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Noncoding RNAs in the regulation of skeletal muscle biology in health and disease

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Abstract

Skeletal muscle is composed of multinucleated myofibers that arise from the fusion of myoblasts during development. Skeletal muscle is essential for various body functions such as maintaining posture, locomotion, breathing, and metabolism. Skeletal muscle undergoes remarkable adaptations in response to environmental stimuli leading to atrophy or hypertrophy. Moreover, degeneration of skeletal muscle is a common feature in a number of muscular disorders including muscular dystrophy. Emerging evidence suggests that noncoding RNAs, such as microRNAs (miRNAs) and long noncoding RNAs (lncRNAs), are critical for skeletal muscle physiology. Several miRNAs and lncRNAs have now been found to control skeletal muscle development and regeneration. Noncoding RNAs also play an important role in the regulation of skeletal muscle mass in adults. Furthermore, aberrant expression of miRNAs and lncRNAs has been observed in several muscular disorders. In this article, we discuss the mechanisms of action of miRNAs and lncRNAs in skeletal muscle formation, growth, regeneration, and disease. We further highlight potential therapeutic strategies for utilizing noncoding RNAs to improve skeletal muscle function.

Keywords

Skeletal muscle; Myogenesis; MicroRNA; Long noncoding RNA; Muscular dystrophy

Introduction

Skeletal muscle is the most abundant and a highly plastic tissue of the human body. During embryonic development, skeletal muscle originates from the paraxial mesoderm, forming somites, then the dermomyotome, and finally the myotome. Myoblasts undergo frequent divisions and fuse together leading to the formation of multinucleated myotubes/myofibers [1]. In postnatal skeletal muscle, a fraction of the muscle progenitor cells enters quiescence and resides underneath the basal lamina of adult muscle fibers as satellite cells [2, 3]. Although adult skeletal muscle is a terminally differentiated tissue, it is capable of regenerating in response to injury. The regenerative capacity of skeletal muscle is attributed to the presence of satellite cells. Upon muscle injury, satellite cells enter the cell cycle,

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proliferate, and give rise to myoblasts. Myoblasts differentiate into myocytes, which fuse with one another or with injured myofibers to complete the repair process [3, 4]. While the majority of satellite cells commit to the myogenic lineage, a fraction of them self-renew and returns to quiescence in order to replenish the satellite cell pool necessary for future rounds of muscle repair.

The term “myogenesis” is used to describe the process of muscle formation during embryonic development and satellite cell-mediated regeneration of injured myofibers [3, 5]. Myogenesis is regulated by the sequential expression of multiple transcription factors (Figure 1). While both paired-box (Pax) 3 and Pax7 transcription factors are involved in early lineage specification [5], Pax7 is exclusively expressed in satellite cells and is required for self-renewal and maintenance of their myogenic potential in adult skeletal muscle [4]. Quiescent satellite cells express high levels of Pax7 protein, whereas other myogenic regulatory factors (MRFs) such as Myf5 and MyoD are undetectable. Following specification to the myogenic lineage, the levels of Pax7 are repressed, whereas the levels of Myf5 and MyoD are increased, giving rise to proliferative myoblasts. Myoblasts differentiate into myocytes, which express the late MRFs, myogenin (MyoG) and MRF4. Myocytes then fuse with one another to form multinucleated myotubes/myofibers, which express both the late MRFs and specific muscle proteins, including the components of thin and thick filaments [4, 6].

Adult skeletal muscle also undergoes changes in size and metabolic activity in response to extracellular and intracellular cues [7]. For example, resistance exercise training, nutritional uptake, and several growth factors cause an increase in skeletal muscle mass (known as hypertrophy), contractility, and metabolic function leading to enhanced force generation capacity and resistance to fatigability [8]. By contrast, in response to inactivity and many chronic disease states, skeletal muscle undergoes atrophy, which is characterized by the reduction in fiber cross-sectional area, protein content, and strength resulting in increased fatigability and insulin resistance [7]. Moreover, skeletal muscle undergoes degeneration in a number of muscle disorders including muscular dystrophy [8, 9].

Accumulating evidence suggests that noncoding RNAs play important roles in the acquisition and maintenance of skeletal muscle mass and function. In contrast to the “housekeeping” noncoding RNAs, microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) regulate gene expression in many biological processes, including myogenesis. Initially discovered in *C. elegans* in the 1990s [10], miRNAs are evolutionarily conserved, short (~22 nucleotides), endogenous, noncoding RNAs, transcribed by RNA polymerase II [11]. miRNAs inhibit post-transcriptional gene expression by inducing mRNA degradation or translational repression [12]. In contrast, lncRNAs (>200 nucleotides) were more recently identified as endogenous non-protein coding RNAs [13], which share several mRNA-like features, including polyadenylation [14]. Since lncRNAs exhibit lower expression levels and poor sequence conservation compared to protein-coding transcripts [13, 15], they were previously deemed non-functional. However, recent studies have demonstrated that lncRNAs are a diverse class of noncoding RNAs, containing several members with a multitude of cellular functions. LncRNAs are classified based on their genomic location or transcriptional orientation, and regulate multiple aspects of gene expression via mechanisms which are still

less understood [16-18]. In this article, we provide a succinct overview of the current knowledge about the role of miRNAs and lncRNAs in skeletal muscle formation, adaptation, and disease.

Noncoding RNAs in myogenesis

It is now evident that both miRNAs and lncRNAs play important roles in the regulation of distinct steps of myogenesis (Tables 1 and 2). The role of miRNAs and lncRNAs in myogenesis has largely been studied using the C2C12 myoblastic cell line, and to some extent in primary myoblasts derived from the hind limb muscles of mice, both of which can differentiate and fuse into multinucleated myotubes in low serum conditions *in vitro*.

Role of miRNAs

The term “myomiRs” was coined to describe miRNAs that are enriched in skeletal and/or cardiac muscle. Among them, “the classical myomiRs”, miR-1, miR-133a/b, and miR-206, were first described in 2004 [19] and exhibit differential expression patterns in skeletal and cardiac muscle. miR-1 and miR-133 are abundant in both skeletal and cardiac muscle, whereas miR-206 is preferentially expressed in skeletal muscle [20, 21]. Distinct transcription factors (including MRFs) upregulate the expression of these classical myomiRs during skeletal myogenesis [21-27]. Interestingly, both miR-1 and miR-133 are derived from the same miRNA polycistron and transcribed together, but they differentially regulate proliferation and differentiation of myogenic cells (Table 1). miR-1 promotes myogenic differentiation by targeting histone deacetylase 4 (HDAC4), a transcriptional repressor of muscle gene expression, which functions by inhibiting the activity of myocyte-specific enhancer factor 2C (MEF2C) transcription factor [22, 28, 29]. Repression of HDAC4 by miR-1 also results in the production of follistatin, which promotes myocyte fusion leading to muscle growth [30]. By contrast, miR-133 promotes myoblast proliferation primarily through repressing the levels of serum response factor (SRF), a transcription factor essential for myogenic differentiation [22, 31].

