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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Contents

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,

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 kg/m^2; LMS is identified by a hand-grip strength of <30 kg in men and <20 kg in women; LPP is identified by a gait speed of ≤0.8 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 sec in five trials, or grip strength is <27 kg for men or <16 kg for women (14). Sarcopenia is diagnosed when the ASM is <20 kg for men or <15 kg for women, or when the ASM/height^2 is <7.0 kg/m^2 for men or <5.5 kg/m^2 for women. Severe sarcopenia is diagnosed when the walking speed is ≤0.8 m/sec, the SPPB score is ≤8 points, the timed up-and-go test requires ≥20 sec, and the 400-m walk test is either not completed or requires ≥6 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 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).

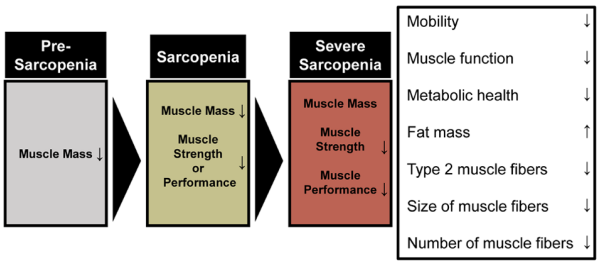

Figure 1. Severity and symptoms of sarcopenia. Sarcopenia is divided into pre-sarcopenia, sarcopenia and severe sarcopenia. Severe sarcopenia is characterized by a decrease in muscle mass, strength and performance.

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.

