

MicroRNA-mediated regulation of muscular atrophy: Exploring molecular pathways and therapeutics (Review)

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Abstract. Muscular atrophy, which results in loss of muscle mass and strength, is a significant concern for patients with various diseases. It is crucial to comprehend the molecular mechanisms underlying this condition to devise targeted treatments. MicroRNAs (miRNAs) have emerged as key regulators of gene expression, serving vital roles in numerous cellular processes, including the maintenance of muscle stability. An intricate network of miRNAs finely regulates gene expression, influencing pathways related to muscle protein production, and muscle breakdown and regeneration. Dysregulation of specific miRNAs has been linked to the development of muscular atrophy, affecting important signaling pathways including the protein kinase B/mTOR and ubiquitin-proteasome systems. The present review summarizes recent work on miRNA patterns associated with muscular atrophy under various physiological and pathological conditions, elucidating its intricate regulatory networks. In conclusion, the present review lays a foundation for the development of novel treatment options for individuals affected by muscular atrophy, and explores other regulatory pathways, such as autophagy and inflammatory signaling, to ensure a comprehensive overview of the multifarious nature of muscular atrophy. The objective of the present review was to elucidate the complex molecular pathways involved in muscular atrophy, and to facilitate the development of innovative and specific therapeutic strategies for the prevention or reversal of muscular atrophy in diverse clinical scenarios.

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1. Introduction

Muscular atrophy refers to the progressive loss of skeletal muscle mass (SMM) and strength and is a disease that has profound effects on the general health and quality of life of patients (1,2). Muscular atrophy is associated with various factors, including aging, immobility, long-term illness, poor nutrition and genetic diseases (3,4). Muscular atrophy involves several intricate molecular mechanisms, an understanding of which is of importance when developing effective treatment strategies. MicroRNAs (miRNAs/miRs) are small RNA molecules, usually 19-23 nucleotides in size, which post-transcriptionally regulate gene expression. miRNAs regulate signaling associated with protein synthesis within cells, thereby controlling a variety of cellular processes, including muscle development and maintenance (5,6). In the context of muscular atrophy, miRNAs can either promote or alleviate muscle loss (7); thus, the genes and pathways involved in muscular atrophy can be targeted to either enhance or reduce muscle wasting. Skeletal muscular atrophy presents as changes, including muscle fiber contraction, as well as the loss of muscle cytoplasm, organelles and all cellular proteins (8). Biomarkers are measurable indicators of biological or pathological processes, and are valuable tools for monitoring,

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diagnosing and predicting treatment responses for diseases (9). Physiological and pathological changes accompanying skeletal muscular atrophy can be biomarkers. Atrophy occurs when the rate of proteolysis exceeds the rate of protein synthesis. This atrophy of skeletal muscle is closely related to high-fat and high-sugar consumption, which are commonly associated with Western diets, as well as aging and long-term illnesses, such as diabetes, obesity, heart failure, Alzheimer's disease and cachexia (10). Understanding why muscular atrophy occurs under various conditions is essential for its prevention and treatment.

2. Sarcopenia and muscular atrophy: Definitions, diagnoses and effects

Sarcopenia is the most representative disease associated with symptoms of muscular atrophy. In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) developed three diagnostic criteria for sarcopenia: Changes in muscle mass, muscle strength and physical performance (11). A diagnosis of sarcopenia requires both low muscle mass (LMM), and either low muscle strength (LMS) or low physical performance (LPP) (12). LMM is identified by a SMM index of $<8.90 \text{ kg/m}^2$; LMS is identified by a hand-grip strength of $<30 \text{ kg}$ in men and $<20 \text{ kg}$ in women; LPP is identified by a gait speed of $\leq 0.8 \text{ m/sec}$ (13). According to the EWGSOP, sarcopenia can be categorized into three subgroups: Pre-sarcopenia, sarcopenia and severe sarcopenia, based on LMM status and the presence or absence of functional impairment (LMS and LPP) (11).