Another myomiR, miR-206, promotes myogenic differentiation by targeting the largest subunit (p180; *Pola1*) of DNA polymerase α , the replicative polymerase with functions in cell proliferation [21]. Suppression of *Pola1* by miR-206 inhibits DNA synthesis, leading to reduced proliferation and increased differentiation of myoblasts [21]. Moreover, miR-206 may promote myogenic differentiation by indirectly reducing the levels of MRF inhibitors, such as Myogenic Repressor (MyoR) and DNA-Binding Protein Inhibitor 1-3 (Id1-3) [21]. The transcription factor MyoD activates the expression of a large number of muscle genes, but it also suppresses the expression of many genes by directly recruiting transcriptional repressors to specific promoters [4, 5]. Forced expression of MyoD converts a number of cell types including fibroblasts, melanocytes, adipocytes, and chondrocytes into myoblasts [32]. Intriguingly, MyoD overexpression in fibroblasts augments the expression of miR-206, which represses gene expression of Follistatin-like 1 (*Fstl1*) and Utrophin (*Utrn*) during differentiation [33]. While the expression of *Utrn* is reduced and the expression of a related protein dystrophin is induced during myogenic differentiation, whether miR-206 mediated repression of *Utrn* is essential for myogenic differentiation remains to be determined.

The transcription factor Pax7 is essential for the survival, self-renewal, and proliferation of satellite cells in adult skeletal muscle [4]. Levels of Pax7 are repressed, whereas the levels of MyoD are induced in satellite cells upon their progression into the myogenic lineage [4]. In an elegant study, Chen et al have demonstrated that miR-1 and miR-206 target Pax7 mRNA to facilitate satellite cell differentiation [23]. We have recently demonstrated that tumor necrosis factor (TNF) receptor associated factor 6 (TRAF6), an adaptor protein which also functions as an E3 ubiquitin ligase, is an important regulator of satellite cell homeostasis in adult skeletal muscle [34]. TRAF6-mediated signaling is required for the activation of the c-JUN/activator protein 1 transcription factor, which increases the expression of Pax7 in satellite cells [34]. Interestingly, lack of TRAF6 dramatically increases the levels of miR-1, miR-133, and miR-206 in cultured myogenic cells and in injured myofibers of satellite-cell specific TRAF6-knockout mice, leading to precocious differentiation of satellite cells. Overexpression of c-JUN represses the levels of these myomiRs in satellite cells [34]. Although the exact mechanisms of this regulation remain unknown, these findings suggest that downstream of TRAF6, c-JUN/AP1 helps maintain the satellite cell pool and prevents precocious differentiation by directly augmenting the transcription of Pax7 and repressing the level of classical myomiRs.

In a genetic screen for miRNAs regulated by myocardin-related transcription factor-A, another myomiR, miR-486, was identified which facilitates myogenic differentiation [35-37]. Pax7 mRNA is a critical target of miR-486 in satellite cells. Overexpression of miR-486 in myogenic cells accelerates differentiation, whereas inhibition of miR-486 causes a persistence of Pax7 protein and reduced differentiation [35]. Notably, this function of miR-486 is shared by two other myomiRs, miR-1 and miR-206, which also target Pax7 mRNA [23, 35]. Since MyoD regulates the expression of these myomiRs, they appear to play an important role in fine-tuning the transition between satellite cell self-renewal and differentiation. Moreover, miR-486 also targets phosphatase and tensin homolog (PTEN) and the transcription factor FoxO1a, which negatively regulate phosphoinositide-3-kinase (PI3K)/Akt signaling [36-38]. Although the role of the PI3K/Akt pathway in satellite cell homeostasis remains enigmatic, activation of this pathway may augment protein synthesis leading to myotube growth during myogenesis [7, 39].

An additional network of myomiRs (miR-208a/b and miR-499) has been identified which regulates the expression of genes involved in regulating muscle fiber type [40]. Interestingly, these myomiRs are encoded in the intronic region of three myosin heavy chain (*Myh*) genes, *Myh6*, *Myh7*, and *Myh7b*, and their expression parallels that of host genes [41]. miR-208a is encoded by the intronic region of *Myh6* and is predominantly expressed in cardiac muscle, whereas miR-208b is encoded by the *Myh7* gene and is expressed at high levels in slow-type skeletal muscle fibers with lower expression in the heart. Finally, miR-499 is encoded by *Myh7b* and is expressed in both cardiac muscle and the slow-type skeletal muscle [41]. Although functionally redundant, miR-208b and miR-499 promote the slow-type muscle phenotype by repressing fast and activating slow myofiber gene programs. Double miR-208b and miR-499 knockout mice exhibit a dramatic reduction in the number of slow-type fibers with a concomitant increase in fast-type fibers in the soleus muscle. Conversely, muscle-specific overexpression of miR-499 resulted in the conversion of all fast-type fibers to slow-type fibers in mice [41]. These myomiRs program skeletal muscle fibers to a slow

fiber type phenotype by reducing the levels of transcriptional repressors of slow fiber muscle genes, such as SRY (Sex-Determining Region Y)-Box 6 (Sox6), Purine rich element binding protein β (Pur β) and Sp3 [41]. Insertion of these myomiRs into *Myh* genes and their co-expression suggests that a finely regulated network involving both transcriptional and post-transcriptional mechanisms controls development, specification, and function of skeletal muscle during development.