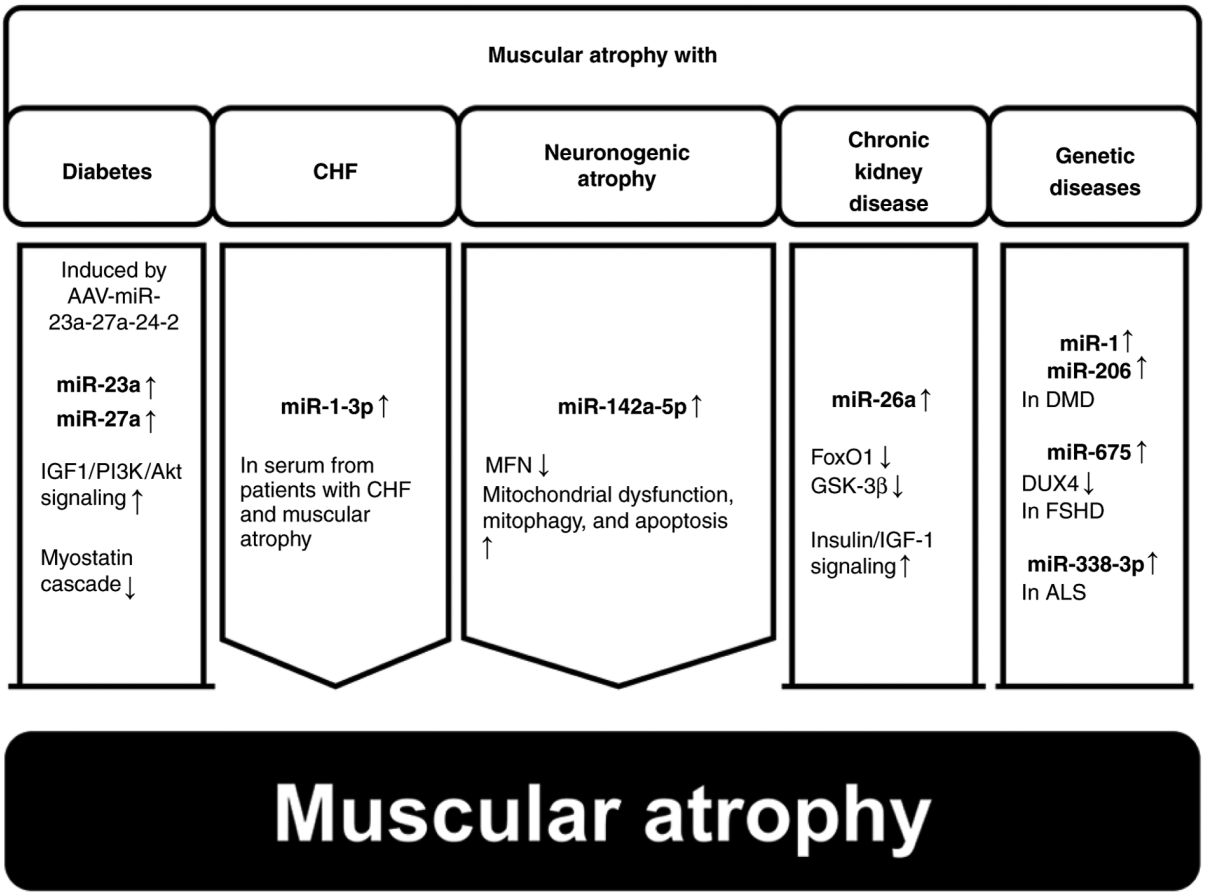

Figure 2. miRNAs regulate muscular atrophy in various types of diseases accompanied by muscular atrophy. miR, microRNA; IGF1, insulin-like growth factor-1; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; CHF, congestive heart failure; MFN, mitofusin; FoxO1, Forkhead box protein O1; GSK-3β, glycogen 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

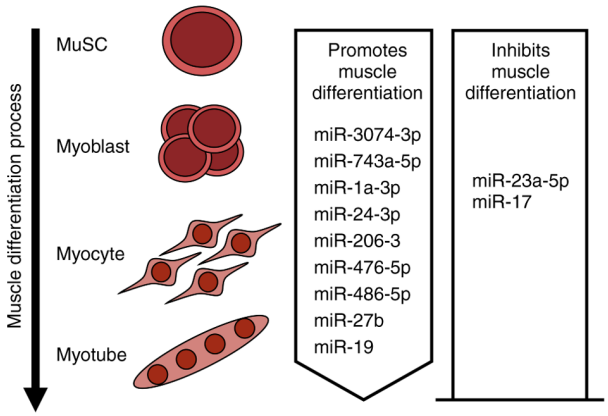

Figure 3. miRNAs that affect muscle cell differentiation. MuSC, muscle stem cell; miR/miRNA, microRNA.

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

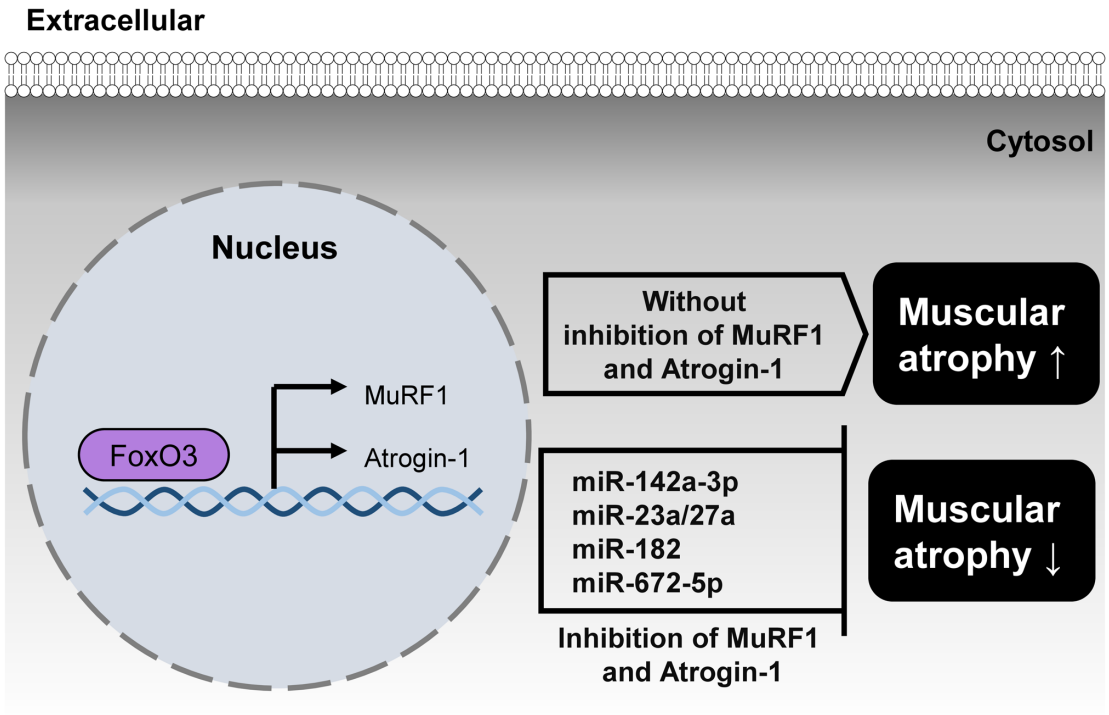

Figure 4. miRNAs that regulate the ubiquitin-proteasome system in muscle. miR/miRNA, microRNA; FoxO3, Forkhead box O3; MuRF1, muscle RING-finger protein-1.

