Critical role of miRNAs in mediating skeletal muscle atrophy (Review)

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Abstract. Skeletal muscle atrophy, a conventional clinical feature in patients with cancer, chronic obstructive pulmonary disease, sepsis and severe burns, is defined as a reduction in muscle mass. During atrophy, the protein degradation is abnormally activated and the aberrance between protein synthesis and protein degradation results in muscle atrophy. Previous studies have demonstrated that miRNAs, small non-coding RNA molecules, serve an important role in the regulation of muscle atrophy. Further studies have indicated the implications of the ubiquitin-proteasome and PI3K/Akt/FoxO signaling pathways and myogenic regulatory factors in miRNA-mediated muscle atrophy. Therefore, in this review, the effects and molecular mechanisms of miRNAs on muscle atrophy are summarized, leading to the suggestion that miRNAs may serve as potential therapeutic targets in muscle atrophy.

Contents

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1. Introduction

Skeletal muscle makes up approximately 40% of the body weight and is essential for locomotion (1). Skeletal muscle atrophy, predominantly resulting from excessive protein degradation, occurs in various conditions including starvation (2), aging (3), sepsis (4), cancer cachexia (5), severe burns (6,7) and chronic kidney disease (8). Muscle atrophy results in reductions in mobility of the patients and an increased risk of mortality (9). In patients with severe burns, skeletal muscle atrophy occurs as a result of prolongation of time spent bed-bound and suppression of wound healing (7). In general, skeletal muscle atrophy predicts poor prognosis of patients.

The ubiquitin-proteasome pathway and cell apoptosis are involved in regulating skeletal muscle atrophy (10-12). The ubiquitin-proteasome pathway contributes to protein degradation, as the targeted proteins for degradation are substrates that can be identified and bound to ubiquitin. Subsequently, poly-ubiquitinated substrates are targeted for degradation by proteasomes (11). Activation of the ubiquitin-proteasome pathway may serve an important role in the mediation of skeletal muscle atrophy (10,11). Previous studies have additionally demonstrated that increased cell apoptosis is accompanied by stress-induced skeletal muscle atrophy (12), and that apoptosis is also a critical factor which leads to muscle atrophy (13,14).

MicroRNAs (miRNAs), the small non-coding RNAs, were first identified in *C. elegans* and are highly conserved in eukaryotes (15). At present, greater than 1,700 miRNAs have been identified, which serve critical roles in regulating proliferation, differentiation and the development of various diseases (16). miRNA exerts its biological activation via binding to the 3'-untranslated region (3'-UTR) of targeted mRNA (17). Accelerating target mRNA degradation or inhibiting its translation are two key ways in which miRNA mediates the control of gene expression (18). The miRNA (miR)-1/206 family, miR-133, miR-208 and miR-488 are identified as muscle-specific miRNAs and serve essential roles in regulating normal myoblast differentiation, proliferation and muscle remodeling in response to stress (19-21). In addition, muscle-specific miRNAs, miR-128a and miR-351, are involved in the regulation of myogenesis (21,22).

The present review will focus upon the miRNAs involved in the regulation of skeletal muscle atrophy and the potential molecular mechanisms. Further studies are required in order

to elucidate the specific miRNAs implicated in stress-induced skeletal muscle atrophy, which may lead to the development of novel targets for clinical therapy.

2. The effect of the ubiquitin-proteasome pathway on miRNA-mediated muscle atrophy

Aberrant activation of protein degradation is the key factor that leads to muscle atrophy, and the ubiquitin-proteasome pathway serves a pivotal role in the mediation of protein degradation (11). The proteasome can identify the poly-ubiquitinated protein and trigger the degradation procedure (23). E3 ligase is the critical mediator of protein ubiquitination. Muscle RING finger 1 (MuRF1) and muscle atrophy F-box (MAFbx) are two muscle specific E3 ligases (24). During muscle atrophy, MuRF1 and MAFbx are overexpressed in muscle, and inhibiting the function of MuRF1 and MAFbx has been demonstrated to suppress muscle loss and subsequently attenuate muscle atrophy (25,26). Previous studies (27-29) have additionally indicated that miRNAs are implicated in the regulation of MuRF1 and MAFbx expression (Fig. 1). miR-23a is able to inhibit the translational activation of MuRF1 and MAFbx via binding with their 3'-UTR, and miR-23a transgenic mice exert resistance against glucocorticoid-induced muscle atrophy (27). In a dexamethasone (Dex)-induced mouse model of atrophy, muscle-specific miR-1 expression is upregulated. miR-1 has been previously reported to induce MuRF1 and MAFbx expression via the HSP70/protein kinase B(Akt)/forkhead box (Fox) O3 signaling pathway and is responsible for Dex-induced muscle atrophy (28). The miR-199/214 cluster is also involved in regulating the ubiquitin-proteasome pathway (29). Taken together, miRNA-dependent activation of the ubiquitin-proteasome pathway is responsible for the promotion of muscle atrophy by directly or indirectly targeting the muscle specific E3 ligases of MuRF1 and MAFbx.