Myogenesis is also regulated by several non-muscle specific miRNAs. Elevated expression of miR-23a inhibits myoblast differentiation by targeting multiple adult fast myosin heavy chain genes, including *Myh 1, 2* and *4* [42]. By contrast, miR-29 facilitates myoblast differentiation by targeting its repressor Yin Yang 1 (YY1) [43] or the downstream target Akt3 [44]. The therapeutic potential of miR-29 is also evident by the findings that overexpression of miR-29 reduced the levels of YY1 and improved differentiation in myoblast cultures derived from hind limb muscles of mice with chronic kidney disease [45]. Moreover, miR-146b facilitates myogenic differentiation through targeting Smad Family Member 4 (*Smad4*), High Mobility Group AT-Hook 2 (*Hmga2*) and *Notch1* [46], whereas miR-181 increases terminal differentiation of myogenic cells by targeting homeobox protein Hox-A11, a repressor of the differentiation process [47]. A recent study has demonstrated that miR-186, which is repressed during myogenic differentiation, targets myogenin in differentiating myoblasts. In addition, overexpression of miR-186 inhibits the terminal differentiation of C2C12 myoblasts by targeting myogenin [48]. In contrast, miR-27a/b promotes satellite cell activation and myoblast proliferation by targeting myostatin. Intriguingly, treatment of myoblasts with myostatin increases the expression miR-27a/b in a Smad3-dependent manner, suggesting a feedback mechanism by which myostatin increases miR-27a/b levels and in turn reduces its own expression [49].

A few miRNAs have been implicated in regulating satellite cell quiescence and activation during embryonic and adult myogenesis (Table 1). Pax3 is required for the maintenance of muscle stem cells in the somite and their migration to sites of myogenesis during embryonic development [1, 5], and elevated levels of Pax3 interfere with muscle stem cell differentiation. Studies show that expression of miR-27b is induced during the initiation of the myogenic differentiation program, and miR-27b promotes differentiation by targeting Pax3 mRNA. Inhibition of miR-27b causes sustained Pax3 expression, resulting in increased myogenic proliferation and a delay in the onset of muscle stem cell differentiation [50]. A more recent study has shown that miR-31 helps maintain satellite cells in a quiescent state through targeting Myf5. Both miR-31 and Myf5 mRNA are sequestered in mRNP granules present in quiescent satellite cells. Activation of satellite cells leads to the dissociation of mRNP granules and repression of miR-31, leading to the increased translation and accumulation of Myf5 protein [51]. These findings suggest that miRNAs are important post-transcriptional regulators with critical roles in muscle stem cell homeostasis and function.

Finally, a few upstream signaling molecules have been identified which regulate the expression of these miRNAs in myogenic cells. Transforming growth factor- β 1 (TGF- β 1) represses miR-24 transcription in a Smad3-dependent manner, resulting in diminished myogenic differentiation [52]. TGF- β 1 also represses miR-29 and miR-206 levels, leading to increased HDAC4 expression, thereby inhibiting myogenesis [53]. Another major regulator

of miRNA expression in myogenic cells is the transcription factor nuclear factor-kappa B (NF- κ B), which represses miR-29 levels through the transcription factor YY1 and the Polycomb group in myoblasts [43]. Conversely, NF- κ B and YY1 downregulation lead to increased levels of miR-29, and, in turn, miR-29 inhibits differentiation by targeting its repressor YY1 [43]. Moreover, fibroblast growth factors (FGFs) delay the induction of miR-1, miR-133 and miR-206 in low serum conditions, whereas bone morphogenetic protein 2 (BMP-2) reduces the levels of miR-206 in myogenic cells [26, 54].

Role of lncRNAs

Compared to miRNAs, lncRNAs have been relatively less studied in myogenesis (Table 2). A few lncRNAs such as *H19* (gene comes from colon pH19), MyoD upstream noncoding RNA (MUNC), and long intergenic noncoding RNA that is associated with muscle differentiation (linc-MD1) are expressed only in skeletal muscle, whereas long noncoding RNA 31 (lnc-31) is expressed in several tissues including skeletal muscle, and lncMyoD is not present in mature skeletal muscle [27, 55-60]. The levels of many lncRNAs are upregulated after induction of myogenic differentiation, and these lncRNAs differentially regulate myogenesis. For example, linc-MD1, Metastasis-associated lung adenocarcinoma transcript 1 (Malat1), Core enhancer RNA (^{CE}RNA), Distal regulatory regions RNA (^{DRR}RNA), MUNC, lncMyoD, and Steroid Receptor RNA activator (SRA) lncRNAs promote myogenesis, whereas Mouse Staufeni-binding site RNAs (m^{1/2}-sbsRNAs) inhibit myogenesis, or both (H19) [27, 57-65, 76]. Furthermore, levels of a few lncRNAs such as lnc-31 and YY1-associated muscle lncRNA (Yam-1), which inhibit myogenic differentiation, are repressed after incubation of myoblasts in low serum conditions [59, 66].

Myogenic regulatory functions of various lncRNAs have been linked to a specific cellular compartment. Cytoplasmic lncRNAs such as linc-MD1, lnc-31, m^{1/2}-sbsRNAs have been implicated in regulating myogenesis [67]. Linc-MD1 was the first cytoplasmic and polyadenylated muscle-specific lncRNA found to positively regulate myogenic differentiation [27]. While the mechanisms by which linc-MD1 regulates myogenesis are not entirely understood, linc-MD1 may act as a sponge for some miRNAs [27, 68]. Interestingly, the sponging activity of linc-MD1 for miR-133, enhanced by the RNA binding protein Human antigen R (HuR), is necessary to maintain myogenic cells in the early differentiation stage, and elevated miR-133 is required for progression into later differentiation stages [68]. Therefore, a regulatory circuitry between linc-MD1, miR-133 and HuR is critical for early myogenic differentiation (Figure 1). However, the sponging activity of linc-MD1 for miR-133 and miR-135, facilitated by inhibition of HuR, is also necessary to facilitate progression to later myogenic stages via regulation of two transcription factors, Mastermind-like-1 (MAML1) and MEF2c, respectively, which activate muscle-specific gene expression [27]. Further investigations are needed to determine how linc-MD1 controls myogenesis via the regulation of miRNAs.

In contrast to linc-MD1, lnc-31 may inhibit myogenic differentiation, although the mechanism remains unknown [59]. Interestingly, lnc-31 controls muscle differentiation independently from miR-31, in spite of genomic overlapping with the miR-31 coding region [59]. Finally, m^{1/2}-sbsRNAs are largely cytoplasmic and polyadenylated lncRNAs which

belong to the class of Short-interspersed element (SINE)-containing lncRNAs. Knockdown of m^{1/2}-sbsRNA2(B2) promotes myogenesis due to a decrease in the efficiency of Staufen-mediated mRNA decay (SMD) of TRAF6 [65], a translation-dependent mechanism important for myogenesis [69] mediated via STAU1 (Staufen 1) and STAU2 (Staufen 2) proteins [65, 70, 71]. While it is clear that m^{1/2}-sbsRNAs inhibit myogenesis, whether this regulation occurs through the STAU1 and STAU2 proteins remains unknown.

