Molecular Therapy
Nucleic Acids
Review

Non-coding RNA basis of muscle atrophy

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Muscle atrophy is a common complication of many chronic diseases including heart failure, cancer cachexia, aging, etc. Unhealthy habits and usage of hormones such as dexamethasone can also lead to muscle atrophy. However, the underlying mechanisms of muscle atrophy are not completely understood. Non-coding RNAs (ncRNAs), such as microRNAs (miRNAs), long ncRNAs (lncRNAs), and circular RNAs (circRNAs), play vital roles in muscle atrophy. This review mainly discusses the regulation of ncRNAs in muscle atrophy induced by various factors such as heart failure, cancer cachexia, aging, chronic obstructive pulmonary disease (COPD), peripheral nerve injury (PNI), chronic kidney disease (CKD), unhealthy habits, and usage of hormones; highlights the findings of ncRNAs as common regulators in multiple types of muscle atrophy; and summarizes current therapies and underlying mechanisms for muscle atrophy. This review will deepen the understanding of skeletal muscle biology and provide new strategies and insights into gene therapy for muscle atrophy.

INTRODUCTION

The Human Genome Project reports that about 80% of human DNAs are transcribed into RNAs, of which only 2% are translated into proteins; most of the rest are classified as non-coding RNAs (ncRNAs).[1] According to their length, ncRNAs can be further classified as smaller ncRNAs (such as microRNAs [miRNAs] and piwi-interacting RNAs) and longer ncRNAs (such as long ncRNAs [lncRNAs] and circular RNAs [circRNAs]). miRNAs consist of approximately 22 nucleotides, whereas lncRNAs consist of over 200 nucleotides.[2] They can also be classified according to their functions, such as housekeeping ncRNAs and regulatory ncRNAs. Housekeeping ncRNAs include ribosomal RNAs, small nuclear RNAs, small nucleolar RNAs, and transport RNAs. Regulatory ncRNAs include miRNAs, lncRNAs and circRNAs.[3]

miRNAs are single-stranded ncRNAs that consist of approximately 22 nucleotides. They are encoded by endogenous genes and are largely evolutionarily conserved.[4] The classical miRNA biogenesis pathway can be divided into three stages: pri-miRNA generation, pre-miRNA generation and nucleation, and mature miRNA generation.[5] miRNAs inhibit translation by negatively regulating or degrading target genes at the post-transcriptional level.[6–8] On the other hand, miRNAs can also enhance target gene translation in other contexts. AGO2-FXR1-iso-a complex is important in selective recruitment for miRNA-mediated upregulation of target genes.[9–13] miRNAs play important roles in cell proliferation, differentiation, metabolism, and apoptosis.[14,15] At the present time, many changes in miRNAs' expression profiles in patients with muscle atrophy have been documented, and a variety of miRNAs involved in muscle atrophy have been identified. Therefore, miRNAs are expected to become new diagnostic markers and therapeutic targets of muscle atrophy.

lncRNAs are ncRNAs with lengths over 200 nucleotides. Based on the transcription sources, lncRNAs can be further divided into intergenic lncRNAs, intron lncRNAs, bidirectional promoter lncRNAs, antisense lncRNAs, enhancer lncRNAs, and sense strand or antisense strand lncRNAs.[16] lncRNAs are common in cells and participate in a variety of biological processes such as RNA processing,[17] gene transcription regulation,[18] chromatin modification,[19] epigenetics, cell cycle, and cell differentiation.[20] lncRNAs have been reported recently to be involved in muscle atrophy by regulating key pathways and core proteins. Smad ubiquitin regulatory factor 2 (SMURF2) upstream lncRNA (lncSMUL) was found to promote myoblast proliferation, suppress myoblast differentiation *in vitro*, induce muscle atrophy, and promote slow-twitch fibers' switch to fast-twitch fibers *in vivo* via the SMURF2/transforming growth factor β (TGF-β)/SMAD pathway.[21]

Skeletal muscle is composed of a variety of cells such as muscle fibers, stem cells, progenitor cells, fibroblasts, muscle satellite cells, etc. Skeletal muscle accounts for 30% to 50% of healthy body weight and is the largest tissue in the body. It is mainly responsible for body movement, protein storage, thermogenesis, metabolism, and internal organ protection.[22] When muscle dysplasia or pathological changes occurs, they lead to muscle atrophy, which manifest as loss of muscle mass and strength.[23] Muscle atrophy often occurs in the elderly, but also

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secondary to chronic heart failure, cancer, chronic obstructive pulmonary disease (COPD), peripheral nerve injury (PNI), chronic kidney failure, and hepatic fibrosis.[24] Usage of hormones such as dexamethasone (Dex), long-term inactivity, excessive fasting, weightlessness, and hibernation can also lead to muscle atrophy. Muscle atrophy significantly reduces the quality of life of patients and increases the incidence of the pathology and mortality.[25] Therefore, investigating the underlying mechanism of muscle atrophy is of great significance to human health.

The pathogenesis of muscle atrophy is mainly related to the disorder of protein synthesis and catabolism. Protein anabolism is mainly regulated by the insulin-like growth factor-1 (IGF-1-phosphatidylinositol 3-kinase (PI3K)-protein kinase B (PKB; also called AKT) signaling pathway.[26–28] The main pathways of protein catabolism include the ubiquitin proteasome system (UPS), autophagy lysosome pathway, and caspase system. UPS can be stimulated by catabolism to degrade muscle protein. Muscle ring finger 1 (MuRF1) and muscle atrophy-related F-box (MAFbx/atrogin-1) are ubiquitin ligases. It has been found that mice deficient in MuRF1 or MAFbx were resistant to muscle atrophy. Furthermore, MuRF1 and MAFbx expressions are increased in almost all types of muscle atrophy, showing their reliability as markers of skeletal muscle atrophy.[29,30] There are two ways to encourage the expression of MuRF1 and MAFbx: the nuclear factor κB (NF-κB)-tumor necrosis factor α (TNF-α) and TNF-like weak inducer of apoptosis (TWEAK)–factor-inducible 14 (FN14) pathways. NF-κB is a key intracellular signal transmitter of muscle atrophy and promotes the secretion of myostatin.[31] Myostatin is a negative regulator of muscle mass, leading to muscle atrophy through a myogenic determination gene (such as MyoD and myogenin). The TWEAK-FN14 pathway is a recently discovered cytokine signal transduction pathway in the pathogenesis of muscle atrophy, which functions by inducing the expression of MuRF1 and MAFbx.[32,33]

