Extracellular vesicle microRNAs mediate skeletal muscle myogenesis and disease (Review)

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Abstract. Skeletal muscle function is important for good health and independent living, and has been subject to numerous studies focused on skeletal muscle development, function and metabolism. However, progressive and degenerative changes in skeletal muscle function often occur following physiological and pathological stress, and these lead to the progression of diabetes, obesity, chronic kidney disease, and cardiovascular or respiratory diseases. Identifying the mechanisms that influence the processes regulating skeletal muscle function is a key priority. Recently, studies have demonstrated that microRNAs (miRNAs) play important roles in regulating biological processes. For instance, exosomes are key tools for communication between cells. Therefore, by determining how select miRNAs are transported to target organs and initiate their effects, these results will help explain muscle and organ crosstalk, improve our understanding and application of current therapeutic approaches and lead to the identification of new therapeutic strategies and targets aimed at maintaining and/or improving skeletal muscle health.

Contents

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1. Introduction

Skeletal muscle is a major organ for all animals, including humans, and it comprises ~40% of the body's mass. Control of movement and posture are its primary functions, and the development and function of skeletal muscle is regulated by different factors. Recently, microRNA (miRNA) studies have provided an opportunity for improved understanding of the molecular processes of skeletal muscle diseases. Research suggests that miRNAs play important roles in skeletal muscle development, and several miRNAs have been identified as biomarkers for myogenesis, muscle mass, and nutrient metabolism in physiological and pathological states (1,2). Several miRNAs are specifically expressed in muscle (myomiRs). Myocyte proliferation and differentiation are influenced by miRNAs, and miRNAs may affect muscle fiber types by regulating several transcriptional repressors.

In addition, miRNAs have recently been identified in extracellular body fluids, such as serum, plasma, urine, milk, and spinal fluid (3-5). These circulating miRNAs (ci-miRs) are embedded in microvesicles (MVs) or exosomes, which transport proteins, lipids, mRNAs and miRNAs to regulate recipient cell functions (6). Multiple cell types have been demonstrated to release vesicles into the extracellular medium, including mesenchymal cells, adipocytes, fibroblasts, immune cells, platelets, myoblasts and tumor cells (7-16). Evidence suggests that exosomes carrying specific miRNAs, such as miR-1, miR-21, miR-133, miR-182, and miR-206, are targeted to myocytes and modulate the physiology and pathology status of myocytes by altering gene expression (5,17). To date, there is limited knowledge regarding miRNAs and exosome biology, therefore, further studies are required to clarify the molecular mechanisms and precise involvement of miRNAs in muscle development and regeneration.

2. miRNAs and microvesicles

miRNAs are small (~20-30 nucleotides in length), non-coding RNAs that are highly conserved between plants and mammals. miRNAs downregulate gene expression post-transcriptionally and fine-tune target genes in the organs of all animals, including humans. Organ-specific miRNAs may be important in controlling their development, function and disease. Furthermore, a single miRNA targets the expression

of multiple genes, whereas one gene is regulated by multiple miRNAs (17,18). It has been predicted that miRNAs regulate ~60% of the protein-coding genes that could be involved in a wide range of biological processes (19). The miRNAs miR-1 and miR-133a are expressed in cardiac and skeletal muscle, whereas miR-206/miR-133b is expressed only in skeletal muscle (20,21).

Several biological processes, including muscle growth and differentiation, are mediated by a collection of specific miRNAs. Numerous miRNAs can be released from cells in the surrounding areas or into circulation, and appear resistant to harsh conditions, such as RNA enzyme degradation (22,23). Researchers hypothesize that miRNAs are also involved in cell-to-cell communication for the epigenetic regulation of recipient cells. miRNAs shuttled between cells appear to be preserved and mediated by extracellular vesicles (exosomes and MVs), which are emerging as potent genetic transfer agents (24,25).

Cells secrete extracellular vesicles (EVs), MVs and exosomes, which are small, membrane-derived particles, usually 30-1,000 nm in diameter (26). Exosomes are defined as nanosized membrane vesicles with a diameter of 30-100 nm, originating from multivesicular endosomes that fuse with the plasma membrane and are released by cells into the extracellular environment. They differ from microvesicles, which have a diameter of 100-1,000 nm and originate from the plasma membrane (27-29).

While the mechanisms of extracellular formation and secretion are not well-defined, evidence indicates that such vesicles possess the capability of 'communicating' with neighboring or distant cells by fusing with the plasma membrane and subsequently delivering their cargo, which consists of various molecules including proteins, mRNAs, and miRNAs (30,31). Moreover, transported miRNAs are capable of targeting mRNAs in recipient cells (30,32).

Exosomes are released from the plasma membrane and can be identified by specific markers, such as Hsp-60/70 in the lumen and CD9, CD63, CD81 and tissue-specific membrane proteins on the cell surface (22,33,34).