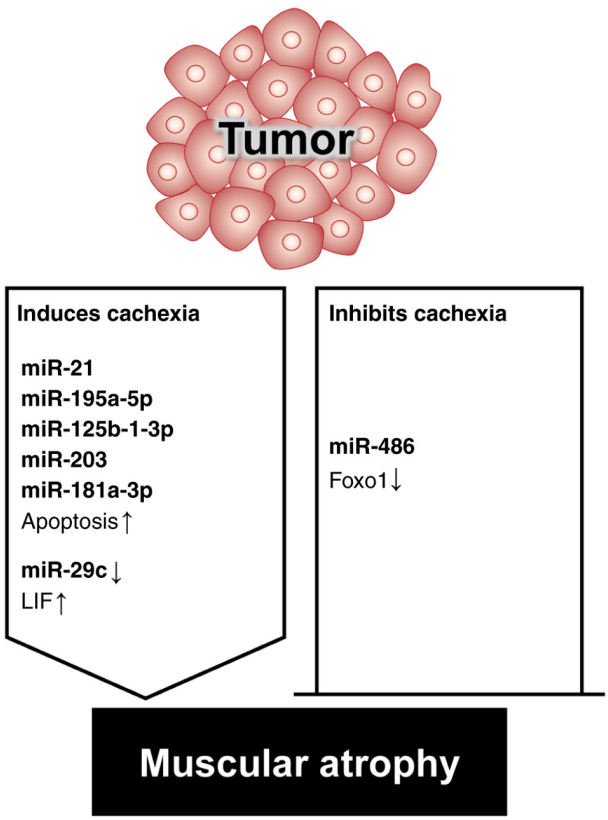

Figure 5. miRNAs that regulate muscular atrophy caused by cancer cachexia. miR/miRNA, microRNA; LIF, leukemia inhibitory factor.

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

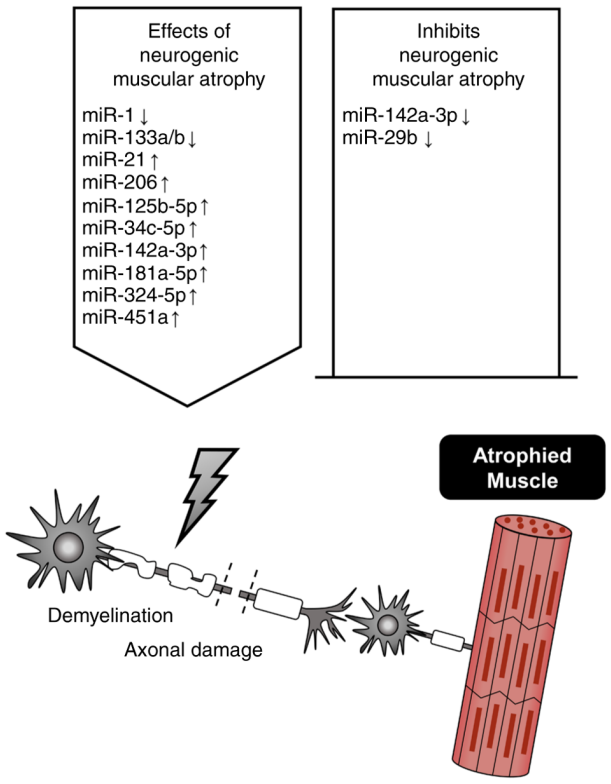

Figure 6. miRNAs that regulate neurogenic muscular atrophy. miR/miRNA, microRNA.

exosomes (79). Furthermore, miR-206 overexpression attenuates denervation-induced skeletal muscular atrophy via the inhibition of TGF-β1 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.