Increased autophagy in skeletal muscle leads to muscle atrophy. It has been found that forkhead box protein O3 (FoxO3) induces the expression of many autophagy-related genes and enhance autophagy in skeletal muscle cells.[34,35] Additionally, FoxO3 can also activate the transcription of E3 ubiquitin ligase MuRF1 and MAFbx, which leads to muscle atrophy.[36,37] Apoptosis is another molecular mechanism involved in muscle atrophy, which is mediated by caspase-3 activity.[38] Oxidative stress, characterized by increased production of reactive oxygen species (ROS) and dysregulation of an antioxidant defense system, is a major trigger factor of muscle atrophy, cascading an imbalance of protein synthesis and metabolism. In skeletal muscle, high levels of ROS can promote the activation of proteolysis and cause mitochondrial dysfunction, both of which contribute to muscle atrophy.[39–41]

ncRNAs affect growth and development of skeletal muscle by regulating key genes that control muscle biology. ncRNAs, as key regulators in physiologic and pathologic processes, are closely related to muscle atrophy. Abnormal expression of selected miRNAs (such as miR-29b, miR-133a, etc.) and lncRNAs is involved in the onset and development of muscle atrophy. Muscle-specific knockout of Dicer can lead to increased muscle cell apoptosis, abnormal muscle fiber morphology, and muscle mass reduction,[42] which indicates that miRNAs are indispensable regulators of skeletal muscle development.

Skeletal muscles are composed of distinct muscle fiber types, which determine the unique muscles' functions and metabolisms. Type myosin heavy chain (MyHC) I is a type of slow muscle fiber, whereas types MyHC IIA and MyHC IIB are fast muscle fibers. Type I and type IIA muscle fibers are rich in myoglobin and mitochondria with consequently high oxidative capacity, whereas type IIB primarily generates ATP through glycolysis. The fourth type of muscle fibers, highly glycolytic MyHC IIX fibers, are relatively rare in healthy humans.[43,44] Numerous studies have found that muscle atrophy is often accompanied by the transition of skeletal muscles from slow to fast fibers. Through deep mRNA sequencing of samples from the soleus (typically consisting of slow-twitch fibers) and quadriceps (typically consisting of fast-twitch fibers) of the hind limb, it was found that alternative splicing, alternative poly-adenylation (APA), and muscle-specific transcription factors were not correlated with the vast differences of gene expression in these two muscle groups, whereas specific ncRNAs, especially muscle-specific miRNAs and lncRNAs, were closely correlated with a muscle type-specific RNA landscape and involved in a classic signaling pathway of muscle atrophy such as calcineurin/NFAT, peroxisome proliferative activated receptor gamma coactivator 1 alpha (PGC1a)/myocyte enhancer factor 2 (MEF2), NF-κB/atrogin, TGF-β, and autophagy.[44–47] ncRNAs function differently in fast and slow muscles or myofibers, which may impact potential therapeutic strategies, as the same miRNA can have different functions in different myofibers or muscle types.

This in-depth review of ncRNAs is expected to provide new clues for understanding the pathogenesis of muscle atrophy and discovering new strategies for clinical treatment thereof. As shown in Figure 1, this review mainly discusses the regulation of miRNAs and lncRNAs in muscle atrophy induced by different stimulations, aims to deepen the understanding of skeletal muscle biology, and offers new methods and ideas for gene therapy of muscle atrophy.

ncRNAs IN MUSCLE ATROPHY INDUCED BY HEART FAILURE

Skeletal muscles play important roles in maintaining overall health of the human body by interacting and communicating with multiple organs. Chronic heart failure, a common final destination for deteriorating hearts with various cardiovascular diseases, has been found to be closely related with the development of muscle atrophy.[48] Accumulating evidence has implicated that chronic heart failure promotes muscle atrophy through multiple pathological mechanisms, including hormone changes (such as angiotensin II (AngII), and myostatin), inflammation, oxidative stress, and apoptosis.[49]

ncRNAs, especially miRNAs, play essential roles in regulating both cardiac and muscle function.[5] miR-29b has been showed to promote many types of muscle atrophy including heart failure-induced muscle