3. miRNAs mediate muscle atrophy via the regulation of myogenesis

In addition to enhancing muscle proteolysis, aberrant myogenesis is also a critical factor during muscle atrophy. Myogenesis is impaired in models of mice with cancer (30), and pigs with chronic obstructive pulmonary disease (31). Inactivation of myogenesis is also observed in diseases such as Duchenne muscular dystrophy and spinal and bulbar muscular atrophy (32,33). Muscle satellite cells are stem cells with self-renewal and differentiation potency, and when muscle disruption occurs, proliferative satellite cells could differentiate into myotubes and contribute to muscle regeneration (34). Defects in post-natal myogenesis and muscle regeneration result in muscle atrophy, and miRNAs are implicated in the regulation of myogenesis and muscle atrophy (35,36). As presented in Fig. 2, paired-box transcription factor (Pax) is essential for satellite cell proliferation and differentiation. miR-1, miR-206 and miR-486 restrict satellite cell proliferation and promote its differentiation through suppression of Pax7 expression (37-39). Pax3 is also the critical factor required to trigger satellite cell proliferation; suppressing miR-27b, miR-1 and miR-206 expression suppresses satellite cell differentiation via enhancement of Pax3 activation (40,41). The myogenic regulatory factor (MRF) family, which includes MyoD, Myf5, myogenin and Myf6, has the pivotal role in myogenic differentiation. MyoD is expressed in activated satellite cells, and miR-27a overexpression elevates the MyoD protein level and enhances myoblast differentiation (42). In C2C12 myoblast cells, miR-26a upregulates MyoD expression and promotes the myogenic process (43). Subsequent to injury, miR-26a is induced during muscle regeneration, and blocking miR-26a expression enhances Smad-dependent muscle differentiation (44). miR-186 suppresses C2C12 myoblast cell myogenic differentiation via targeting myogenin (45). In addition to the MRF family, miRNAs also regulate myogenesis through targeting a variety of proteins. Myostatin is the negative mediator of myogenesis; miR-27a and miR-27b promote satellite cell proliferation and post-natal myogenesis by suppressing myostatin expression (46-48). miR-125b, miR-133 and miR-199a-3p are involved in the regulation of the insulin-like growth factor/insulin-like growth factor receptor signaling pathway and inhibit cell differentiation and muscle regeneration (49-51). miR-203 functions as the suppressor of myoblast differentiation by repressing c-Jun and myocyte enhancer factor 2C (MEF2C) expression (52). miR-155 inhibits MEF2A expression and suppresses the myogenic process (53). miR-29 is a pro-myogenic factor, which acts through downregulation of Akt3 or RING1 and YY1-binding protein (54,55). Thus, miRNAs have critical roles in regulating satellite cell proliferation, myogenic differentiation and muscle regeneration.