In 2018, a new consensus was reached in terms of both the definition and diagnosis of sarcopenia. The EWGSOP2 criteria were defined based on sarcopenia research conducted after 2010. The operational definitions of pre-sarcopenia, sarcopenia and severe sarcopenia are generally defined by LMS, LMM and LPP, respectively (14). Several sarcopenia tests and cut-offs have been suggested. LMS can be tested by measuring grip strength and the ability to stand from a seated position (15). Appendicular SMM (ASM) is measured to evaluate muscle mass and quality, and LPP is assessed by measuring walking speed, determining the Short Physical Performance Battery (SPPB) score, and conducting timed up-and-go and 400-m walk tests. Pre-sarcopenia is diagnosed when rising from a chair takes $>15 \text{ sec}$ in five trials, or grip strength is $<27 \text{ kg}$ for men or $<16 \text{ kg}$ for women (14). Sarcopenia is diagnosed when the ASM is $<20 \text{ kg}$ for men or $<15 \text{ kg}$ for women, or when the ASM/height^2 is $<7.0 \text{ kg/m}^2$ for men or $<5.5 \text{ kg/m}^2$ for women. Severe sarcopenia is diagnosed when the walking speed is $\leq 0.8 \text{ m/sec}$, the SPPB score is ≤ 8 points, the timed up-and-go test requires $\geq 20 \text{ sec}$, and the 400-m walk test is either not completed or requires $\geq 6 \text{ min}$ for completion (16). Muscle mass can be estimated via dual-energy X-ray absorption or bioelectrical impedance analysis, and the results can be modified based on height or body mass index (17). Muscle quality can be evaluated via computed tomography or magnetic resonance imaging; both provide comprehensive data on the SMM, ASM, third lumbar muscle cross-sectional area and middle thigh cross-sectional area (14,18). In addition, EWGSOP2 recommends the use of the self-reporting SARC-F questionnaire, which is a screening test for sarcopenia consisting of

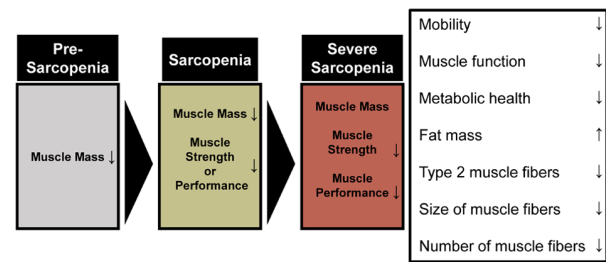


Figure 1. Severity and symptoms of sarcopenia. Sarcopenia is divided into pre-sarcopenia, sarcopenia and severe sarcopenia. Severe sarcopenia is characterized by a decrease in muscle mass, strength and performance.

five questions; SARC-F predicts LMS with low-to-moderate sensitivity but very high specificity and can therefore detect even the most severe cases (14).

Sarcopenia is linked to reduced mobility (19), lower muscle function (20) and poor metabolic health (21). Additionally, sarcopenia decreases the ease of movement and resting energy expenditure, and increases fat mass, non-exercise physical activity (22) and obesity. Metabolic health is closely associated with all of these factors. Accumulating evidence has suggested that the size and number of muscle fibers decrease more rapidly >50 years of age. Prior to that age, muscle loss is small ($<10\%$); however, between the ages of 50 and 80 years, there is a notable loss of 30–40% of muscle mass (22,23). Notably, this process is gradual and can be mitigated by regular exercise. Muscle loss can directly trigger fat storage because energy that was previously stored in atrophying muscles becomes stored as fat, and indirectly, due to lower total energy expenditure (24). The selective atrophy of stronger and faster-contracting type II muscle fibers further compounds the decline in function with age, resulting in a reduction of muscle power (Fig. 1).