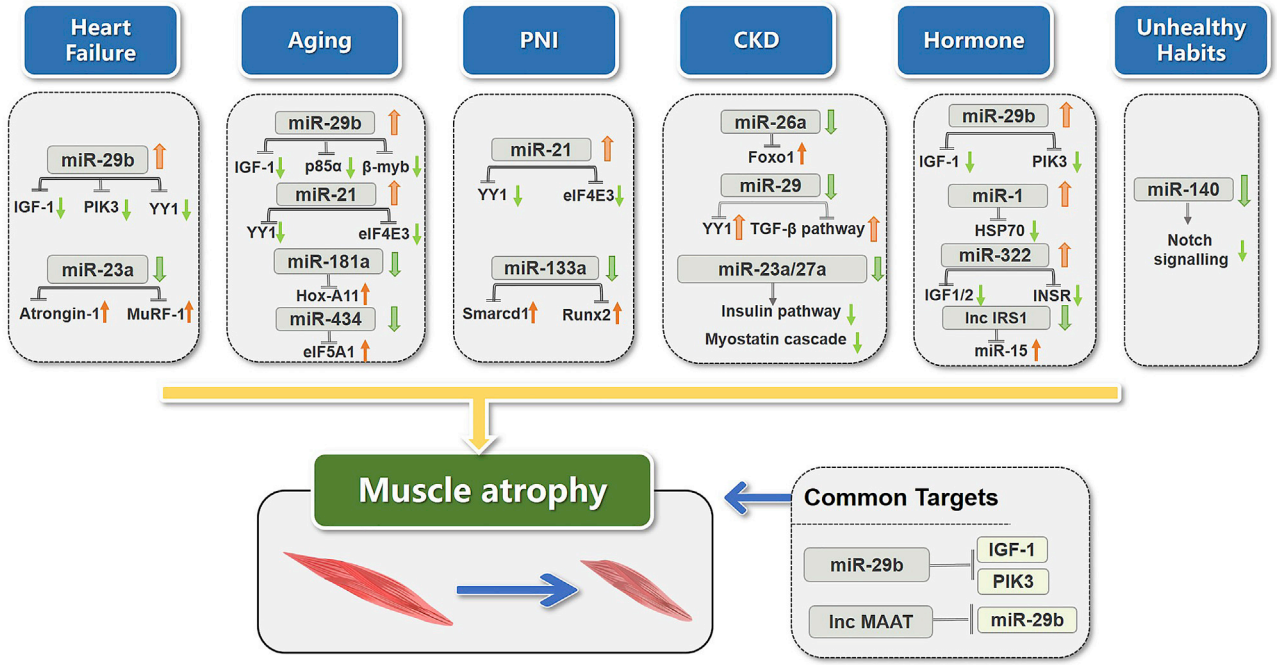

Figure 1. Different inducers lead to muscle atrophy through ncRNAs

wasting via regulating target genes IGF-1, PI3K, and YY1.[50,51] Peroxisome proliferator activated receptor gamma (PPARγ) was found to inhibit AngII-induced muscle atrophy and improve muscle function by targeting and downregulating miR-29b;[51,52] similarly, inhibition of miR-29b by the CRISPR-Cas9 editing system significantly attenuated AngII-induced muscle atrophy *in vivo*.[53] It is noteworthy that several muscle-specific miRNAs, including miR-1, miR-133a, miR-133b, miR-208a, and miR-208b, have been found to be involved in the regulation of both cardiac and skeletal muscle functions.[54–56] miR-23a was reported to play a role in cardiac hypertrophy, in which it was identified by a bioinformatics approach to negatively regulate muscle atrophy through inhibiting atrogin-1 and MuRF1 expression. Likewise, the overexpression of miR-23a in mice attenuated Dex-induced muscle atrophy.[57,58] Further studies are still needed to elucidate the roles and mechanisms of ncRNAs in the regulation of heart failure and muscle atrophy, which may provide valuable therapeutic targets to counteract related diseases.[59]

ncRNAs IN MUSCLE ATROPHY INDUCED BY CANCER CACHEXIA

Cachexia is an energy-wasting syndrome, with disturbed energy balance, decreased energy intake, and increased energy expenditure. It is usually associated with progressive weight loss, skeletal muscle wasting, and impaired muscle function.[60,61] About 50% to 80% of cancer patients present with cachexia, which accounts for 20% to 40% of cancer patient deaths. One of the hallmarks of cachexia is skeletal muscle loss, characterized by increased muscle loss, decreased myofibrillar proteins, and reduced myofiber size, but not myofiber number.[62]

Research studies with experimental muscle atrophy models have been conducted to identify miRNAs involved in cachexia-associated muscle mass loss.[63] Muscle-specific miRNAs, also called myo-miRNAs, include miR-1, miR-133a, miR-133b, miR-206, etc. have been characterized as essential contributors to myogenesis and muscle homeostasis. By using the TaqMan Human microRNA Array, 754 unique miRNA expression patterns were generated from vastus lateralis muscle biopsies collected from 8 cachexic patients with newly diagnosed lung cancer and 8 age- and sex-matched controls. 28 miRNAs were identified to be differentially expressed in cachexic lung cancer patients.[64] The majority of changed miRNAs was downregulated, whereas 5 miRNAs were upregulated. Of the upregulated miRNAs, miR450a-5p, miR-450b-5p, miR-424-5p, and miR-424-3p belong to the same miRNA cluster. Six top-ranked miRNAs was selected based on their expression differences and relevance in muscle mass modulation (four upregulated and two downregulated miRNAs) for a subsequent study, which compared the miRNA expression patterns between lung cancer patients with and without cachexia and healthy controls with qPCR. Among the miRNAs compared, miR-450b-5p expression levels could not be reliably detected (qPCR Cycle > 40) and hence were not considered for further analyses. Meanwhile, miR-424-5p, miR-424-3p, and miR-450a were significantly increased, whereas miR-451a and miR-144-5p were clearly decreased in cachectic lung cancer patients. Additionally, miR-451a and miR-144-5p downregulation seemed to be specific to lung cancer cachexia, whereas miR450a-5p, miR-424-3p, and miR-424-5p upregulation may be involved in the development thereof.