Nuclear lncRNAs, such as Malat1, ^{CE}RNA, ^{DRR}RNA, and SRA also play important functions during myogenesis. Malat1 lncRNA has been linked to both epigenetic repression and pre-mRNA splicing in the nucleus via interacting with serine/arginine (SR) splicing factors [72]. Malat1 is a positive regulator of myogenic proliferation and differentiation [61, 62], whose regulation and mechanisms of action in myogenesis have just begun to be understood. Malat1 expression is reduced following treatment of myogenic cells or mouse muscles with myostatin [61], a protein that suppresses muscle growth [73]. In addition, the transcription factor SRF reduces Malat1 levels, and, in turn, Malat1 knockdown leads to decreased *SRF* levels, indicating reciprocal regulation during myogenesis [62]. Finally, Malat1 acts as a sponge for miR-133 in myogenic cells. Upon Malat1 knockdown, miR-133 bound to Malat1 is released, allowing miR-133 to act on the *SRF* 3'UTR, thereby inhibiting myogenesis [62]. In addition to Malat1, other nuclear lncRNAs modulate myogenesis by various mechanisms. Enhancer RNAs (eRNAs), such as ^{CE}RNA and ^{DRR}RNA lncRNAs improve differentiation via promoting chromatin accessibility and RNA polymerase II residency at *MYOD1* and *MYOG* loci, respectively [63]. Similar to eRNAs, SRA and the RNA helicases p68/p72 co-activate MyoD-dependent transcription at chromatin regulatory regions of actively transcribed muscle loci (Figure 1). Moreover, the Steroid Receptor RNA activator protein (SRAP) can also bind to SRA and counteract the SRA-mediated activation of MyoD and muscle differentiation [64, 74].

Interestingly, some lncRNAs, such as H19, have been localized to both the nucleus and cytoplasm and may exert multiple functions. H19 is enriched in the cytoplasm of myogenic cells [75] and plays a dual role in myogenesis, as H19 knockdown leads to both accelerated and inhibited myogenic differentiation [57, 76]. Interestingly, H19 controls myogenic differentiation by regulating miRNA levels. H19 acts as a molecular sponge for let-7 miRNA, leading to inhibition of myogenic differentiation by promoting the gene expression of High Mobility Group AT-Hook 2 (*Hmga2*), *Dicer*, and Insulin-like growth factor 2 (*Igf-2*), which have been identified as downstream effectors of H19 during differentiation [76]. In contrast, a more recent study has shown that H19 promotes myogenic differentiation via two conserved miRNAs, miR-675-3p and miR-675-5p, encoded by the exon 1 of *H19* [57]. In turn, miR-675-3p promotes myogenic differentiation by repressing levels of the BMP pathway transcription factors Smad1 and Smad5, whereas miR-675-5p represses levels of Cell Division Cycle 6 (*Cdc6*), a DNA replication initiation factor [57]. Future studies are needed to clarify whether the miRNA sponging and miRNA precursor functions of H19 lncRNA are critical for regulating specific stages of muscle development.

Another important lncRNA that negatively regulates myogenesis is YY1-associated muscle lincRNA (Yam-1), which is equally detected in both the nucleus and cytoplasm of myogenic cells [66]. Yam-1 functions to suppress differentiation, as Yam-1 knockdown in C2C12

myoblasts and myotubes led to increases in several myogenic markers [66]. Moreover, knockdown of Yam-1 can overcome the inhibitory effect of the transcription factor YY1 on myogenic differentiation. Finally, Yam-1 knockdown also leads to elevated expression of the pro-myogenic protein Wnt7b, which is a target of miR-715. Based on these observations, a model emerges in which YY1 positively regulates expression of Yam-1, which acts as an anti-myogenic factor likely by regulating miR-715, which in turn targets Wnt7b to repress differentiation [66].

Finally, a few other lncRNAs (e.g. MUNC, LncMyoD) have been found to regulate myogenic differentiation by various mechanisms without being localized to a specific cellular compartment in differentiated muscle cells. MUNC directly enhances endogenous *MyoD*, *myogenin* and *Myh3* gene expression from a heterologous promoter [58], establishing MUNC as a positive regulator of myogenesis. Similarly, LncMyoD, located upstream of the *MYOD1* gene, also promotes myogenesis. Although LncMyoD inhibits translation of proliferation genes *N-RAS* and *c-Myc* via IGF-2 mRNA binding protein (IMP2) [60], the relevance of this regulation for myogenesis is still unknown. Collectively, these reports establish lncRNAs as major regulators of skeletal muscle formation.

Noncoding RNAs in skeletal muscle regeneration

Accumulating evidence suggests that similar to *in vitro* myogenesis, both miRNAs and lncRNAs regulate skeletal muscle regeneration (Tables 1 and 2). In this section, we summarize the functions of several miRNAs and lncRNAs in regulating muscle regeneration in response to cardiotoxin (CTX) or BaCl₂, two commonly utilized myotoxins for acute muscle injury in rodents.

Role of miRNAs

The classical myomiRs have been implicated in the regeneration of injured skeletal muscle. The expression of miR-1 is increased during muscle regeneration, most notably at 7-21 days following BaCl₂ injury, and this increase can be blocked by rapamycin, an inhibitor of mammalian target of rapamycin (mTOR) [30]. We have recently demonstrated that the regeneration of skeletal muscle is severely impaired in hind limb muscles from satellite cell-specific Traf6-knockout (Traf6^{scko}) mice [34]. Levels of miR-1, miR-133a, and miR-206 are dramatically induced in tibialis anterior muscle of Traf6^{scko} mice at day 5 post BaCl₂ injury, suggesting that aberrant regulation of these classical myomiRs is one of the potential reasons for the inhibition of muscle regeneration in Traf6^{scko} mice [34]. In contrast, one study has reported reduced expression of miR-1, miR-133a/b and miR-206 (to a lesser extent) at day 3 post CTX injury [23]. Finally, another study showed repression of miR-1, miR-133a and miR-206 expression at early time points after CTX injury, followed by induction and sustained expression later during muscle regeneration, with miR-206 showing the most drastic changes [25]. Increased expression of miR-206 in regenerating myofibers at days 5 and 7 following CTX injury further indicates a major role of miR-206 in skeletal muscle repair [25]. However, the causal relationship between the expression of these myomiRs and muscle regeneration remains to be investigated.

