) and FGF5 are also potential targets for muscle atrophy treatment [134, 135].

Another strategy used in gene therapy is gene transfer vectors. Vectors transport genes to target cells. They are usually adeno-associated virus (AAV) – a group of viruses that cause low risk of genotoxicity [136]. Plus, they have long-term stable transgene expression [137]. Preclinical and clinical studies have been carried out using AAV as tools to deliver therapeutic genes [138–140]. In muscle atrophy, AAVs like rAAV6 and AAV2/9 have been used to deliver microutrophin to improve muscle function [141, 142]. In neurogenic muscle atrophy, AAVs containing neurotrophin3 were injected in the mouse model. Reevaluation showed an increased muscle fiber size as well as a change in oxidative state [143]. In malignancy-related striated muscle wasting, Smad7 gene delivery by rAAV6 was able to inhibit the expression of atrophy-related ubiquitin ligase MuRF1 and MAFbx through ActR2b pathway [144, 145]. Similarly, other studies with therapeutic genetic molecules carried by AAVs validated their efficacy by checking downstream factors like vascular endothelial growth factor (VEGF), sarcoplasmic reticulum Ca^{2+} ATPase 1 (SERCA), and β2-adrenoceptor or associated Gα proteins [146–148].

Lack of clinical trials is the main disadvantage of gene therapy. Safety issues with these therapies remain unknown since current studies mainly focus on the positive effects on muscle atrophy. More studies need to be carried out for safety and capability.

29.5.3 Stem Cell Therapy

Stem cell therapy (also called cellular therapy or cytotherapy) refers to a process during which cellular material is injected to treat disease. The effectiveness of stem cell therapy has been studied in a variety of diseases [149–155].

Satellite cell is the original stem cell in muscle tissue. These cells are usually located between muscle fiber or in basal lamina. Under normal conditions, they are naturally quiescent. They start to actively proliferate and differentiate to compensate muscle fibers loss in response to stimuli. In a healthy individual, the compensation is usually adequate. However, in patients with muscle atrophy, the self-renewal capacity of satellite cell was significantly decreased [156, 157]. Hence, increasing satellite cells or enhancing the functions of them could potentially solve the problem of atrophy. Studies have been conducted to transplant myogenic stem cells into atrophied muscle. Promising results have been observed in some studies, showing the tremendous capacity of regenerating new muscle fibers and fusion with the host myofibers after transplantation [158–161]. Unlike skin or adipose tissue transplantation, technical difficulty complicates muscle fiber grafting and makes it difficult to apply in clinical practice. Other stem cells, such as mesenchymal stem cells [162, 163], iPSCs [164], pericytes [165], and endothelial cells [166], could also be used as stem cell therapy.

29.6 Conclusions and Remarks

Muscle atrophy is one of the most common and devastating events in chronic diseases. Unlike the diseases that cause muscle atrophy, muscle atrophy itself is not life-threatening. But it can lead to devastating consequences including but not limited to osteoporosis, blood clot, pressure ulcer, and, more importantly, psychological effects. Preventing muscle atrophy can prolong the patient's life span and improve life quality. However, studies exploring the biology nature and molecular mechanisms of muscle atrophy only started in the recent two decades. Our knowledge in this field is way lag behind compared to other diseases.

We have made a great number of achievements in learning this disease in the recent years. Challenges still exist. Lacking appropriate markers make it hard to monitor muscle atrophy. As we have discussed in this chapter, either proteins or noncoding RNAs could be a candidate to indicate muscle atrophy, but more clinical trials need to be conducted. The causes of muscle atrophy are multifactorial which makes the treatment more complex. In the future, gene therapy and stem cell therapy will be applied in muscle atrophy treatment.

Competing Financial Interests The authors declare no competing financial interests.

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