The miRNA profiles of skeletal muscle cells from cachexic lung cancer mice and control mice were investigated by Ingenuity Pathway

analysis. 371 miRNAs were found to be present in the tested skeletal muscles, of which 9 miRNAs (miR-147-3p, miR-299a-3p, miR-1933-3p, miR-511-3p, miR-3473d, miR-233-3p, miR-431-5p, miR-665-3p, and miR-205-3p) were revealed to be differently expressed. The 9 altered miRNAs were categorized by their significant gene functions, which were cancer oncogenesis, cell-to-cell signaling, and cellular development.[65]

Another study performed a meta-analysis with previously published gene-expression data to reveal the role of miRNA-regulated networks of cachexic muscle atrophy in cancer patients.[66] The miRNA-mRNA interactions, predicated through the meta-analysis, contribute to muscle atrophy in cancer cachexia, such as miR-27a/Mef2c, miR-27a/Foxo1, miR-140/cxcl12, miR-199a/junb, miR-199a/cav1, miR-27b/MSTN, miR-27b/Mef2c, and miR-27b/Cxcl12. The identification of these miRNA-mRNA interactions may help to discover novel therapeutic targets.

ncRNAs IN MUSCLE ATROPHY INDUCED BY AGING

Skeletal muscles undergo a declining change in older adults through loss of mass and function deterioration, which in turn affects their mobility and quality of life. Age-related muscle-wasting and function decline develop gradually over several decades, with 1%–2% muscle loss per year in adults over 30 years old.[67,68] Muscle atrophy is also known as sarcopenia in the elderly population with approximately 5%–13% prevalence over 60 years,[69] caused by numerous factors such as stem cell exhaustion, inefficient anabolic hormones, mitochondrial dysfunction, chronic inflammation, insulin resistance, oxidative stress, cellular senescence, metabolic impairment, inefficient amino acid intake, and decreased physical activity.

Previous studies have demonstrated that ncRNAs play critical roles in the regulation of age-associated muscle degeneration and sarcopenia.[70] Among the multiple types of ncRNAs, miRNAs are the most extensively studied. A subset of miRNAs including miR-127 (by targeting S1PR3),[71] miR-410 (by targeting sFRP2),[72] miR-431 (by targeting Smad4),[73] miR-433 (by targeting sFRP2),[72] and miR-434 (by targeting eIF5A1)[74] is clustered within the delta-like homolog 1 (Dlk1) and the type III iodothyronine deiodinase (Dio3) genomic region, which were found to be downregulated in aged mouse skeletal muscle and involved in the regulation of muscle regeneration and myogenic differentiation.

Differentiated myotubes were treated with 42 miRNA mimics to examine the anti-atrophic effects of miRNAs. Of the top five candidates of miRNAs that most obviously increased myotube diameter *in vitro* (miR-377, miR-495, miR-1197, miR-379, and miR-376c) in the DLK1-Dio3 cluster, miR-376c-3p was found to be the most significantly decreased one in the aged tibialis anterior (TA) muscle. Meanwhile, overexpression of miR-373c-3P attenuated muscle atrophy via targeting atrogin-1 and is thereby considered a valuable therapeutic target to combat sarcopenia. The 5 miRNAs (miR-377, miR-495, miR-1197, miR-379, and miR-376c) that were downregulated in aged mice were also negatively correlated with age in the gluteus maximus muscles from humans.[75] When the primary miRNA (pri-miRNA) and mature miRNA expression levels were compared among six elderly (70 ± 2 years) and six younger (29 ± 2 years) men in a study of skeletal muscle biopsies, it was found that pri-miRNA-1-1, pri-miRNA-1-2, pri-miRNA-133a-1, and pri-miRNA-133a-2 were upregulated in the elderly; however, mature miRNA-1 and miRNA-133a were not disturbed.[76,77]

Another study was performed among 109 non-sarcopenic and 109 sarcopenic subjects to ascertain whether the expressions of miR-1, miR-133a, miR-133b, miR-206, miR-208b, and miR-499 are age associated.[78] Lower levels of miR-133b and miR-206 were found to be closely related with poor nutritional statuses and the presence of sarcopenia. Aging is associated with increased inflammation and enhanced circulating inflammatory cytokines such as TNF-α and interleukin (IL)-6.

miR-21, a proposed circulating marker of inflammation in aging, may be trigged by elevated TNF-α and IL-6 in satellite cells and myofibers. Inhibition of miR-21 in muscle satellite cells from elderly mice has been found to exert beneficial effects on myogenesis and could improve the decreased myotube size *in vitro*.[79]

miR-434-3p was significantly downregulated in the skeletal muscles of aging mice. miR-434-3p was observed to inhibit apoptosis, prevent the activation of pro-apoptosis proteins including caspase-3 and caspase-9, and improve the mitochondrial transmembrane potential by targeting the eukaryotic translation initiation factor 5A1 (eIF5A1).[74]

miR-29b was significantly upregulated in muscles of aged rodents compared with their young counterparts, which was considered to be a potential mechanism of sarcopenia. miR-29b in muscle progenitor cells (MPCs) was stimulated by wnt-3a in muscle senescence, as evidenced by reduced expressions of several singling proteins including p85α, IGF-1, and β-myb. Increased levels of miR-29b coordinately impaired MPC proliferation and promoted muscle atrophy.[80]

Mitochondrial dysfunction is present in aged muscles and is an important risk factor of sarcopenia. miR-181a has been characterized as an intrinsic positive regulator of mitochondrial dynamics through regulating Park2, p62/SQSTM1, and DJ-1. Downregulation of miR-181a during aging was found to increase mitochondria abnormality and activate autophagy-related proteins; meanwhile, restoration of miR-181a expression improved mitochondrial dynamics and muscle function.[81]

Recently, many types of lncRNAs, such as MAR1, MUMA, insulin receptor (INSR) substrate 1 (IRS1), Malat1, and lncR-12b, were observed to participate in muscle differentiation and muscle regeneration.[82] DLEU2, a lncRNA, was found to negatively regulate skeletal muscle regeneration and differentiation, acting as a sponge of miR-181a that inhibits its expression and promotes SEPP1 expression.[83] Correlation analysis of the risk of sarcopenia with the expressions of lncDLEU2,

SEPP1, and miR-181a found that the lncDLEU2-miR-181a-SEPP1 signal was closely associated with the prevalence of sarcopenia and thus could be developed as a highly accurate, predictive tool of sarcopenia risk.[83]