4. Implications of miRNAs in cell apoptosis-mediated muscle atrophy

Cell apoptosis is programmed cell death and is a promoting factor of muscle atrophy (14,56). Studies using a mouse model have demonstrated that cell apoptosis is involved in the progression of heart failure, severe burns and age-associated muscle atrophy (57-60). The mitochondria and caspase-mediated apoptotic pathways are some of the mechanisms of burn, age or stress-induced muscle atrophy (12,57,61,62). miRNA is an important mediator of myoblast cell apoptosis (63). In skeletal muscle, pre-conditional activation of interleukin (IL)-11/signal transducer and activator of transcription (STAT)3 pathway protects human skeletal myoblasts from oxidant-induced apoptosis (64), and miR-21 is a key regulator of extracellular signal-related kinase 1/2-STAT3 signaling downstream of IL-11 and inhibits the apoptosis of skeletal myoblasts (65). Skeletal muscle loss in cancer cachexia is partially associated with cell apoptosis, and a previous study indicated that miR-21 in microvesicles of cancer cachexia triggers muscle cell apoptosis via enhancement of c-Jun N-terminal kinase activation (66). In acute muscle injury, myogenic progenitor cell apoptosis is triggered by miR-351 knockdown (21). MyoD is a critical factor in the regulation muscle differentiation; MyoD knockout in myoblasts decelerates miR-1 and miR-206 expression and results in resistance to apoptosis (67). Forced MyoD expression in MyoD knockout myoblasts enhances the expression of miR-1 and miR-206 and triggers cell apoptosis via Pax3 downregulation (67). Thus, it is suggested that miRNA is a critical mediator in regulating myoblast apoptosis and implicated in muscle atrophic process.

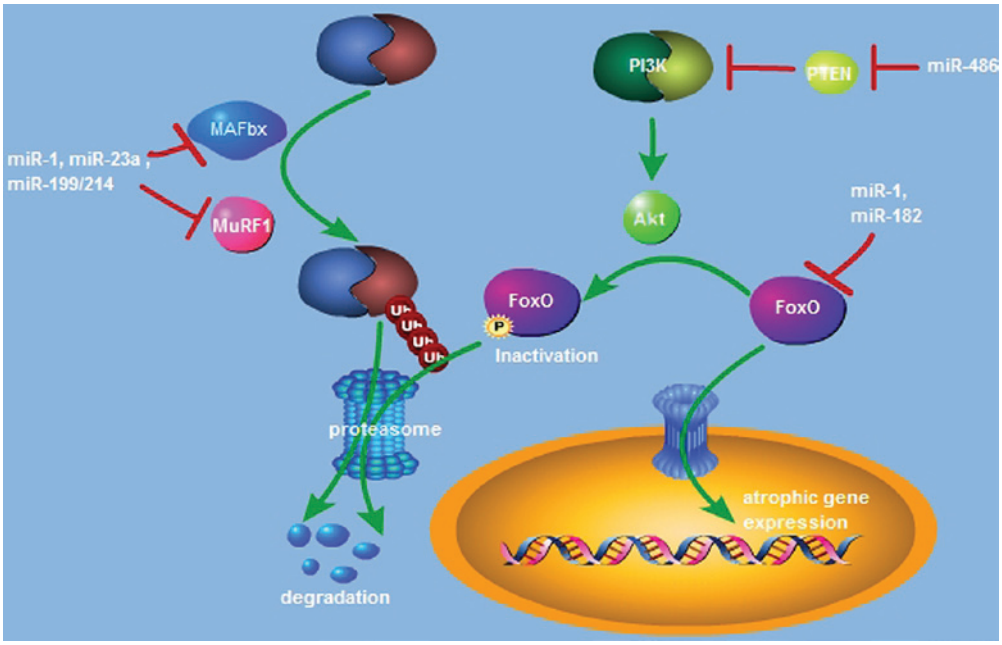

Figure 1. Schematic of the involvement of miRs in regulating muscle protein degradation and atrophic gene expression. MuRF1 and MAFbx are critical E3 ligases for mediating muscle protein ubiquitin, and ubiquitinated protein is degraded by proteasomes. miR-1, miR-182 and the miR-192/214 cluster exert inhibition of protein degradation by targeting MuRF1 and MAFbx. miRNAs are also implicated in the regulation of atrophic gene expression in a PI3K/Akt/FoxO-dependent manner. PTEN, the phosphatase of PI3K, is the target of miR-486. Suppressing PTEN expression enhances PI3K/Akt activation and promotes FoxO phosphorylation. Phosphorylated FoxO is located in the cytoplasm and is degraded by the proteasome. miR-1 and miR-182 are able to repress atrophic gene expression via inhibition of FoxO protein translation. miR, microRNA; MuRF1, muscle RING finger 1; MAFbx, muscle atrophy F-box; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; FoxO, forkhead box O; PTEN, phosphatase and tensin homolog.