3. miRNAs regulated during disease-induced muscle loss

Disease-induced muscular atrophy is regulated by various miRNAs (Fig. 2). For example, increases in muscular levels of miR-23a/27a induced by the addition of adeno-associated virus-miR-23a-27a-24-2 can alleviate skeletal muscular atrophy caused by diabetes through downregulation of the myostatin cascade and upregulation of the insulin-like growth factor-1 (IGF-1)/phosphoinositide 3-kinases/Akt signaling pathway (25). In addition, plasma miR-1-3p levels have been reported to be higher in patients with sarcopenia and congestive heart failure compared with those in patients without sarcopenia; plasma miR-1-3p levels in these patients were shown to be strongly correlated with both hand-grip strength and the SMM index, and a significant correlation was also observed between miR-1-3p expression and activation of the PKB/mTOR signaling pathway (26). Thus, miR-1-3p may act as a robust, specific and sensitive biomarker for sarcopenia accompanying congestive heart failure. Another study showed that miR-142a-5p triggers mitochondrial dysfunction, mitophagy and apoptosis by targeting mitofusin 1, suggesting that it may be a crucial controller of neurogenic skeletal muscular atrophy (27). Chronic kidney disease stress has been linked to both skeletal muscular atrophy and uremic cardiomyopathy, which are associated with reduced miR-26a levels.

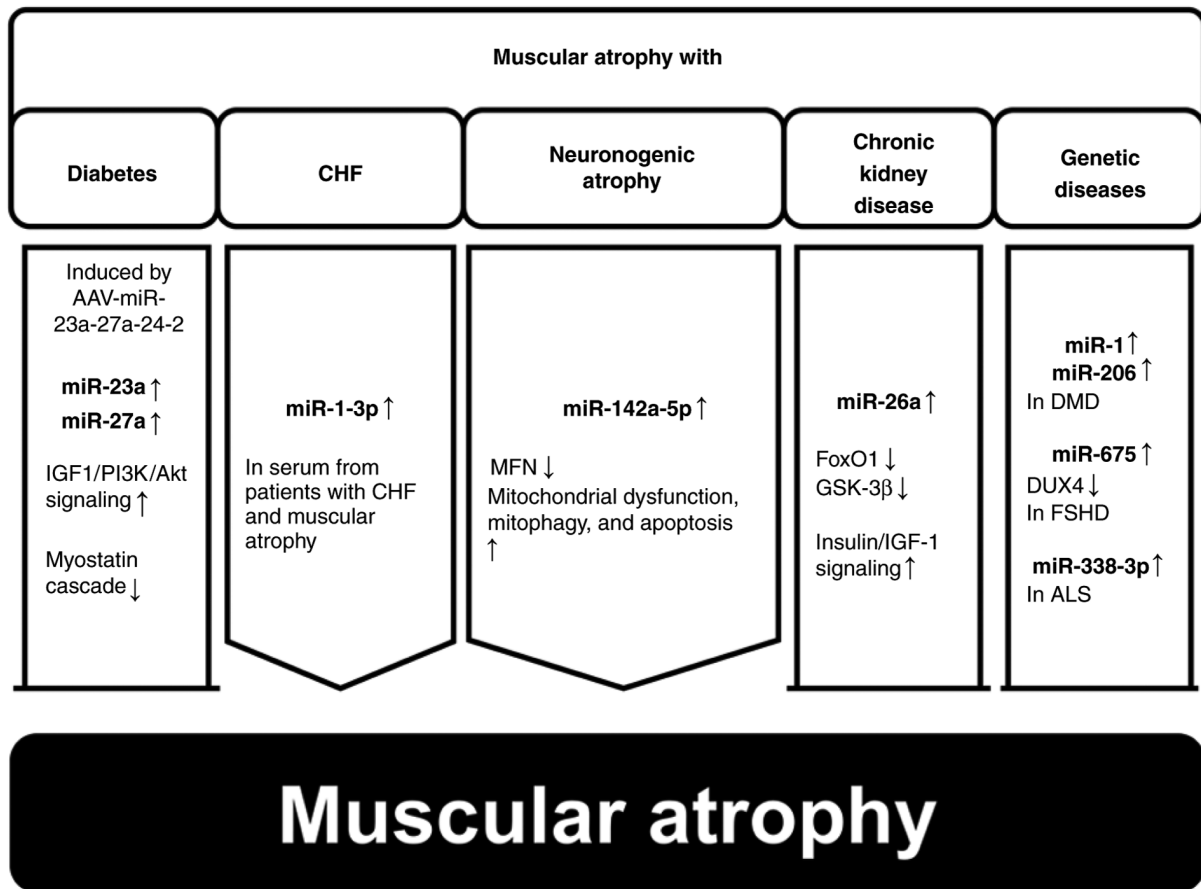


Figure 2. miRNAs regulate muscular atrophy in various types of diseases accompanied by muscular atrophy. miR, microRNA; IGF1, insulin-like growth factor-1; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; CHF, congestive heart failure; MFN, mitofusin; FoxO1, Forkhead box protein O1; GSK-3β, glycogen synthase kinase 3β; DMD, Duchenne muscular dystrophy; DUX4, double homeobox 4; FSHD, facioscapulohumeral muscular dystrophy; ALS, amyotrophic lateral sclerosis.