Other myomiRs, such as miR-486, have also been implicated in skeletal muscle regeneration. miR-486 inhibits regenerative myogenesis, since transgenic overexpression of miR-486 in mice showed delayed muscle regeneration following CTX-mediated injury [36]. While miR-486 inhibits PTEN/PI3K/Akt signaling in regenerating myofibers [36, 38], the importance of this pathway for muscle repair downstream of miR-486 is not yet known. Finally, the majority of non-myomiRs implicated in muscle regeneration (e.g. miR-23a, miR-24, miR-29b, miR-181a, miR-221 and miR-222) are modestly upregulated to varying degrees at day 3 post CTX injury [23], whereas levels of miR-146b are increased between days 3-5 post BaCl₂ injury [46]. Together, these studies suggest miRNAs may play critical roles in the regulation of regenerative myogenesis.

Role of lncRNAs

Recent studies have shown that lncRNAs including H19, Yam-1, MUNC, and lncMyoD play important roles in skeletal muscle regeneration in the CTX model of muscle injury. The lncRNA H19 appears to regulate the entire muscle regeneration process. H19 levels decrease at days 1-3, increase at days 5-7, and decrease slightly at day 14 following CTX-mediated injury. Indeed, smaller myofibers and inflammatory cells are observed at day 14 post CTX injury in *H19*-knockout mice, establishing H19 as a positive regulator of muscle regeneration [57]. Interestingly, H19 may promote muscle regeneration via miR-675, evident by the findings that the expression of H19 and its encoded miR-675-3p and miR-675-5p follow the same expression pattern during muscle regeneration, and miR-675-3p and miR-675-5p can rescue the regeneration defects observed in *H19*-knockout mice [57]. In addition, miR-675-3p and miR-675-5p repress gene expression of Smad1, Smad5 and Cdc6 during muscle regeneration following CTX-mediated injury [57], further indicating that H19 may promote muscle repair through controlling downstream targets of miR-675.

Other lncRNAs are also involved in regulating specific stages of muscle regeneration. In contrast to H19, Yam-1 expression is induced at day 2 following CTX-mediated injury, and then sharply declines and remains low for the remainder of the regeneration process [66], indicating a function for Yam-1 in early muscle regeneration. Interestingly, Yam-1 knockdown in CTX-injured muscles leads to a higher number of newly formed regenerating myofibers [66], indicating Yam-1 is a negative regulator of muscle regeneration. Similar to *in vitro* myogenesis, the YY1-Yam-1-miR-715 regulatory axis also plays a role in muscle regeneration and Yam-1 may inhibit muscle regeneration through miR-715 mediated downregulation of Wnt7b [66]. Like Yam-1, the expression of lncMyoD is upregulated between days 3-5 following CTX injury, and decreases during later regeneration stages [60], suggesting a role for lncMyoD in early muscle regeneration. Although MyoD could be an important upstream regulator of lncMyoD expression [60], this regulation remains to be investigated during muscle regeneration following CTX injury. In contrast to these lncRNAs, knockdown of MUNC leads to a reduced average myofiber diameter at day 14 following CTX injury [58], suggesting that MUNC is involved in the regulation of later stages of muscle regeneration (Table 2). Whether other lncRNAs with known roles in myogenesis also regulate specific stages of muscle regeneration is an important avenue of future research.

Noncoding RNAs in skeletal muscle atrophy

Skeletal muscle atrophy occurs when the rate protein degradation exceeds that of protein synthesis [39]. The ubiquitin-proteasome system (UPS) is one of the most important proteolytic systems that causes selective degradation of muscle structural proteins in several catabolic states. Two muscle-specific E3 ubiquitin ligases, muscle RING-finger 1 (MuRF1) and muscle atrophy F-box (MAFBx; also known as Atrogin-1) are the key enzymes of the UPS involved in muscle proteolysis in almost all atrophy conditions [77]. The role of a few miRNAs (but not lncRNAs) in skeletal muscle atrophy has been studied in both cultured myotubes and rodent models (Table 3).

Proinflammatory cytokines are important stimuli for the induction of muscle atrophy, especially in chronic disease states [7, 78]. Treatment of C2C12 myotubes with the muscle-wasting cytokine, TNF-like weak inducer of apoptosis (TWEAK), leads to reduced expression of several miRNAs (e.g. miR-1, miR-133a/b, and miR-206) and increased expression of other miRNAs (e.g. miR-146a) [79]. Some of these findings were recapitulated in the hind limb muscles of TWEAK-transgenic mice, where miR-1 and miR-133 levels are reduced, whereas miR-146a levels are increased [79]. Although the physiological significance of these findings has not yet been investigated, these results indicate that dysregulation of miRNA expression may constitute a mechanism underlying cytokine-induced muscle atrophy.

Several miRNAs exhibit changes in expression pattern in the rat soleus muscle following hind limb suspension (HS), a model of muscle atrophy. Importantly, expression levels of miR-208b and miR-499 are reduced at 28 days post HS [80, 81]. These miRNAs are proposed to be part of the myosin gene (myomiRs) network regulating myosin heavy chain (MHC) expression, as well as the previously described role in skeletal muscle fiber type [81]. Interestingly, the decreased expression of these miRNAs was paralleled by the upregulation of Sox6 and Pur β , two predicted targets of miR-499 and repressors of β -myosin heavy chain expression [80]. This mechanism suggests the myomiRs network regulates β -myosin heavy chain expression in skeletal muscle atrophy indirectly via targeting transcription factors such as Sox6. In addition, miR-499 overexpression promotes a fast-to-slow-twitch fiber type transition, partly mediated by Sox6 downregulation [80, 81]. In addition, miR-499 and miR-23b may also regulate skeletal muscle mass by targeting myostatin [80]. Further studies will define the mechanisms by which these miRNAs regulate skeletal muscle mass in models of disuse atrophy.

Glucocorticoids such as dexamethasone are important mediators of muscle wasting in many conditions [7]. Treatment of myotubes with dexamethasone or injection of dexamethasone into the hind limb muscle of mice leads to increased expression of miR-1, additionally facilitated by myostatin. Increased miR-1 expression during dexamethasone-induced atrophy reduces heat shock protein (HSP70) levels [82]. HSP70 is required for the phosphorylation of Akt, a major kinase of the IGF-1/Akt/mTOR pathway that mediates protein synthesis and prevents activation of the UPS through inhibiting the activity of the FOXO family of transcription factors. Loss of Akt phosphorylation (due to increased expression of miR-1) enhances the activation of FoxO3 which upregulates the transcription of MuRF1 and

MAFBx [82]. By contrast, overexpression of miR-23a counteracts dexamethasone-induced muscle atrophy in cultured myotubes and in adult muscle fibers, potentially by inhibiting the translation of MuRF1 and MAFBx mRNAs [83].