Circulating miRNAs (c-miRs) are related to aging-associated processes including chronic inflammation and cellular senescence.[84] However, the underlying mechanism of c-miRs in regulating aging-associated muscle atrophy still need to be further studied. An investigation with 77 eligible older adults divided into three groups (one normal group and two sarcopenic groups according to their muscle loss and function) showed that myo-related c-miR-486 and inflammation-related miR-146a expression was decreased in the sarcopenic group and was positively correlated with the skeletal muscle mass index (SMI). c-miR-486 was increased in skeletal muscle and regulated myoblast differentiation by targeting Pax7.[85] c-miR-486 reduced phosphatase and tensin homolog (PTEN) and FoxO1a but activated the PI3K/AKT signaling pathway, which is one of the most important signaling cascades' protein synthesis regulation.[86,87] miR-146a has been found to regulate mitochondria NADPH oxidase 4 expression and modulate oxidative status and cellular senescence.[88] On the other hand, the inhibition of miR-146a was correlated with increased mitochondrion ROS production-related oxidative damage in the aging process.[89] Therefore, lower c-miR-486 and c-miR-146a may impair skeletal muscle function during the course of sarcopenia, suggesting that c-miR-486 and miR-146a could serve as potential biomarkers of sarcopenia.

ncRNAs IN MUSCLE ATROPHY INDUCED BY COPD

COPD, induced by air pollution, smoking, or chronic lung infections etc., is characterized by progressive airflow limitation and usually leads to many types of comorbidities, such as muscle atrophy.[90] One-third of patients with COPD exhibits quadriceps muscle dysfunction even at the early stage of COPD. Furthermore, limb muscle function and muscle mass loss serve as important predictors of COPD mortality.[91]

ncRNAs contribute to muscle dysfunction and muscle loss in patients with COPD.[91] 31 patients with COPD and 14 healthy age-matched controls were recruited to a study of muscle-specific miRNA expressions, which found that the myocardin-related transcription factor (MRTF)/serum response factor (SRF)/miR-1 axis was downregulated in the quadriceps of patients with COPD, whereas its downstream targets, IGF-1 and histone deacetylase 4 (HDAC4) were upregulated, which may contribute to COPD-related muscle dysfunction.[92]

In another study, 41 patients with COPD were randomized to two groups: with or without muscle weakness. These two groups, together with 19 healthy controls, were studied to measure the differences in the expression of muscle-enriched miRNAs. miR-1, miR-206, and miR-27a were increased in the vastus lateralis in all COPD patients with severe muscle weakness, whereas their target genes were decreased including the miR-1 target HDAC4 and miR-27a target Pax3. However, SRF expression was upregulated, and the sizes of fast-twitch myofibers were clearly reduced.[91] Further studies are still need to characterize the varying expression patterns of the epigenetic profiles in different muscles and their contribution to muscle weakness in COPD patients.

The expression levels of muscle-specific miRNAs such as miR-1, miR-499, miR-133, and miR-206 were tested in the blood of 103 COPD patients and 25 age-matched healthy controls. The plasma levels of all of these myo-specific c-miRNAs were increased in patients with COPD in distinct patterns, which may be closely related to muscle turnover. miR-1 was negatively correlated with fat-free mass (FFM) in the cohort. miR-499 was associated with strength and the proportion of quadriceps type I fibers, whereas plasma miR-499 was correlated with the muscle NF-κB p50 subunit but not the p65 subunit in patients with COPD in the early stage. miR-206 was associated with plasma inflammatory cytokines in patients with more advanced disease.[93] A PCR screening of 750 miRNAs in a small group of COPD patients' low FFM phenotype found that an increased level of miR-675/H19 might be associated with a low FFM index (FFMI) in these patients.[94]

ncRNAs IN MUSCLE ATROPHY INDUCED BY PNI

PNI, defined as damage or destruction of peripheral nerves, always causes skeletal muscle atrophy. The functional recovery of target muscle is usually poor due to the slow rate of axon regeneration. Axon continuity is interrupted when nerve damage occurs, which is the underlying etiology of skeletal muscle fibers' loss and progressive muscle atrophy.[95] Current studies have shown that ncRNAs play vital roles in denervation-induced skeletal muscle atrophy. Furthermore, studies focused on the whole transcriptome involved in denervated muscle atrophy after PNI also detected significant expression changes in ncRNAs in the gastrocnemius muscle.[96] Denervation alters the expression of myofiber-derived miRNAs, including miR-206, miR-1, miR-133a, miR-22, miR-378, miR-720, etc.[97] It is reported that miR-1 plays an important role in myoblast differentiation by regulating the Notch3 signaling.[98] Exosomes released by myofibers lead to the reduction of miR-133a targets, proteins Smarcd1 (BAF60 variants a) and Runx2 (Runt-related transcription factor 2) in NIH 3T3 cells, indicating that these exosomes have biological activity.

miR-22 has been reported to regulate vascular smooth muscle cell phenotype switching via modulating the EVI1 (ecotropic virus integration site 1) protein homolog. However, studies focused on the regulatory mechanism of miR-22 in denervation-induced skeletal muscle atrophy are limited. miR-378 is found to promote myogenesis via targeting the myogenic repressor MyoR.[99]

Studies focused on denervation-induced muscle atrophy also identified two denervation-induced miRNAs, miR-206 and miR-21, which targeted transcription factor Yin Yang 1 (YY1) and translational initiator factor eIF4E3.[100] Overexpression of these two miRNAs *in vivo* led to muscle atrophy, whereas their inhibition reduced denervation-induced muscle loss. However, whether miR-206 contributes

to denervation-induced muscle atrophy remains controversial. Another research group showed that the overexpression of miR-206 in muscle significantly prevented muscle loss in denervation-induced skeletal muscle atrophy.[101] miR-206 functions by promoting the differentiation of satellite cells, thus preventing skeletal muscle atrophy. The controversial role of miR-206 may partly be due to differences in experimental conditions, such as variances in animal models. Thus, further study is needed to explore the specific mechanism of miR-206 in denervation-induced muscle atrophy.