The injection of exosomes enriched in miR-26a into the skeletal musculature of murine models of chronic kidney disease has been reported to result in decreased muscular atrophy and ameliorated cardiomyopathy symptoms, indicating that the augmentation of miR-26a expression effectively attenuates insulin resistance. Additionally, Forkhead box protein O1 (FoxO1) has been recognized as a direct target of miR-26a; its modification is associated with changes in insulin/IGF-1 signaling axis protein levels. PKB activation by miR-26a has also been shown to enhance the insulin/IGF-1 signaling pathway, whereas the suppression of FoxO1 and glycogen synthase kinase 3β by miR-26a reduces insulin resistance (28). In addition, genetic diseases are major pathological factors in muscular atrophy. miR-1 is the most abundant miRNA in muscle tissue and is involved in the regulation of muscle formation and muscle differentiation. miR-206 is another muscle-specific miRNA that is involved in muscle regeneration and repair (29). Upregulation of miR-1 has been observed in Duchenne muscular dystrophy (30). Facioscapulohumeral muscular dystrophy (FSHD) is a myopathy caused by impaired repression of the double homeobox 4 (DUX4) gene in skeletal muscle. miR-675 can be used as a potential treatment for FSHD by suppressing the mRNA and protein levels of DUX4 (31). Furthermore, upregulated miR-338-3p in amyotrophic lateral sclerosis may contribute to motor neuron degeneration (32).

4. miRNA-induced regulation of muscle differentiation

Muscle cell differentiation serves a crucial role in muscular atrophy. After exercise or damage, skeletal muscle can effectively regenerate through the actions of versatile satellite cells (33). Upon activation, satellite cells transition from a state of dormancy to engage in proliferation and differentiation, ultimately transforming into myoblasts, which further differentiate and merge to form multinucleated myotubes (34). This intricate myogenic process is carefully regulated by a complex network of genes. At the core of this network are basic helix-loop-helix transcription factors known as myogenic regulatory factors (MRFs), which include myogenic factor 5, myoblast determination protein 1, myogenin and MRF4 (35,36). miRNAs, which do not code for proteins, are vital components of this network, targeting specific mRNAs to finely adjust gene expression (37-40). Various miRNAs regulate muscle differentiation by targeting genes involved in muscle cell differentiation (Fig. 3).

Skeletal muscle differentiation involves various miRNAs, including miR-24, miR-3074, miR-743a, miR-1a/206, miR-486, miR-23a, miR-27, miR-19 and miR-17. In neonatal mice, miR-24-3p leads to increased numbers of actively dividing PAX7-positive muscle stem cells, which is attributable to decreased inhibition of muscle differentiation and

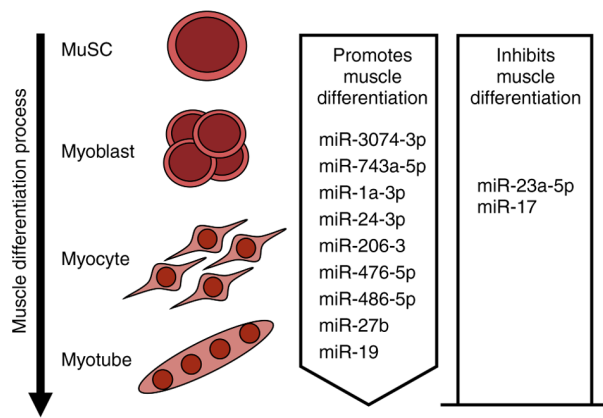


Figure 3. miRNAs that affect muscle cell differentiation. MuSC, muscle stem cell; miR/miRNA, microRNA.