References

1. Duan K, Gao X and Zhu D: The clinical relevance and mechanism of skeletal muscle wasting. Clin Nutr 40: 27-37, 2021.
2. Larsson L, Degens H, Li M, Salviati L, Lee YI, Thompson W, Kirkland JL and Sandri M: Sarcopenia: Aging-Related loss of muscle mass and function. Physiol Rev 99: 427-511, 2019.
3. Damluji AA, Alfaraidhy M, AlHajri N, Rohant NN, Kumar M, Al Malouf C, Bahrainy S, Ji Kwak M, Batchelor WB, Forman DE, *et al*: Sarcopenia and cardiovascular diseases. Circulation 147: 1534-1553, 2023.
4. Nishio H, Niba ETE, Saito T, Okamoto K, Takeshima Y and Awano H: Spinal muscular atrophy: The past, present, and future of diagnosis and treatment. Int J Mol Sci 24: 11939, 2023.
5. O'Brien J, Hayder H, Zayed Y and Peng C: Overview of MicroRNA biogenesis, mechanisms of actions, and circulation. Front Endocrinol (Lausanne) 9: 402, 2018.
6. Gebert LFR and MacRae IJ: Regulation of microRNA function in animals. Nat Rev Mol Cell Biol 20: 21-37, 2019.
7. Brzeszczynska J, Brzeszczynski F, Hamilton DF, McGregor R and Simpson AHRW: Role of microRNA in muscle regeneration and diseases related to muscle dysfunction in atrophy, cachexia, osteoporosis, and osteoarthritis. Bone Joint Res 9: 798-807, 2020.
8. De Paepe B: Progressive skeletal muscle atrophy in muscular dystrophies: A role for toll-like receptor-signaling in disease pathogenesis. Int J Mol Sci 21: 4440, 2020.
9. Vo TT, Kong G, Kim C, Juang U, Gwon S, Jung W, Nguyen H, Kim SH and Park J: Exploring scavenger receptor class F member 2 and the importance of scavenger receptor family in prediagnostic diseases. Toxicol Res 39: 341-353, 2023.
10. Jun L, Robinson M, Geetha T, Broderick TL and Babu JR: Prevalence and mechanisms of skeletal muscle atrophy in metabolic conditions. Int J Mol Sci 24: 2973, 2023.
11. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel JP, Rolland Y, Schneider SM, *et al*: Sarcopenia: European consensus on definition and diagnosis: Report of the European working group on sarcopenia in older people. Age Ageing 39: 412-423, 2010.
12. Cho MR, Lee S and Song SK: A review of sarcopenia pathophysiology, diagnosis, treatment and future direction. J Korean Med Sci 37: e146, 2022.
13. Jang JY, Kim D and Kim ND: Pathogenesis, intervention, and current status of drug development for sarcopenia: A review. Biomedicines 11: 1635, 2023.
14. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyere O, Cederholm T, Cooper C, Landi F, Rolland Y, Sayer AA, *et al*: Sarcopenia: Revised European consensus on definition and diagnosis. Age Ageing 48: 16-31, 2019.
15. Guttikonda D and Smith AL: Sarcopenia assessment techniques. Clin Liver Dis (Hoboken) 18: 189-192, 2021.
16. Koo BK: Assessment of muscle quantity, quality and function. J Obes Metab Syndr 31: 9-16, 2022.
17. Cheng KY, Chow SK, Hung VW, Wong CH, Wong RM, Tsang CS, Kwok T and Cheung WH: Diagnosis of sarcopenia by evaluating skeletal muscle mass by adjusted bioimpedance analysis validated with dual-energy X-ray absorptiometry. J Cachexia Sarcopenia Muscle 12: 2163-2173, 2021.
18. Faron A, Sprinkart AM, Kuetting DLR, Feisst A, Isaak A, Endler C, Chang J, Nowak S, Block W, Thomas D, *et al*: Body composition analysis using CT and MRI: intra-individual intermodal comparison of muscle mass and myosteatosis. Sci Rep 10: 11765, 2020.
19. Dufour AB, Hannan MT, Murabito JM, Kiel DP and McLean RR: Sarcopenia definitions considering body size and fat mass are associated with mobility limitations: The Framingham Study. J Gerontol A Biol Sci Med Sci 68: 168-174, 2013.
20. Singh H, Kim D, Kim E, Bemben MG, Anderson M, Seo DI and Bemben DA: Jump test performance and sarcopenia status in men and women, 55 to 75 years of age. J Geriatr Phys Ther 37: 76-82, 2014.
21. Lee J, Hong YP, Shin HJ and Lee W: Associations of sarcopenia and sarcopenic obesity with metabolic syndrome considering both muscle mass and muscle strength. J Prev Med Public Health 49: 35-44, 2016.
22. Hunter GR, McCarthy JP and Bamman MM: Effects of resistance training on older adults. Sports Med 34: 329-348, 2004.