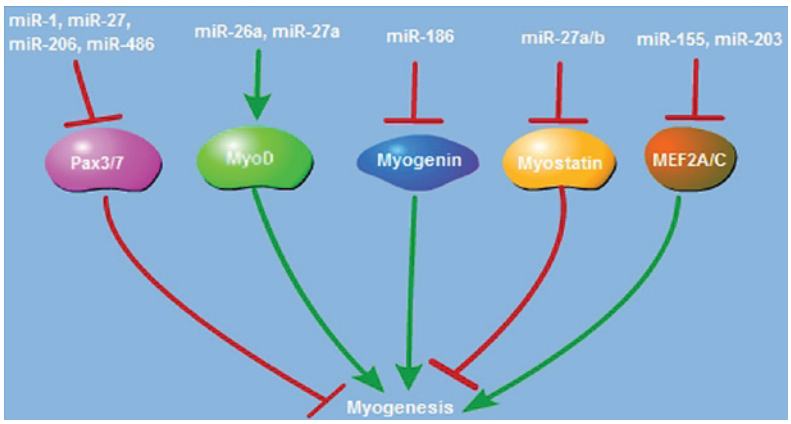

Figure 2. miRs and myogenesis regulation. The transcription factors Pax3/7 are essential for the maintenance of satellite cell proliferation and suppression of the myogenic process. Myostatin also functions as the suppressor of myogenesis. miR-1, miR-27, miR-206 and miR-486 are implicated in restriction of Pax3/7 or myostatin expression, respectively. Myogenic regulator factors, such as MyoD and myogenin, trigger myogenic process and are regulated by miR-26a, miR-27a and miR-186. miR-155 and miR-203 also suppress myogenesis by targeting MEF2A/C. miR, microRNA; Pax3/7, paired-box 3/7; MEF2A/C, myocyte enhancer factor 2A.

5. PI3K/Akt/FoxO signaling pathway in miRNA-mediated muscle atrophy

The PI3K/Akt/FoxO signal pathway serves an important role in muscle atrophy (Fig. 1). Attenuated activation of the PI3K/Akt signaling pathway results in rat skeletal muscle atrophy (13,68). Akt inactivation functions as the promoter of burn-induced muscle atrophy (69). FoxO is phosphorylated and exported into the cytoplasm by the upstream kinase Akt, and cytoplasmic FoxO is degraded with loss of transactivation (70). FoxO is additionally implicated in promoting muscle atrophy (71). Tumor necrosis factor receptor-associated factor 6 promotes starvation-induced atrophy in an Akt/FoxO3a-dependent manner (2). FoxO1, the dominant mediator of muscle atrophy, serves a critical role in chronic kidney disease or burn-induced muscle atrophy (8,72). miR-486, the regulator of PTEN, is overexpressed in Duchenne muscular dystrophy; and miR-486 transgenic mice exert the impairment of muscle regeneration in a PTEN/Akt dependent manner (73). In patients with breast patients, miR-486 is downregulated, and the expression of its target genes PTEN and FoxO1A are elevated (74). Myostatin is well known as a negative regulator of muscle mass by reducing protein synthesis. Overexpression of miR-486 is observed in skeletal muscle of myostatin knockout mice and is essential to maintain skeletal

muscle size through the Akt/mTOR signaling pathway (75). In the C2C12 myotube cells, miR-182 was reported to suppress FoxO3a protein expression via binding to the 3'-UTR of FoxO3a mRNA, and prevent glucocorticoid-induced rat muscle atrophy (76). Muscle-specific miR-1 is involved in dephosphorylating and activating FoxO3a in an HSP70/Akt dependent manner and promotes Dex- or myostatin-induced atrophy in skeletal muscle (28). In summary, PI3K/Akt inactivation reduces FoxO protein phosphorylation and dephosphorylated FoxO enters into the nucleus and promotes muscle atrophy.

6. Conclusion

Aberrant muscle protein degradation, impairment of myogenesis, and promotion of muscle cell apoptosis are all important factors that contribute to muscle atrophy. miRNAs are critical mediators of protein degradation and myogenesis through regulation of the ubiquitin-proteasome and PI3K/Akt/FoxO signaling pathways and other myogenic regulatory factors. Thus, miRNAs may be potential and effective therapeutic targets for muscle atrophy.

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