regeneration by Hmga1 and Id3 (41). A conserved miRNA termed miR-3074-3p is involved in the regulation of Cav1 expression in both C2C12 cells and human skeletal muscle myoblasts, which ultimately enhances myogenesis (42). The modulation of miR-743a-5p activity is key to the regulation of myoblast differentiation, and is achieved by targeting Mob1b, another key player in skeletal muscle development and regeneration. Notably, elevated levels of miR-743a actively promote the differentiation of C2C12 myoblasts (43). miR-1a-3p, miR-206-3p, miR-24-3p and miR-486-5p act as regulators of myoblast differentiation that repress MRTF-A synthesis via the MRTF-A 3'-untranslated region (UTR). Upregulation of these miRNAs during myogenesis inhibits the translation of MRTF-A, allowing progression to late stages of differentiation. The inhibitory effect of MRTF-A on muscle differentiation is reduced upon the binding of miR-1a-3p, miR-24-3p and miR-486-5p to the MRTF-A 3'-UTR (44). miR-23a-5p enhances the proliferation of C2C12 myoblasts while simultaneously inhibiting their differentiation, thereby influencing muscle fiber composition (45). Myogenic differentiation is facilitated by the downregulation of PAX3 protein levels under the control of miR-27b, which targets the 3'-UTR of Pax3 mRNA. This process ensures the strong, rapid initiation of differentiation (46). miR-17 influences cell proliferation to some extent by directly affecting Ccnd2 and Jak1 and reduces cell motility and cell fusion by targeting Rhoc. Notably, treatment of C2C12 myoblast cells with miR-19 has been shown to counteract the harmful effects of miR-17 and to aid myotube development (47).

5. miRNA-induced regulation of the ubiquitin proteasome system of skeletal muscle

Muscular atrophy, or the wasting of muscle tissue, is primarily caused by abnormal protein degradation (48). The ubiquitin-proteasome pathway serves a crucial role in this process, through the identification and breakdown of poly-ubiquitinated proteins (49). The key players in protein ubiquitination are E3 ligases, with muscle RING finger 1 (MuRF1) and Atrogin-1 being specific to muscle tissue (50). In patients with muscular atrophy, both MuRF1 and Atrogin-1 are overexpressed; inhibition of the activity of these proteins effectively prevents muscle

loss and mitigates the effects of muscular atrophy (51,52). FOXO1, Atrogin1, and MuRF1 regulate muscular atrophy by promoting the breakdown of muscle proteins through the ubiquitin-proteasome pathway. Several miRNAs regulate muscular atrophy by targeting FoxO1, MuRF1, and Atrogin-1, which induce muscle protein degradation. (Fig. 4).

A previous study indicated that suppression of miR-142a-3p decreases the expression levels of Atrogin-1, MuRF1 and Nedd4, potentially hindering activation of the ubiquitin-proteasome system and other pathways associated with muscular atrophy (53). In skeletal muscle, miR-23a/27a reduces atrophy by lowering the levels of the E3 ubiquitin ligases TRIM63/MuRF1 and FBXO32/Atrogin-1, which contribute to muscle wasting (54). When miR-182 is introduced into C2C12 myotubes treated with dexamethasone, it interacts specifically with the 3'-UTR of FoxO3, decreasing the expression of various genes controlled by FoxO3, such as Atrogin-1 (7). Additionally, miR-672-5p treatment reduces ovariectomy-induced increased expression by targeting Atrogin-1 and MuRF1 (55).

6. miRNA-induced regulation of cachexia

Cachexia is a medical condition associated with the unintended loss of muscle and fat tissue in individuals with cancer or chronic inflammatory diseases; this disease significantly compromises patient outcomes and increases mortality. However, few established interventions or treatments are available for cachexia (56). The pathogenesis of cancer cachexia is marked by an imbalance between protein and energy levels, caused by various factors, including decreased metabolism and diminished appetite (57-61). Various miRNAs are involved in cachexia-induced muscular atrophy (Fig. 5).