23. Hepple RT: Sarcopenia-a critical perspective. Sci Aging Knowledge Environ 2003: pe31, 2003.
24. Hunter GR, Singh H, Carter SJ, Bryan DR and Fisher G: Sarcopenia and its implications for metabolic health. J Obes 2019: 8031705, 2019.
25. Zhang A, Li M, Wang B, Klein JD, Price SR and Wang XH: miRNA-23a/27a attenuates muscle atrophy and renal fibrosis through muscle-kidney crosstalk. J Cachexia Sarcopenia Muscle 9: 755-770, 2018.
26. Xu R, Cui S, Chen L, Chen XC, Ma LL, Yang HN and Wen FM: Circulating miRNA-1-3p as biomarker of accelerated sarcopenia in patients diagnosed with chronic heart failure. Rev Invest Clin 74: 276-268, 2022.
27. Yang X, Xue P, Chen H, Yuan M, Kang Y, Duscher D, Machens HG and Chen Z: Denervation drives skeletal muscle atrophy and induces mitochondrial dysfunction, mitophagy and apoptosis via miR-142a-5p/MFN1 axis. Theranostics 10: 1415-1432, 2020.
28. Wang B, Zhang A, Wang H, Klein JD, Tan L, Wang ZM, Du J, Naqvi N, Liu BC and Wang XH: miR-26a limits muscle wasting and cardiac fibrosis through exosome-mediated microRNA transfer in chronic kidney disease. Theranostics 9: 1864-1877, 2019.
29. Oikawa S, Yuan S, Kato Y and Akimoto T: Skeletal muscle-enriched miRNAs are highly unstable in vivo and may be regulated in a Dicer-independent manner. FEBS J 290: 5692-5703, 2023.
30. Meng Q, Zhang J, Zhong J, Zeng D and Lan D: Novel miRNA biomarkers for patients with duchenne muscular dystrophy. Front Neurol 13: 921785, 2022.
31. Saad NY, Al-Kharsan M, Garwick-Coppens SE, Chermahini GA, Harper MA, Palo A, Boudreau RL and Harper SQ: Human miRNA miR-675 inhibits DUX4 expression and may be exploited as a potential treatment for Facioscapulohumeral muscular dystrophy. Nat Commun 12: 7128, 2021.
32. De Felice B, Annunziata A, Fiorentino G, Borra M, Biffali E, Coppola C, Cotrufo R, Brettschneider J, Giordana ML, Dalmay T, *et al*: miR-338-3p is over-expressed in blood, CFS, serum and spinal cord from sporadic amyotrophic lateral sclerosis patients. Neurogenetics 15: 243-253, 2014.
33. Dumont NA, Wang YX and Rudnicki MA: Intrinsic and extrinsic mechanisms regulating satellite cell function. Development 142: 1572-1581, 2015.
34. Feige P, Brun CE, Ritso M and Rudnicki MA: Orienting muscle stem cells for regeneration in homeostasis, aging, and disease. Cell Stem Cell 23: 653-664, 2018.
35. Yafe A, Shklover J, Weisman-Shomer P, Bengal E and Fry M: Differential binding of quadruplex structures of muscle-specific genes regulatory sequences by MyoD, MRF4 and myogenin. Nucleic Acids Res 36: 3916-3925, 2008.
36. Gunther S, Kim J, Kostin S, Lepper C, Fan CM and Braun T: Myf5-positive satellite cells contribute to Pax7-dependent long-term maintenance of adult muscle stem cells. Cell Stem Cell 13: 590-601, 2013.
37. Chen JF, Mandel EM, Thomson JM, Wu Q, Callis TE, Hammond SM, Conlon FL and Wang DZ: The role of microRNA-1 and microRNA-133 in skeletal muscle proliferation and differentiation. Nat Genet 38: 228-233, 2006.
38. Lee SW, Yang J, Kim SY, Jeong HK, Lee J, Kim WJ, Lee EJ and Kim HS: MicroRNA-26a induced by hypoxia targets HDAC6 in myogenic differentiation of embryonic stem cells. Nucleic Acids Res 43: 2057-2073, 2015.
39. Wu R, Li H, Zhai L, Zou X, Meng J, Zhong R, Li C, Wang H, Zhang Y and Zhu D: MicroRNA-431 accelerates muscle regeneration and ameliorates muscular dystrophy by targeting Pax7 in mice. Nat Commun 6: 7713, 2015.
40. Ma G, Wang Y, Li Y, Cui L, Zhao Y, Zhao B and Li K: MiR-206, a key modulator of skeletal muscle development and disease. Int J Biol Sci 11: 345-352, 2015.
41. Dey P, Soyer MA and Dey BK: MicroRNA-24-3p promotes skeletal muscle differentiation and regeneration by regulating HMGA1. Cell Mol Life Sci 79: 170, 2022.
42. Lee B, Shin YJ, Lee SM, Son YH, Yang YR and Lee KP: miR-3074-3p promotes myoblast differentiation by targeting Cav1. BMB Rep 53: 278-283, 2020.
43. Zhang Y, Yao Y, Wang Z, Lu D, Zhang Y, Adetula AA, Liu S, Zhu M, Yang Y, Fan X, *et al*: MiR-743a-5p regulates differentiation of myoblast by targeting Mob1b in skeletal muscle development and regeneration. Genes Dis 9: 1038-1048, 2022.