lnc-miR22hg promoted myoblast differentiation *in vitro*, whereas its knockdown aggravated TA muscle injury induced by 1.2% $BaCl_2$ injection and promoted muscle mass loss *in vivo*, achieved by encouraging miR-22-3p maturation while inhibiting its target HDAC4 and increasing the downstream MEF2C.[102] lncRNA Pvt1 was recently characterized to modulate denervation-induced muscle atrophy, whereas its downregulation attenuated denervation-induced muscle atrophy *in vivo* via regulating mitochondrial respiration and morphology, apoptosis, and autophagy *in vivo*.[103]

As shown in Tables 1 and 2, we summarize the upregulated and downregulated ncRNAs in muscle atrophy induced by various factors. However, studies on the regulatory roles of ncRNAs in the pathogenesis of denervated muscle atrophy are limited, which warrant further investigation.

ncRNAs IN MUSCLE ATROPHY INDUCED BY CHRONIC KIDNEY DISEASE (CKD) AND CIRRHOSIS

CKD is characterized by renal damage and kidney dysfunction, and it usually involves loss of muscle mass. Many ncRNAs have been reported to participate in CKD-induced muscle wasting (Table 2). miR-26a overexpression reduced CKD-induced muscle atrophy by inhibiting the transcription factor FOXO1.[104,105] miR-29 attenuated muscle wasting in CKD by downregulating YY1 and TGF-β pathway proteins.[106,107] Atrolnc-1, a lncRNA, is also found to be increased in muscles of mice with CKD. Atrolnc-1 overexpression upregulated atrophy-related gene expression, whereas its depletion of Atrolnc-1 prevented CKD-induced muscle mass loss.[108] Mechanistically, Atrolnc-1 is known to interact with the A20 binding inhibitor of NF-κB-1 (ABIN-1), which leads to the activation of NF-κB signaling and increased MuRF1 expression. Finally, ncRNAs play a role in preventing muscle wasting in diabetics, which is significant, as diabetes is the leading cause of CKD. Overexpression of miR-23a and miR-27a in muscle prevented diabetes-induced muscle wasting and improved muscle function by regulating the insulin signaling pathway and the myostatin cascade.[109]

Sarcopenia (severe skeletal muscle loss) is prevalent in patients with cirrhosis. The underlying molecular mechanisms that contribute to cirrhosis-induced muscle loss are not clear. Limited studies have reported the role of ncRNAs in sarcopenia, requiring further investigations to provide clarification on their relationship to the prevention and treatment of cirrhosis-induced muscle atrophy.

ncRNAs IN MUSCLE ATROPHY INDUCED BY HORMONES

The endocrine system plays important roles in muscle metabolism in both health and disease. Hormones such as growth hormone (GH), IGF-1, testosterone, thyroid hormone (TH), and glucocorticoids (GCs) exert major effects on skeletal muscle growth and function.[110]

GH regulates the metabolism and has a crucial role in somatic growth and development. It stimulates the synthesis of IGF-1, which is one of the major regulators of muscle size and function. The GH/IGF-1 axis is one of the essential axes that contributes to bone growth. Of note, IGF-2, which is the predominant circulating IGF, also acts in response to GH and promotes placental and fetal growth.[111] Several ncRNAs have been reported to regulate IGF-1 signaling in skeletal muscle. miR-29b has been reported to promote skeletal muscle atrophy via targeting IGF-1 and PI3K (p85α).[50] miR-29b overexpression in mouse gastrocnemius muscles resulted in muscle wasting, whereas miR-29b inhibition prevented muscle atrophy. Through RNA sequencing, researchers identified attenuated muscle atrophy in skeletal muscles enriched with lncIRS1, which functions as a molecular sponge for the miR-15 family, thus regulating the expression of the IRS1 and IGF-1 pathway.[112] Mechanistically, lncRNAs can function as a competing endogenous RNA (ceRNA) to protect mRNAs by sponging miRNAs that specifically target mRNAs.

Skeletal muscles are a principal target of TH, a major determinant of muscle fiber composition. It is reported that miR-133a1 is a direct target gene of TH in muscle.[113] miR-133a is enriched in fast-twitch muscle and controls muscle fiber composition.

Dex is an effective synthetic GC used as a potent anti-inflammatory, anti-shock, and immunosuppressive agent. High-dose or long-term use of Dex causes severe skeletal muscle atrophy. A previous study showed that muscle-specific miR-1 promoted Dex-induced muscle atrophy by targeting heat shock protein (HSP)70, which bound to and protected the phosphorylation of AKT.[114] A recent study also reported that miR-322 inhibition prevented Dex-induced muscle wasting by targeting IGF-1 receptor (IGF-1R) and INSR.[115] The expression of circular spermine oxidase RNA (circ-SMOX) was increased in a Dex-induced C2C12 muscle atrophy model *in vitro* and in two murine models of amyotrophic lateral sclerosis *in vivo*. circ-SMOX was mainly localized in the cytoplasm, indicating that it might function as a sponge for miRNAs and contribute to muscle atrophy regulation.[116] lncRNAs play important roles in regulating gene expression by ceRNAs. A novel ceRNA lncRNA named lncIRS1 has been found to be specifically enriched in skeletal muscle. lncIRS was found to regulate myoblast proliferation and differentiation *in vitro*, whereas it attenuated Dex-induced muscle atrophy *in vivo*. Mechanistically, lncIRS1 functioned as a ceRNA for the miR-15 family miRNA, increasing its target gene IRS1 expression and further activating the IGF-1-PI3K-PKB (also called AKT) signaling pathway, thus rescuing from muscle atrophy.[112]