The degradation of muscle protein in patients with cachexia is usually facilitated by the ubiquitin-proteasome system and is initiated via E3 ligase activation (62). The inhibition of FoxO transcriptional activity has been reported to curb muscle fiber atrophy in patients with cachexia (63). miR-486 inhibits E3 ubiquitin ligase activity by reducing FoxO1 protein expression and increasing FoxO1 phosphorylation (64). However, miR-21 binds to and triggers the action of Toll-like receptor 7, resulting in muscle cell apoptosis via the c-Jun N-terminal kinase pathway, ultimately resulting in atrophy (65). Muscle catabolism in patients with lung cancer is attributable to the activation of the leukemia inhibitory factor (LIF) via the downregulation of miR-29c expression. LIF has been shown to promote muscle wasting via the mitogen-activated protein kinase and JAK/signal transducers and activators of transcription pathways (66). Tumor-released exosomal miRNAs, such as miR-195a-5p and miR-125b-1-3p, target Bcl-2 and induce muscle wasting by reversing Bcl-2-mediated inhibition of cell death in patients with colon cancer and cachexia (67). Elevated serum miR-203 levels in patients with colorectal cancer have also been reported to act as independent risk factor for sarcopenia; miR-203 induces apoptosis through the downregulation of survivin in human skeletal muscle cells (68). Notably, miR-181a-3p in oral squamous cell carcinoma exosomes regulates the endoplasmic reticulum stress pathway, triggering muscular atrophy and muscle

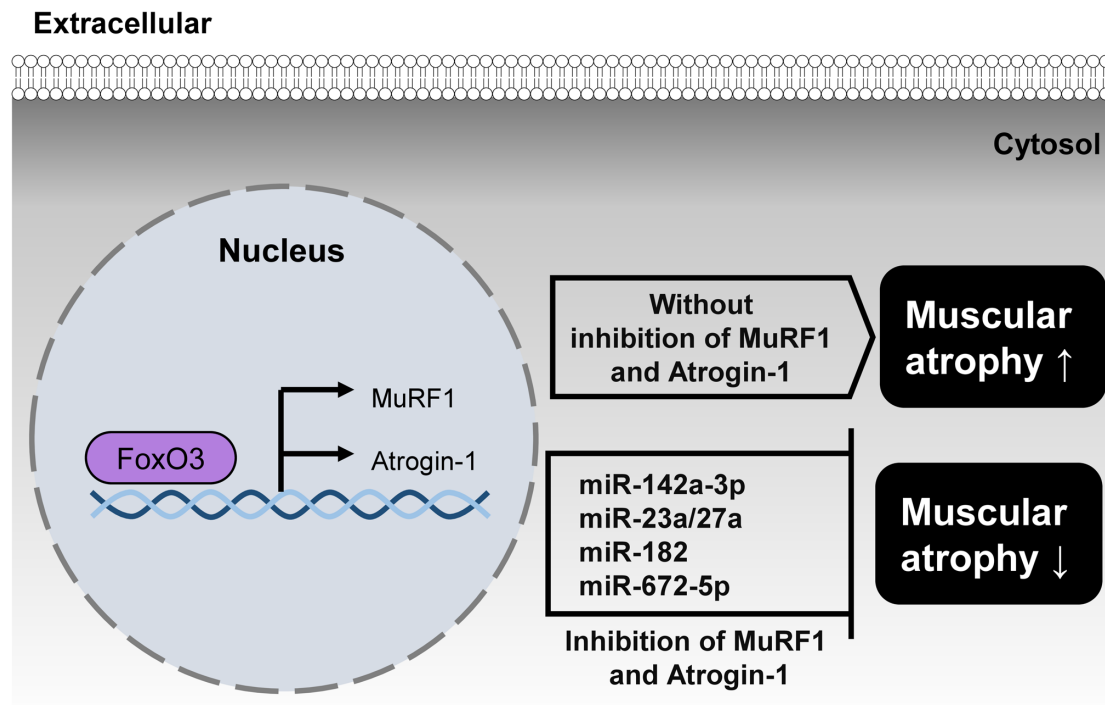


Figure 4. miRNAs that regulate the ubiquitin-proteasome system in muscle. miR/miRNA, microRNA; FoxO3, Forkhead box O3; MuRF1, muscle RING-finger protein-1.