44. Holstein I, Singh AK, Pohl F, Misiak D, Braun J, Leitner L, Huttelmaier S and Posern G: Post-transcriptional regulation of MRTF-A by miRNAs during myogenic differentiation of myoblasts. Nucleic Acids Res 48: 8927-8942, 2020.
45. Zhao X, Gu H, Wang L, Zhang P, Du J, Shen L, Jiang D, Wang J, Li X, Zhang S, *et al*: MicroRNA-23a-5p mediates the proliferation and differentiation of C2C12 myoblasts. Mol Med Rep 22: 3705-3714, 2020.
46. Crist CG, Montarras D, Pallafacchina G, Rocancourt D, Cumano A, Conway SJ and Buckingham M: Muscle stem cell behavior is modified by microRNA-27 regulation of Pax3 expression. Proc Natl Acad Sci USA 106: 13383-13387, 2009.
47. Kong D, He M, Yang L, Zhou R, Yan YQ, Liang Y and Teng CB: MiR-17 and miR-19 cooperatively promote skeletal muscle cell differentiation. Cell Mol Life Sci 76: 5041-5054, 2019.
48. Attaix D, Combaret L, Bechet D and Taillandier D: Role of the ubiquitin-proteasome pathway in muscle atrophy in cachexia. Curr Opin Support Palliat Care 2: 262-266, 2008.
49. Hartmann-Petersen R and Gordon C: Proteins interacting with the 26S proteasome. Cell Mol Life Sci 61: 1589-1595, 2004.
50. Bodine SC, Latres E, Baumhueter S, Lai VK, Nunez L, Clarke BA, Poueymirou WT, Panaro FJ, Na E, Dharmarajan K, *et al*: Identification of ubiquitin ligases required for skeletal muscle atrophy. Science 294: 1704-1708, 2001.
51. Eddins MJ, Marblestone JG, Suresh Kumar KG, Leach CA, Sterner DE, Mattern MR and Nicholson B: Targeting the ubiquitin E3 ligase MuRF1 to inhibit muscle atrophy. Cell Biochem Biophys 60: 113-118, 2011.
52. Clavel S, Coldefy AS, Kurkdjian E, Salles J, Margaritis I and Derijard B: Atrophy-related ubiquitin ligases, atrogin-1 and MuRF1 are up-regulated in aged rat Tibialis Anterior muscle. Mech Ageing Dev 127: 794-801, 2006.
53. Gu X, Wang S, Li D, Jin B, Qi Z, Deng J, Huang C and Yin X: MicroRNA-142a-3p regulates neurogenic skeletal muscle atrophy by targeting Mef2a. Mol Ther Nucleic Acids 33: 191-204, 2023.
54. Xhuti D, Nilsson MI, Manta K, Tarnopolsky MA and Nederveen JP: Circulating exosome-like vesicle and skeletal muscle microRNAs are altered with age and resistance training. J Physiol 601: 5051-5073, 2023.
55. Ahmad N, Kushwaha P, Karvande A, Tripathi AK, Kothari P, Adhikary S, Khedgikar V, Mishra VK and Trivedi R: MicroRNA-672-5p identified during weaning reverses osteopenia and sarcopenia in ovariectomized mice. Mol Ther Nucleic Acids 14: 536-549, 2019.
56. Webster JM, Kempen LJAP, Hardy RS and Langen RCJ: Inflammation and skeletal muscle wasting during cachexia. Front Physiol 11: 597675, 2020.
57. Emery PW, Edwards RH, Rennie MJ, Souhami RL and Halliday D: Protein synthesis in muscle measured in vivo in cachectic patients with cancer. Br Med J (Clin Res Ed) 289: 584-586, 1984.
58. Warnold I, Lundholm K and Schersten T: Energy balance and body composition in cancer patients. Cancer Res 38: 1801-1807, 1978.
59. Chang VT, Xia Q and Kasimis B: The functional assessment of anorexia/cachexia therapy (FAACT) Appetite Scale in veteran cancer patients. J Support Oncol 3: 377-382, 2005.
60. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, Murphy R, Ghosh S, Sawyer MB and Baracos VE: Cancer cachexia in the age of obesity: Skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol 31: 1539-1547, 2013.
61. Yang W, Huang J, Wu H, Wang Y, Du Z, Ling Y, Wang W, Wu Q, and Gao W: Molecular mechanisms of cancer cachexia-induced muscle atrophy (Review). Mol Med Rep 22: 4967-4980, 2020.
62. Bilodeau PA, Coyne ES and Wing SS: The ubiquitin proteasome system in atrophying skeletal muscle: Roles and regulation. Am J Physiol Cell Physiol 311: C392-C403, 2016.
63. Reed SA, Sandesara PB, Senf SM and Judge AR: Inhibition of FoxO transcriptional activity prevents muscle fiber atrophy during cachexia and induces hypertrophy. FASEB J 26: 987-1000, 2012.
64. Xu J, Li R, Workeneh B, Dong Y, Wang X and Hu Z: Transcription factor FoxO1, the dominant mediator of muscle wasting in chronic kidney disease, is inhibited by microRNA-486. Kidney Int 82: 401-411, 2012.
65. He WA, Calore F, Londhe P, Canella A, Guttridge DC and Croce CM: Microvesicles containing miRNAs promote muscle cell death in cancer cachexia via TLR7. Proc Natl Acad Sci USA 111: 4525-4529, 2014.