The data presented in the study by Yang *et al* (35) suggests that NF-κB may regulate exosomal protein expression at a remote site via circulation following ischemia-reperfusion injuries. Myoblasts and myotubes utilize exosome clustered miRNAs as endocrine signals to regulate important signaling pathways (e.g., the Wnt signaling pathway) for muscle homeostasis and regeneration. Furthermore, muscle behavior is influenced by the release of vesicles from multiple sources, such as mesenchymal stem cells. Recent evidence has demonstrated that miRNAs (e.g., miR-494 and myomiRs) released in exosomes from mesenchymal stem cells can promote muscle regeneration following injury by enhancing myogenesis and angiogenesis (24,36). Furthermore, stress may promote the release of exosomes that are carrying a variety of cargoes, inducing transfer to other cells in the local environment or farther away through systemic circulation (37).

3. miRNAs, microvesicles and muscle growth

Several miRNAs are highly enriched in skeletal muscle, and these can influence myocyte proliferation and differentiation. The importance of miRNAs in muscle development has been established in a previous study involving conditional transgenic mice lacking Dicer in myogenic progenitors. The study resulted in aberrant muscle differentiation accompanied by hyperplasia (38). Furthermore, miR-206 has been identified as the most abundant miRNA in adult vertebrate skeletal muscle and is known to promote skeletal muscle development and differentiation (22,39).

In fact, myotube-derived exosomes promoted the differentiation of target myoblasts by downregulating Cyclin-D1 and Myogenin (40). However, it was unclear whether miR-186, -329 and -362 were involved, since they were predicted binders for the 3'-UTRs of both genes. Intriguingly, using the same myoblast model, atrophic myotubes presented decreased intracellular levels, while showing increased exosomal fractions of miR-23a (41) and miR-182 (42). This result indicated that the exosome load was selectively choosing miRNAs under stressful conditions (43).

The upregulation of miR-1, miR-133, and miR-206 levels during myoblast differentiation is known to protect myocytes against atrophy (44). Interestingly, a mutation in the myostatin gene that causes a dramatic muscle increase in textile sheep, creates a target site for miR-206 and miR-1. In these sheep, myostatin downregulation determines the phenocopy of the double muscling Belgian Blue cattle (22).

Muroya *et al* (45) investigated the effects of grazing on the expression of miRNAs in cattle plasma with the hypothesis that the plasma miRNA profile reflects the physiological adaptation of different tissue types, such as skeletal muscle and adipose tissue. The miR-451 levels were elevated in the grazing cattle in comparison with the housed cattle. Synchronous miR-451 expression was also observed in the skeletal muscle, which may result in the secretion or intake of miRNAs between circulation and tissue cells in grazing cattle. Nakamura *et al* (36) investigated the role of mesenchymal stem cell (MSC) exosomes in skeletal muscle regeneration. MSC exosomes promoted myogenesis and angiogenesis *in vitro*, and muscle regeneration in an *in vivo* model of muscle injury. Although MSC exosomes had low concentrations of muscle-repair-related cytokines, several repair-related miRNAs were identified. The results of the study by Nakamura *et al* (36) suggest that the MSC-derived exosomes promoted muscle regeneration by enhancing myogenesis and angiogenesis, which is partially mediated by miRNAs, such as miR-494.

4. miRNAs, microvesicles and muscle wasting

Numerous previous studies have indicated that miRNA expression is involved in skeletal muscle diseases. In muscular dystrophy, inflammatory, myopathies, and congenital myopathies rhabdomyosarcomas (muscle tumor), individual miRNAs have been shown to cause or alleviate disease. It is known that ci-miRs are traceable in plasma or serum and appear resistant to harsh conditions, such as RNase activity. Among the vesicle-based carriers, exosomes are emerging as important regulators of long-range miRNA shuttling (43,46).

Many miRNAs may potentially be used as biomarkers, since they circulate in the blood, are often tissue-specific and resistant to degradation due to circulation in protective exosomes (47-49). Several miRNAs, including miR-1,

-133, -206, and -499, involved in muscle homeostasis and metabolism were demonstrated to be associated with muscle wasting (50-52). Furthermore, miR-30b and -181a are involved in the regulation of muscle regeneration and inflammation (50,53). Those muscle-specific miRNAs may be useful biomarkers for the early development of acute muscle wasting in critically ill patients (49).

A previous study demonstrated that tumor-derived microvesicles induced apoptosis in skeletal muscle cells. This proapoptotic activity was mediated by miRNA cargo, miR-21, which signals through the toll-like 7 receptor (TLR7) on murine myoblasts to promote cell death (5,54,55). Xu *et al* (56) verified that miRNA-486 decreases FoxO1 protein expression and promotes FoxO1 phosphorylation to suppress E3 ubiquitin ligases, and thus presents an excellent candidate for future studies on the mechanisms of regulation of muscle atrophy by miRNAs in cachexia. In addition, miR-206 and miR-21 were recently described as being important in muscle wasting during catabolic conditions (57).

miR-29a, a key regulator of tissue fibrosis, is highly expressed in the exosomes and marginal area of a remote ischemic conditioning (RIC) group. Even in the differentiated C2C12-derived exosomes, miR-29a expression is significantly increased under hypoxic conditions (58). Hu *et al* (59) confirmed that age-induced muscle senescence resulted from the activation of miR-29 by wnt-3a, which led to suppressed expression of the signaling proteins p85α, IGF-1 and B-myb, which coordinate to impair the proliferation of the MPCs and contribute to muscle atrophy.