Muscle atrophy is also a major problem in chronic kidney disease (CKD). Interestingly, enhancing miR-486 levels attenuates muscle atrophy in a mouse model of CKD [84]. Overexpression of miR-486 rescues muscle atrophy in CKD by targeting FoxO1 and PTEN, which are required for the gene expression of MuRF1 and MAFBx [37, 84]. Finally, miRNAs have also been implicated in the age-associated muscle loss known as sarcopenia. However, most of these sarcopenia studies measured the changes in various miRNAs in young and aged subjects without understanding the physiological significance and targets of these miRNAs [85].

Noncoding RNAs in skeletal muscle hypertrophy

Skeletal muscle hypertrophy is characterized by an increase in myofiber diameter and force output [7]. A few miRNAs (but not lncRNAs) have been implicated in the regulation of skeletal muscle hypertrophy in response to different stimuli (Table 3). Repression of miR-206 promotes hypertrophy and increases protein synthesis in cultured C2C12 myotubes. Mechanistically, inhibition of miR-206 causes hypertrophy of cultured myotubes through derepression of HDAC4 [86]. Thus, miR-206 inhibition leads to increased HDAC4 levels, whereas miR-206 overexpression leads to decreased HDAC4 levels in myotubes [86]. Intriguingly, overexpression or inhibition of miR-206 using adeno-associated virus constructs did not affect skeletal muscle fiber size in adult mice in basal conditions or after subjecting them to conditions of hypertrophy (i.e. treatment with follistatin) and atrophy (i.e. denervation), despite significant changes in the endogenous levels of miR-206 in these conditions. These findings suggest that miR-206 is a negative regulator of myotube size but is dispensable for the regulation of muscle mass *in vivo* in specific conditions of atrophy or hypertrophy, potentially through the activation of compensatory mechanisms [86]. Another model of *in vivo* hypertrophy is functional overload. In this model, miR-206 expression is unchanged, whereas levels of miR-1 and miR-133 are reduced [87]. However, the role of miR-1 and miR-133 in overload-induced hypertrophy has not been yet investigated.

Myostatin, a major negative regulator of skeletal muscle mass, reduces muscle protein synthesis by inhibiting the IGF-1/Akt/mTOR pathway [39, 88]. The levels of miR-486 are significantly increased in the hind limb muscles of myostatin-knockout mice [38]. Further analysis showed that overexpression of miR-486 increases, whereas its inhibition reduces, the diameter of cultured C2C12 myotubes, suggesting that miR-486 is an important player in regulating muscle mass *in vitro* [38]. Moreover, miR-486 was essential for maintaining skeletal muscle size *in vivo* [38]. Inhibition of miR-486 results in suppression of Akt activity in C2C12 myotubes, implying that miR-486 is part of a regulatory axis between myostatin signaling and the IGF-1/Akt/mTOR pathway in skeletal muscle [38]. Further investigation is required to understand the role of various miRNAs and lncRNAs in the regulation of skeletal muscle hypertrophy and atrophy.

Noncoding RNAs and skeletal muscle disorders

Muscular dystrophy is a group of human muscular disorders caused by mutations in specific genes encoding various structural proteins, signaling molecules, proteolytic enzymes, and proteins involved in posttranslational modifications [9, 89]. Among these, Duchenne muscular dystrophy (DMD) is one of the most prevalent and severe forms of muscular dystrophy. DMD results from the loss of functional dystrophin protein, a major component of the dystrophin-glycoprotein complex on the sarcolemma, which connects the cytoskeleton of the muscle fibers to the extracellular matrix [90]. In the absence of dystrophin, the dystrophin-glycoprotein complex becomes functionally impaired, and the mechanical stress associated with contraction results in the degeneration of skeletal muscle fibers, muscle wasting, and ultimately death of the afflicted individuals [91, 92]. Another important type of muscular dystrophy is Facioscapulohumeral muscular dystrophy (FSHD), a progressive disease of the muscles of the face, shoulder blades and upper arms. FSHD is caused by a heterozygous partial deletion of a critical number of repetitive elements (D4Z4) on chromosome 4q35 [93]. While miRNAs are linked to both dystrophic and non-dystrophic muscle diseases, lncRNAs have only been studied in models of muscular dystrophy (Table 4).

Role of miRNAs

Dysregulation of miRNA expression is a common feature of muscle diseases, evident by microarray profiling of miRNAs in both muscles from human patients and animal models of various muscular disorders [89]. Interestingly, miRNAs exhibit differential expression patterns in various muscular disorders, including several types of muscular dystrophy, as well as in non-dystrophic muscle diseases. Microarray profiling studies show that several miRNAs (e.g. miR-146b, miR-221 and miR-222) are upregulated in both DMD and FSHD, whereas miR-181d is upregulated in DMD, and miR-146a is upregulated in FSHD human patient muscles, among other muscle diseases. In contrast, among the muscular dystrophies examined, miR-486 is only decreased in human patient muscles from DMD patients, and miR-29a/b is decreased in DMD but upregulated in FSHD human patient muscle samples [36, 89]. In addition, the levels of miR-486 and miR-29 are also reduced in dystrophic muscles of *mdx* mice, a well-established mouse model of DMD [36, 94]. A recent study has further demonstrated that muscle-specific transgenic overexpression of miR-486 ameliorates myopathy in a mouse model of DMD through regulating the dedicator of cytokinesis 3 (DOCK3)/PTEN/Akt signaling pathway [95]. Similarly, overexpression of a miR-29 mimic increases regeneration and inhibits fibrosis in the dystrophic muscles of *mdx* mice [94]. Moreover, some miRNAs can serve as biomarkers to monitor DMD disease progression. For example, the levels of miR-1, miR-133 and miR-206 are upregulated in the serum of DMD patients [96], and the expression of miR-206 is also upregulated in the regenerating myofibers of *mdx* mice [25]. Very few studies have examined the mechanisms by which miRNAs regulate muscular dystrophy. Some miRNAs directly regulate the expression of cytoskeletal proteins in dystrophic muscles. Thus, miR-31, which targets the dystrophin mRNA, is elevated in both DMD patients and skeletal muscles of *mdx* mice [96]. In addition, the expression of miR-199a is also upregulated in dystrophic muscles of *mdx* mice, and miR-199a may thus modulate muscle regeneration in *mdx* mice through targeting

components of the Wnt signaling pathway [97]. While the role of a few miRNAs with dysregulated expression in dystrophic muscles has been recently validated by loss-of-function or gain-of-function approaches, whether and how the changes in the levels of several other miRNAs contribute to muscle disease remains to be investigated. Additionally, the changes in the levels of these miRNAs may also be secondary to the degeneration/regeneration responses in dystrophic muscles.