66. Xie K, Xiong H, Xiao W, Xiong Z, Hu W, Ye J, Xu N, Shi J, Yuan C, Chen Z, *et al*: Downregulation of miR-29c promotes muscle wasting by modulating the activity of leukemia inhibitory factor in lung cancer cachexia. Cancer Cell Int 21: 627, 2021.
67. Miao C, Zhang W, Feng F, Gu X, Shen Q, Lu S, Fan M, Li Y, Guo X, Ma Y, *et al*: Cancer-derived exosome miRNAs induce skeletal muscle wasting by Bcl-2-mediated apoptosis in colon cancer cachexia. Mol Ther Nucleic Acids 24: 923-938, 2021.
68. Okugawa Y, Toiyama Y, Hur K, Yamamoto A, Yin C, Ide S, Kitajima T, Fujikawa H, Yasuda H and Koike Y *et al*: Circulating miR-203 derived from metastatic tissues promotes myopenia in colorectal cancer patients. J Cachexia Sarcopenia Muscle 10: 536-548, 2019.
69. Qiu L, Chen W, Wu C, Yuan Y and Li Y: Exosomes of oral squamous cell carcinoma cells containing miR-181a-3p induce muscle cell atrophy and apoptosis by transmissible endoplasmic reticulum stress signaling. Biochem Biophys Res Commun 533: 831-837, 2020.
70. Su SF, Chang YW, Andreu-Vieyra C, Fang JY, Yang Y, Han B, Lee AS and Liang G: miR-30d, miR-181a and miR-199a-5p cooperatively suppress the endoplasmic reticulum chaperone and signaling regulator GRP78 in cancer. Oncogene 32: 4694-4701, 2013.
71. Liu J, Huang Y, Cai F, Dang Y, Liu C and Wang J: MicroRNA-181a regulates endoplasmic reticulum stress in offspring of mice following prenatal microcystin-LR exposure. Chemosphere 240: 124905, 2020.
72. Wei Y, Tao X, Xu H, Chen Y, Zhu L, Tang G, Li M, Jiang A, Shuai S, Ma J, *et al*: Role of miR-181a-5p and endoplasmic reticulum stress in the regulation of myogenic differentiation. Gene 592: 60-70, 2016.
73. Zhang M, Zhang Q, Hu Y, Xu L, Jiang Y, Zhang C, Ding L, Jiang R, Sun J, Sun H and Yan G: miR-181a increases FoxO1 acetylation and promotes granulosa cell apoptosis via SIRT1 downregulation. Cell Death Dis 8: e3088, 2017.
74. Cisterna BA, Vargas AA, Puebla C, Fernandez P, Escamilla R, Lagos CF, Matus MF, Vilos C, Cea LA, Barnafi E, *et al*: Active acetylcholine receptors prevent the atrophy of skeletal muscles and favor reinnervation. Nat Commun 11: 1073, 2020.
75. Burke RE: Sir Charles Sherrington's the integrative action of the nervous system: A centenary appreciation. Brain 130: 887-894, 2007.
76. Dulhunty AF: Excitation-contraction coupling from the 1950s into the new millennium. Clin Exp Pharmacol Physiol 33: 763-772, 2006.
77. Canfora I, Tarantino N and Pierno S: Metabolic pathways and ion channels involved in skeletal muscle atrophy: A starting point for potential therapeutic strategies. Cells 11: 2566, 2022.
78. Bruusgaard JC and Gundersen K: In vivo time-lapse microscopy reveals no loss of murine myonuclei during weeks of muscle atrophy. J Clin Invest 118: 1450-1457, 2008.
79. De Gasperi R, Hamidi S, Harlow LM, Ksiezak-Reding H, Bauman WA and Cardozo CP: Denervation-related alterations and biological activity of miRNAs contained in exosomes released by skeletal muscle fibers. Sci Rep 7: 12888, 2017.
80. Magnusson C, Svensson A, Christerson U and Tagerud S: Denervation-induced alterations in gene expression in mouse skeletal muscle. Eur J Neurosci 21: 577-580, 2005.
81. Ehmsen JT and Hoke A: Cellular and molecular features of neurogenic skeletal muscle atrophy. Exp Neurol 331: 113379, 2020.
82. Daeschler SC, Feinberg K, Harhaus L, Kneser U, Gordon T and Borschel GH: Advancing nerve regeneration: Translational perspectives of tacrolimus (FK506). Int J Mol Sci 24: 12771, 2023.
83. Zheng H, Liu X, Katsurada K and Patel KP: Renal denervation improves sodium excretion in rats with chronic heart failure: Effects on expression of renal ENaC and AQP2. Am J Physiol Heart Circ Physiol 317: H958-H968, 2019.
84. Tokinoya K, Shirai T, Ota Y, Takemasa T and Takekoshi K: Denervation-induced muscle atrophy suppression in renalase-deficient mice via increased protein synthesis. Physiol Rep 8: e14475, 2020.
85. Sandri M: Protein breakdown in muscle wasting: Role of autophagy-lysosome and ubiquitin-proteasome. Int J Biochem Cell Biol 45: 2121-2129, 2013.
86. Bongers KS, Fox DK, Ebert SM, Kunkel SD, Dyle MC, Bullard SA, Dierdorff JM and Adams CM: Skeletal muscle denervation causes skeletal muscle atrophy through a pathway that involves both Gadd45a and HDAC4. Am J Physiol Endocrinol Metab 305: E907-E915, 2013.