In chronic kidney disease (CKD), muscle atrophy is a serious complication as it is associated with increased morbidity and mortality. Hu *et al* (60) confirmed that CKD suppresses miR-29 in the muscle, which leads to higher expression of the transcription factor YY-1, thereby suppressing myogenesis. However, further studies are required to identify whether miR-29 is transported by exosomes and microvesicles to affect muscle atrophy.

5. miRNAs, microvesicles and exercise

Exercise stimulates numerous structural, metabolic, and morphological adaptations in skeletal muscle. These adaptations are vital in order to maintain human health over a life span, and miRNAs constitute a new regulatory component that may be important in these adaptations (61). Since miRNAs are incorporated into exosomes, microvesicles, or protein complexes, they can be detected in human plasma (62). miRNAs in skeletal muscle are modified after physical exercise, especially after acute exercise. miR-1, -133a, and -206 are potential novel biomarkers for aerobic exercise capacity since they are highly correlated to standard performance parameters (62). Baggish *et al* (63) demonstrated altered expression of specific ci-miRs in response to both acute and chronic exercise interventions.

Circulating miRNA-126 increases in response to different forms of endurance exercise in healthy adults, however, there is no impact on the levels of miRNA-133, a marker for muscle damage (64). Nielsen *et al* (65) examined miRNAs in human plasma as a response to acute exercise and chronic endurance training with a novel methodological approach. Their data indicated that eight ci-miRs (miR-106a, -221, -30b, -151-5p, let-7i, miR-146a, -652,-151-3p) were downregulated immediately following acute exercise. Six ci-miRs (miR-338-3p, -330-3p, -223, -139-5p, miR-143, -1) were upregulated 1-3 h following acute endurance exercise. Basal ci-miRs levels were altered following 12 weeks of endurance training, and seven ci-miRs (miR-342-3p, let-7d, miR-766, -25, -148a, -185, -21) were decreased, while two ci-miRs (miR-185, -21) were increased following the training period (65).

Guescini *et al* (66) investigated muscle tissue release of EVs carrying miRNAs in the bloodstream during physical exercise. A significant positive correlation was found between the aerobic fitness and muscle-specific miRNAs, and EV miR-133b and -181a-5p were significantly upregulated following acute exercise. Therefore, EVs could be a novel means for muscle communication involved in muscle remodeling and homeostasis.

6. Muscle and organ cross talk through microvesicles

Organ crosstalk may also be achieved by the release of miRNAs packaged in exosomes that are transported through circulation and delivery to other tissues (67,68). Accumulating evidence suggests that skeletal muscle is also involved in the crosstalk between other organs (69,70).

In the past year, multiple publications have introduced exciting details regarding cell-to-cell communication, and exosomes are quickly becoming biomarkers for disease progression and cancer recurrence. Research has shown that cell-to-cell communication using microvesicles and exosomes, produced by MSCs, can be transferred to damaged tissues to help repair skeletal muscle injuries (71).

The data confirmed that β-F1-ATPase translation was lower in obese individuals compared with healthy weight controls and was correlated with miR-127-5p expression. Moreover, studies demonstrated that miR-127-5p is present in muscle-derived blood exosomes, suggesting their putative involvement in intracellular cross-talk (72).

The field of direct cell-to-cell communication, especially myocyte to other neighboring cells, is an exciting one (73). miRNA enriched exosomes are highly regulated by various stressors and disease conditions, and have been implicated in skeletal muscle function (19). Therefore, it is possible that exercise leads to the release of miRNA-enriched exosomes into the circulatory system from working muscles, the heart, or adipose tissue to facilitate organ crosstalk and control gene expression (67).

Muscles and kidneys can crosstalk with the slow progression of CKD. The mechanisms for this interaction involve muscle secretomes, consisting of a variety of growth factors and cytokines that are expressed and secreted by skeletal muscle (69). Akt1-mediated fast/glycolytic skeletal muscle growth reversed muscle wasting and reduced renal damage in a UUO model (74). However, it is unclear if microvesicles and exosomes mediate muscle-kidney crosstalk.

7. Conclusion

The emergence of the exosome field provides an exciting opportunity to further understand cell-cell communication in

skeletal muscle and muscle-organ crosstalk. miRNAs transported via extracellular vesicles may mediate skeletal muscle development, regeneration, function and diseases. miRNAs are potential biomarkers that may be powerful and exciting tools for the diagnosis and treatment of skeletal muscle diseases in the future.

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