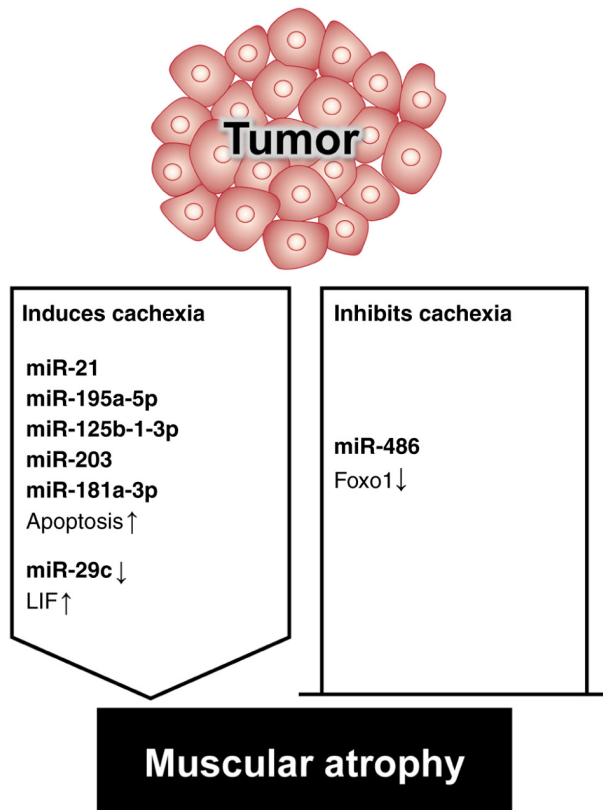


Figure 5. miRNAs that regulate muscular atrophy caused by cancer cachexia. miR/miRNA, microRNA; LIF, leukemia inhibitory factor.

cell apoptosis (69). Several studies have reported that the miR-181a family targets the 3'-UTR of Grp78, reducing its

expression and increasing the susceptibility of cancer cells and muscle cells to apoptosis (70-73).

7. Roles of regulatory miRNAs in neurogenic muscular atrophy

The denervation of skeletal muscle causes severe muscular atrophy preceded by several cellular changes that increase the permeability of the plasma membrane, decrease resting membrane potential and accelerate protein breakdown (74). The nerves of skeletal muscles have crucial roles in maintaining physiological muscle tone and function (75-77). Denervation is followed by significant muscular atrophy and weakness, accompanied by various cellular alterations (78-80) that disrupt the ionic balance (81-83) and accelerate protein catabolism (84-86). Neurogenic muscular atrophy may regulate miRNA levels, whereas the downregulation of miRNAs may alleviate neurogenic muscular atrophy (Fig. 6).

miR-142a-3p has been reported to exhibit the most significant differential expression among miRNAs in mouse skeletal muscle after denervation (87). This miRNA is considered to be a key modulator of cell fate in the hematopoietic system (88). The knockdown of miR-142a-3p alleviates decreases in body weight, muscle strength and muscle fiber cross-sectional area caused by nerve injury, and increases the number of mesenchymal stem cells, as well as the expression levels of genes related to proliferation and differentiation that are susceptible to Mef2a-mediated inhibition. Additionally, nerve regeneration in areas of nerve damage has been detected (53). In another study, denervation was shown to trigger a significant increase in miR-206 levels, and a decrease in the expression levels of miR-1, miR-133a and miR-133b in muscle fiber-derived