Table 1. Changed ncRNAs in muscle atrophy induced by various factors

Induction of muscle atrophy	Upregulated ncRNAs	Verified/predicted target	Downregulated ncRNAs	Verified/predicted target
Heart failure			miR-23a	MuRF1, atrogin-1
			miR-1[a]	HDAC4
	miR-29b[a]	IGF-1, PI3K, YY1	miR-133a[a]	SRF, RhoA
			miR-133b[a]	EGFR
			miR-208a	myostatin, GATA4
			miR-208b	SOX6
Cancer cachexia	miR-450a-5p	EGFR, CREB1	miR-451a	PSMB8, IRF8
	miR-450b-5p	SOX2	miR-144-5p	CCNE1, CCNE2, CDC25A, PKMYT1
	miR-424-5p	E2F7, DCLK1	miR-27a[a]	FoxO1, Pax3
	miR-424-3p	YAP1	miR-27b	MDF1, MSTN
	miR-199a	eIF4EBP1, Smad1	miR-299a-3p	VEGFA
	miR-140	WNT11	miR-1933-3p	Impa1, Mrpl27
	miR-147-3p	AKT, CDK4, RB1	miR-431-5p	Pax7, LRSAM1, Smad4
	miR-511-3p	TRIB2, PIK3R3	miR-665-3p	TRIM8, ATG4B
	miR-223-3p	IGF-1R		
	miR-205-5p	PTEN, RUNX2, CREB1		
Aging			miR-127	S1PR3
			miR-410	sFRP2
			miR-431	smad4
			miR-433	sFRP2
	miR-29b[a]	IGF-1, P85α, β-myb	miR-434	eIF5A1
	miR-21[a]	YY1, eIF4E3	miR-434-3p	GATA4
			miR-486	PTEN, FOXO1, Pax7
			miR-146a	Smad3, Smad4
			miR-376c-3p	atrogin-1
			miR-133b[a]	BAF60a, BAF60b
			miR-206[a]	HDAC4
			miR-181a	Hox-A11
			lncRNA DLEU2	miR-181a
			lncRNA Mar1	miR-487b
			lncRNA MUMA	miR-762
COPD	miR-1[a]	HDAC4		
	miR-499	SOX6		
	miR-133	SRF, BAF60a, BAF60b		
	miR-206[a]	FST1, Pola1, Utrn		
	miR-27a[a]	FoxO1, Pax3		
	miR-675	TGF-βR1, Smad1, Smad5		
PNI			miR-1[a]	Notch3
			miR-133a[a]	Smarcd1, Runx2
	miR-21[a]	YY1 and eIF4E3	miR-378	MyoR
			miR-22	EVI1

[a]miRNAs commonly altered in at least two conditions.

Table 2. Changed lncRNAs in muscle atrophy induced by different factors

Induction of muscle atrophy	ncRNAs	Verified/predicted target
Aging	lncRNA DLEU2	miR-181a
	lncRNA Mar1	miR-487b
	lncRNA MUMA	miR-762
PNI	lncRNA miR22hg	HDAC4
CKD	lncRNA Atrolnc-1	ABIN-1
Hormone	lncRNA IRS1	miR-15
Common target	lncRNA MAAT	miR-29b
–	lncRNA SMUL	SMURF2

ncRNAs IN MUSCLE ATROPHY INDUCED BY UNHEALTHY HABITS

Skeletal muscles account for 30% to 50% of human body weight, and their mass and function may be affected by lifestyle. Unhealthy habits such as alcoholism, long-term skeletal muscle inactivity, excessive fasting, weightlessness, and over-nutrition can cause muscle mass loss.[117–119] Chronic ethanol exposure decreased muscle fiber sizes and altered swimming behaviors in zebrafish.[120] Using the zebrafish model of chronic ethanol exposure, researchers identified that miR-140 was significantly decreased in the ethanol-treatment group.[120] Further study indicated that the members of the Notch signaling pathway, including Hey1 and Notch1, were significantly increased in ethanol-treated muscle, suggesting that miRNAs targeting Notch are likely to play important roles in alcohol-induced muscle loss.

Long-term skeletal muscle inactivity also causes muscle atrophy. Physical exercise is thought to be the most efficient way to combat muscle wasting. Long-term physical activity is able to prevent age-related muscle loss.[121] In a further study, differentially expressed ncRNAs and miRNAs in muscle atrophy were induced by long-term inactivity mainly involved in cell-cycle regulation, cytoskeleton control, and an AMP-activated protein kinase (AMPK) pathway.[122]

Starvation or excessive fasting can cause loss of skeletal muscle mass; therefore, it is vital to investigate the detailed molecular mechanisms related to fasting-induced muscle wasting. Using the serum-starved C2C12 cell model and the starved mouse muscular atrophy model, the expression levels of miR-206, miR-23a, and miR-27b were found to be downregulated in both *in vitro* and *in vivo* starvation models. Six lncRNAs (Atrolnc-1, Dum, lncMD1, lncMYoD, Myolinc, and muscle anabolic regulator 1 [MAR1]) were enriched in the atrophic C2C12 cells and tissues.[123] Additionally, the expression levels of lncRNAs, including H19, Gtl2, and IG-DMR, were significantly downregulated in fasting-induced muscle atrophy.[124]

ncRNAs AS COMMON TARGETS FOR MUSCLE ATROPHY

As muscle atrophy can be induced by various risk factors, it is of significance to uncover ncRNAs as common therapeutic targets of muscle atrophy that could meet clinical needs.[125] We previously reported that miR-29b controlled multiple types of muscle atrophy including those induced by aging, cancer, fasting, Dex, H_2O_2, and TNF-α. Overexpression of miR-29b promoted muscle atrophy, whereas miR-29b inhibition attenuated atrophy via targeting IGF-1 and PI3K. The inhibition of miR-29b is a promising therapeutic method for attenuating muscle atrophy induced by various stimuli.[50] Recently, we found that lncRNAs muscle atrophy-associated transcript (lncMAAT) was downregulated in multiple types of muscle atrophy models (induced by aging, AngII, H_2O_2, TNF-α, fasting, denervation, or immobilization). Inhibition of lncMAAT induced muscle atrophy, whereas overexpression of lncMAAT ameliorated multiple types of muscle atrophy by inhibiting transcription of miR-29b through sex-determining region Y-box (SOX) 6 and increasing the expression of the neighboring gene Mbnl1. Targeting lncMAAT is a promising strategy for preventing muscle atrophy induced by a variety of factors.[126] Together, our findings bring hope for the treatment of muscle atrophy.