Role of lncRNAs

Similar to miRNAs, the expression of several lncRNAs is dysregulated in muscular dystrophy (Table 4). A recent study has shown that the dystrophin gene encodes several lncRNAs in its introns, and these lncRNAs are co-expressed with it. Although the role of these lncRNAs in the pathogenesis of DMD remains unknown, some of them repress the expression of endogenous full-length dystrophin isoforms through interactions with the dystrophin promoter [98]. The lncRNA lnc-31, which promotes myoblast proliferation but inhibits differentiation, is upregulated in skeletal muscles of *mdx* mice and in skeletal muscles of DMD patients [59]. However, the potential role of lnc-31 in the pathophysiology of DMD has not yet been investigated. Similar to lnc-31, linc-MD1 is also dysregulated in skeletal muscles of *mdx* mice and DMD patients [27]. The mechanisms by which lncRNAs regulate DMD pathogenesis are still unknown. However, expression of linc-MD1 mimics the expression of pri-miR-133b and pri-miR-206 in skeletal muscles of *mdx* mice. Because linc-MD1 and miR-206 are both expressed only in newly regenerated *mdx* myofibers [25, 27, 96], linc-MD1 could regulate the levels of miR-206 in *mdx* muscles. Interestingly, the levels of linc-MD1 are greatly reduced in myoblasts derived from muscles of DMD patients, and myoblasts from DMD patients exhibit impaired differentiation [27]. Importantly, linc-MD1 overexpression in DMD myoblasts restored myogenic differentiation, as well as expression of several downstream targets, such as MALM1 and MEF2C, suggesting that overexpression of linc-MD1 can be used as a therapeutic approach to ameliorate DMD pathogenesis [27]. In addition to DMD, the lncRNA D4Z4 binding element-transcript (DBE-T) is implicated in FSHD, evident by the findings that DBE-T transcription selectively occurs in FSHD patients or in FSHD-like conditions [99]. Mechanistically, DBE-T is mainly associated with chromatin at the FSHD locus and DBE-T directly binds to the Trithorax group protein Ash1L and recruits it to the FSHD locus, leading to derepression of FSHD candidate genes, and contributing to FSHD pathogenesis [99]. Thus, DBE-T could potentially be utilized as a therapeutic target for FSHD. Given the very small number of lncRNAs associated with muscular dystrophies, future studies should address role of other lncRNAs in muscle diseases.

Therapeutic potential of noncoding RNAs in muscle diseases

The ability of miRNAs and lncRNAs to modulate gene expression provides critical insights into the molecular mechanisms of muscular disease. Expression of many miRNAs and few lncRNAs is aberrantly regulated in various muscle diseases. Because several miRNAs are upregulated in muscular disorders, reducing their levels via modified antisense RNA oligonucleotides, such as antagomirs, locked-nucleic acids, or locked-nucleic-acid-modified oligonucleotides are promising therapeutic avenues. An alternative method for decreasing

miRNA levels in muscle disease is to exploit the function of lncRNAs acting as miRNA sponges. Conversely, as some miRNAs exhibit decreased expression in various muscle diseases, enhancing their levels through overexpression of miRNAs in cultured myoblasts, followed by injection of myoblasts into hindlimb muscles of mice, or alternatively by using direct intramuscular injection of miRNAs *in vivo*, are other potential therapeutic avenues. In addition, miRNA mimics can enhance the levels of beneficial miRNAs and repress the expression of specific targets involved in pathological changes in skeletal muscle. Importantly, the specific miRNA and lncRNA expression patterns in muscular disorders also enable the development of potential disease biomarkers. Whereas lncRNAs have not been studied extensively in skeletal muscle diseases, manipulating their levels by siRNA-mediated knockdown or overexpression may also constitute a therapeutic strategy. In addition, drugs can be developed to modulate the expression and activity of miRNAs or lncRNAs in the context of a specific muscle disease. It is noteworthy that delivering miRNAs and lncRNAs for therapeutic purposes pose technical challenges including efficiency of delivery method, stability, and target specificity *in vivo*. Instead of targeting miRNAs and lncRNAs themselves, manipulating the levels of their downstream targets is also a potential strategy that can be utilized to improve skeletal muscle health and function.

Conclusions and future perspectives

The above discussion demonstrates that noncoding RNAs clearly regulate multiple aspects of skeletal muscle health and disease and show therapeutic promise for muscular disorders. However, there are still many outstanding questions to be addressed. For example, the mechanisms by which noncoding RNAs function in skeletal muscle physiology and pathophysiology remain poorly understood. It is important to understand whether manipulating a particular miRNA can influence muscle disease progression. Moreover, miRNAs have dozens or hundreds of targets participating in multiple molecular pathways, and understanding how these pathways are coordinated by various noncoding RNAs in muscle diseases is another important area of future research.

In contrast to miRNAs, lncRNAs have just begun to emerge as regulators of muscle formation and pathology. The development of novel high-throughput methods will likely allow the identification of many more lncRNAs with important functions in skeletal muscle physiology. Functions of lncRNAs have so far been linked to only a few stages of myogenesis. Future investigations should address the potential functions of lncRNAs in regulating other steps of myogenesis, as well as deciphering the molecular pathways by which lncRNAs regulate myogenesis. Performing in-depth studies of lncRNA function in myogenesis and their regulation and potential role in muscular disorders is currently a major challenge because of their low expression level, lack of sequence conservation, and variability in terms of genomic location and context. Examining lncRNA interactions with other molecules such as miRNAs and proteins may provide mechanistic insights into their mode of action during myogenesis and muscle diseases. Finally, future studies will likely uncover novel functions for noncoding RNAs with critical roles in the regulation of skeletal muscle health and disease.