87. Weng J, Zhang P, Yin X and Jiang B: The whole transcriptome involved in denervated muscle atrophy following peripheral nerve injury. Front Mol Neurosci 11: 69, 2018.
88. Nimmo R, Ciau-Uitz A, Ruiz-Herguido C, Soneji S, Bigas A, Patient R and Enver T: MiR-142-3p controls the specification of definitive hemangioblasts during ontogeny. Dev Cell 26: 237-249, 2013.
89. Huang QK, Qiao HY, Fu MH, Li G, Li WB, Chen Z, Wei J and Liang BS: MiR-206 Attenuates Denervation-Induced Skeletal Muscle Atrophy in Rats Through Regulation of Satellite Cell Differentiation via TGF-beta1, Smad3, and HDAC4 Signaling. Med Sci Monit 22: 1161-1170, 2016.
90. Li J, Wang L, Hua X, Tang H, Chen R, Yang T, Das S and Xiao J: CRISPR/Cas9-Mediated miR-29b editing as a treatment of different types of muscle atrophy in mice. Mol Ther 28: 1359-1372, 2020.
91. Srivastava S, Rathor R, Singh SN and Suryakumar G: Emerging role of MyomiRs as biomarkers and therapeutic targets in skeletal muscle diseases. Am J Physiol Cell Physiol 321: C859-C875, 2021.
92. Gu XY, Jin B, Qi ZD and Yin XF: MicroRNA is a potential target for therapies to improve the physiological function of skeletal muscle after trauma. Neural Regen Res 17: 1617-1622, 2022.
93. Abiusi E, Infante P, Cagnoli C, Lospinoso Severini L, Pane M, Coratti G, Pera MC, D'Amico A, Diano F, Novelli A, *et al*: SMA-miRs (miR-181a-5p, -324-5p, and -451a) are overexpressed in spinal muscular atrophy skeletal muscle and serum samples. Elife 10: e68054, 2021.