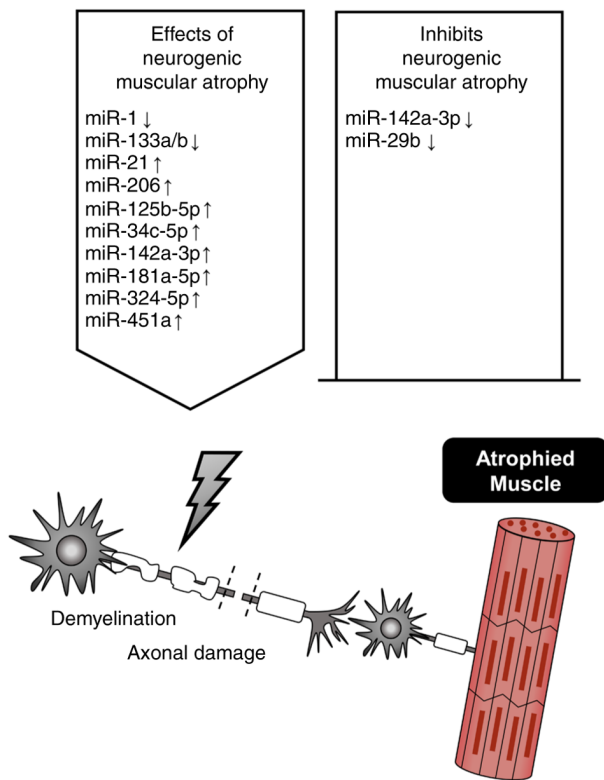


Figure 6. miRNAs that regulate neurogenic muscular atrophy. miR/miRNA, microRNA.

exosomes (79). Furthermore, miR-206 overexpression attenuates denervation-induced skeletal muscular atrophy via the inhibition of TGF- β 1 and HDAC4 signaling, and the promotion of satellite cell differentiation (89). CRISPR/Cas9-mediated editing of miR-29b prevents denervation-induced muscular atrophy via PKB-FoxO3A-mTOR signaling pathway activation and inhibits angiotensin II-induced myocyte apoptosis in mice, increasing their exercise capacity (90). Notably, an exploration of the impact of denervation on muscle tissue miRNA expression showed that denervation triggers significant changes in the miRNA expression profile; specifically, miR-21 and miR-206 levels were revealed to be markedly increased after 3, 7 and 14 days. Srivastava *et al* (91) reported that miR-125b-5p is elevated under similar conditions and could potentially act as a therapeutic target in patients with denervated muscular atrophy. Both miR-34c-5p and miR-142a-3p were significantly upregulated in denervated skeletal muscle (92). Abiusi *et al* (93) showed that three miRNAs (miR-181a-5p, miR-324-5p and miR-451a) were overexpressed in skeletal muscle and serum samples from patients with spinal muscular atrophy.

8. Future perspectives

Recent research on muscle miRNAs has significantly advanced our understanding of the intricate regulatory mechanisms governing muscle development, maintenance and disease. Explorations of the roles played by miRNAs in muscle biology have yielded valuable insights into the post-transcriptional control of gene expression, highlighting the pivotal roles played by these small RNA molecules in orchestrating various cellular processes. Despite significant progress, a number of challenges

and knowledge gaps remain; notably, the specific mechanisms by which miRNAs exert their effects on target genes in muscle cells remain unclear. Further research is therefore considered necessary. Additionally, the context-dependent functions of miRNAs and their interactions with other non-coding RNAs remain crucial areas of investigation. The integration of omics technologies, such as genomics, transcriptomics and proteomics, will likely enhance our comprehension of the regulatory networks underlying muscle biology. The future of research on miRNA-mediated regulation of muscular atrophy offers notable possibilities but poses significant challenges. It is essential to improve miRNA-based therapeutic strategies for clinical application. To effectively translate research findings into treatments for muscle-wasting conditions, it is essential to explore the efficacy, safety and specificity of miRNA mimics or inhibitors in preclinical models and clinical trials. The development of personalized medicine approaches is also very promising. An understanding of how various miRNA levels vary among individuals, and tailoring of interventions based on these differences, will improve treatment efficacy and minimize potential side effects. Furthermore, miRNAs may be useful as valuable biomarkers for the early detection and monitoring of muscular atrophy. The establishment of miRNA signatures associated with different stages of muscular atrophy may aid timely intervention and improve patient outcomes.

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Availability of data and materials

Not applicable.

Authors' contributions

WJ, UJ, SG, HN and JP contributed to the conception and design of the study. WJ wrote the first draft of the manuscript. WJ, UJ, SG, HN, QH, SL and JP wrote sections of the manuscript. WJ, UJ, SG, HN, SL and BL searched the relevant literature. SoHK, SeHK and JP critically reviewed the manuscript. Data authentication is not applicable. All authors contributed to manuscript revision and read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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