THERAPIES FOR MUSCLE ATROPHY

According to the present pathophysiological understanding of muscle atrophy, current clinical treatments mainly focus on exercise therapy and drug therapy. Drug therapy such as testosterone has been shown to enhance muscle strength and function. However, due to possible side effects, the use of testosterone is controversial.[48]

Exercise therapy has been an important method of clinical prevention and treatment of muscle atrophy.[127,128] Many clinical and basic science experiments have proven that resistance training and aerobic exercise effectively inhibit skeletal muscle atrophy by improving the antioxidant capacity of skeletal muscles, reducing oxidative stress and protein degradation, and regulating the expression of skeletal muscle growth factors.[129] The latest research showed that exercise, as an effective intervention, can alleviate muscle atrophy, and its mechanism is closely related to the regulation of miRNAs.[130] Resistance exercise usually has the characteristics of high intensity and short duration. It can effectively activate satellite cells and promote the synthesis of contractile proteins and structural proteins, thus inducing skeletal muscle hypertrophy in varying degrees. It is the best recommended method to improve the quality of skeletal muscle and prevent muscular atrophy.[131] Resistance exercise has been shown to activate the PI3K/AKT/mammalian target of rapamycin signaling pathway by downregulating miR-1, which promotes muscle protein synthesis and improves skeletal muscle quality and function.[132,133] Resistance exercise upregulates the levels of miR-23a and miR-27a. Overexpression of miR-23a/miR-27a attenuated muscle loss by activating the AKT/FOXO1 pathway.[134] Aerobic exercise decreased miR-494 expression in gastrocnemius muscle of mice and promoted the upregulation of transcription factor A (TFAM) and FOXJ3, which are two regulatory factors of mitochondrial

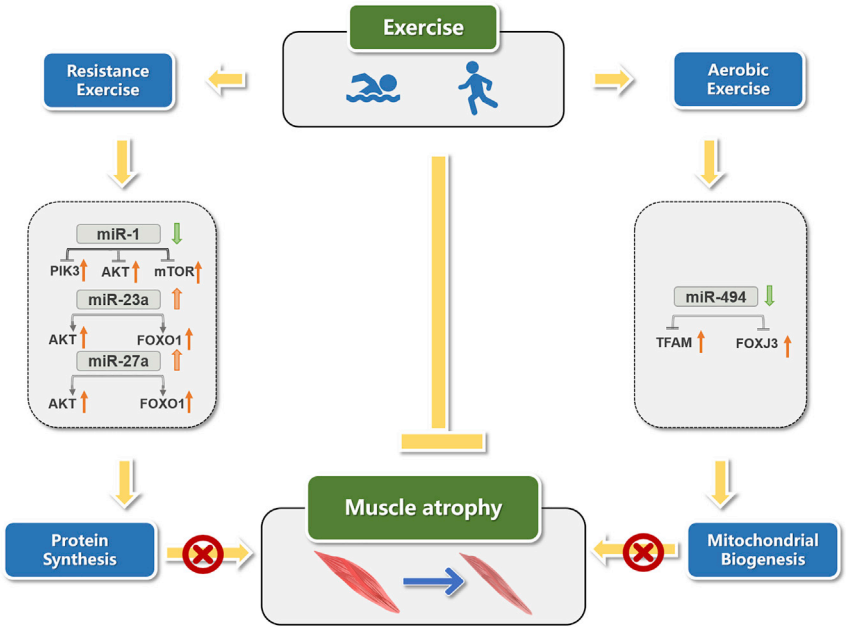

Figure 2. Exercise protects against muscle atrophy through ncRNAs

biogenesis, as well as increased mitochondrial biosynthesis.[135] As shown in Figure 2, these findings suggest that exercise can delay muscle atrophy by regulating miRNAs. However, the role and mechanism of ncRNAs in muscle atrophy still need more experiments based on animal and human models to support and verify previous findings.

Conclusions

ncRNAs have been confirmed by numerous studies to play important roles in the occurrence and development of muscle atrophy, which are expected to become new biomarkers as diagnostic tools or therapeutic targets for muscle atrophy. However, the functions of many ncRNAs are still unknown. Our understanding of ncRNAs, especially circRNAs, is still in its infancy, and they are rarely used in clinical diagnosis and treatment. Further research is needed to provide evidence for clinical practice. Identifying novel ncRNA species, looking for their targets, studying their functions in muscle atrophy, and explaining their specific mechanisms of action can give us comprehensive views to the regulatory roles of ncRNAs in muscle atrophy, which may allow further drug development targeting the expression and activity of disease-related ncRNAs. In addition, due to the flexible and diverse influences of ncRNAs, the mechanisms of ncRNAs are more complex than those of coding genes. There are many problems worthy of study, which include the elucidation of proteins that participate in the formation of ncRNAs, discovery of factors that determine the cellular localization of ncRNAs, and clarification of whether the interactions between circRNAs and miRNAs are universal. In the future, ncRNA research can be carried out in the following aspects: (1) determining whether ncRNAs can become new therapeutic targets or diagnostic markers; (2) elucidating the most effective treatment methods, which may include ncRNAs, in order to provide a new theoretical basis for optimizing rehabilitative treatment of muscular atrophy; and (3) clarifying the molecular mechanism of ncRNAs in muscular atrophy conducive to the development of novel and effective nutritional supplements, drugs, and targeted therapy in order to provide effective and non-invasive methods for muscle atrophy prevention or treatment.

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AUTHOR CONTRIBUTIONS

Q.L., J.D., Y.Q., J.G., L.G., L.J., H.L., Q.Z., and J.X. all participated in the draft of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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