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List of abbreviations

BMP-2	Bone morphogenetic protein 2
Cdc6	Cell Division Cycle 6
CE^{RNA}	Core enhancer RNA
CKD	Chronic kidney disease
CTX	Cardiotoxin
DBE-T	D4Z4 binding element-transcript
DMD	Duchenne muscular dystrophy
DOCK3	Dedicator of cytokinesis 3
DRR^{RNA}	Distal regulatory regions RNA
eRNA	Enhancer RNAs
FGF	Fibroblast growth factor
FSHD	Facioscapulohumeral muscular dystrophy
Fstl1	Follistatin-like 1
HDAC4	Histone Deacetylase 4
Hmga2	High Mobility Group AT-Hook 2
HS	Hindlimb suspension
HSP70	Heatshock protein 70
HuR	Human antigen R
Id1-3	DNA-Binding Protein Inhibitor 1-3
IGF2	Insulin-like growth factor 2
IMP2	IGF2-mRNA-binding protein 2
Linc-MD1	Long intergenic ncRNA that is associated with muscle differentiation
LincRNA	Long intergenic non-coding RNA
Lnc-31	Long non-coding RNA 31

LncRNA	Long non-coding RNA
m^{1/2}-sbsRNAs	Mouse Staufen1-binding site RNAs
MAFBx	Muscle atrophy F-box
Malat1	Metastasis-associated lung adenocarcinoma transcript 1
Maml1	Mastermind-like-1
MEF2C	Myocyte enhancer factor-2C
miR, miRNA	MicroRNA
MRF	Myogenic regulatory factor
mTOR	Mammalian target of rapamycin
MUNC	MyoD upstream noncoding RNA
MuRF1	Muscle RING-finger 1
Myh	Myosin heavy chain
MyoR	Myogenic Repressor
NF-κB	Nuclear factor-kappa B
Pax 3/7	Paired box 3/7
PI3K	Phosphoinositide-3-kinase
PTEN	Phosphatase and tensin homolog
Purβ	Purine rich element binding protein β
SINE	Short-interspersed element
SMD	Staufen-mediated degradation
Sox6	(Sex-Determining Region Y)-Box 6
SRA	Steroid receptor RNA activator
SRF	Serum response factor
STAU	Staufen
TGF-β1	Transforming growth factor-β1
TRAF6	TNF receptor associated factor 6
TWEAK	TNF-like weak inducer of apoptosis
UPS	Ubiquitin-proteasome system
Utrn	Utrophin

Yam-1	YY1-associated muscle lincRNA
YY1	Yin Yang 1

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FIGURE 1. Interactions between miRNAs and lncRNAs during myogenesis

During *in vitro* myogenesis, a fraction of the satellite cells undergoes self-renewal to maintain the satellite cell pool. Satellite cells proliferate and give rise to myoblasts, which differentiate into myocytes and fuse to one another to form myotubes. Several lncRNAs either promote (green box) or inhibit (red box) various steps of myogenesis. Some of these lncRNAs function as sponges (pink inhibitory lines) for various miRNAs (blue boxes). In turn, miRNAs target downstream molecules (black boxes), which mediate myogenesis. The transcription factors expressed in myogenic cells at distinct stages of myogenesis are shown in green boxes at the bottom.

TABLE 1

Role of major miRNAs in the regulation of myogenesis and skeletal muscle regeneration.

miRNA	Function	Target(s)
miR-1	Promotes differentiation	HDAC4 [22, 30], Pax7 [23]
miR-23a	Inhibits differentiation	Myh 1, 2, 4 [42]
miR-24	Promotes differentiation	Unknown
miR-27a/b	Promotes satellite cell activation and myoblast proliferation	Myostatin [49]
	Promotes differentiation	Pax3 [50]
miR-29	Promotes differentiation	YY1 [43], Akt3 [44], HDAC4 [53]
miR-31	Promotes satellite cell quiescence	Myf5 [51]
miR-133	Promotes proliferation	SRF [22]
miR-146b	Promotes differentiation	Smad4, Hmga2, Notch1 [46]
miR-181	Promotes terminal differentiation	Hox-A11 [47]
miR-186	Inhibits terminal differentiation	Myogenin [48]
miR-206	Promotes differentiation and inhibits proliferation	Pax7 [23, 35], Pola1 [21], MyoR [21], Id1-3 [21], HDAC4 [53]
	May promote regeneration [25]	Unknown
miR-208b	Promotes the slow-fiber type phenotype	Sox6, Purβ, Sp3 [41]
miR-486	Promotes differentiation	Pax7 [35], PTEN/FoxO1a [36-38]
	Inhibits regeneration [36]	Unknown
miR-499	Promotes the slow-fiber type phenotype	Sox6, Purβ, Sp3 [41]

TABLE 2

Role of major lncRNAs in the regulation of myogenesis and skeletal muscle regeneration.

LncRNA	Function	Mode of Action
CE ^{RNA} , DRR ^{RNA}	Promotes myogenesis	Increases levels of MyoD and Myogenin [63]
H19	Inhibits differentiation Promotes differentiation and regeneration	Let-7 (sponging) [76]; Increases Dicer, HMGA2, IGF-2 (let-7 targets) [76] Produces miR-675-3p and miR-675-5p, which target Smad1, Smad5, Cdc6 [57]
Linc-MD1	Promotes early differentiation Facilitates progression to later myogenic stages	miR-133 (sponging) and regulated by HuR [68] miR-133, miR-135 (sponging) [27]; Increases MAML1, MEF2c (targets of miR-133/135) [27]
LncMyoD	Promotes in vitro myogenesis and may promote early stages of muscle regeneration [60]	Unknown
Lnc-31	Inhibits differentiation [59]	Unknown
Malat1	Promotes myogenesis	Sponges miR-133, leading to increased SRF levels [62]
MUNC	Promotes in vitro myogenesis and later stages of muscle regeneration	Enhances expression of MyoD, Myogenin, Myh3 [58]
m ^{1/2} -sbsRNA2(B2)	Inhibits myogenesis	Reduces TRAF6 by Staufen-mediated mRNA decay [65]
SRA	Promotes differentiation	Augments MyoD-dependent muscle gene expression [64]
Yam-1	Inhibits differentiation and may interfere with later stages of muscle regeneration	Activates miR-715 which targets Wnt-7b [66]

TABLE 3

Role of noncoding RNAs in the regulation of skeletal muscle atrophy and hypertrophy.

Condition	Noncoding RNA	Mode of action
Atrophy	miR-1, miR-1331a/b miR-206, miR-146a	TWEAK decreases expression of miR-1, miR-133a/b and miR-206 and increases expression of miR-146a [79]
	miR-221, miR-499, miR-208b	Hind limb suspension decreases expression of miR-221, miR-499 and miR-208b [80]; increases the levels of Sox6 (miR-499 target) and decreases β -myosin heavy expression [80, 81]
	miR-1	Dexamethasone increases the expression of miR-1 which targets HSP70 resulting in loss of Akt phosphorylation and enhanced FoxO3 activation [82]
	miR-23a	Overexpression of miR-23a counteracts dexamethasone-induced atrophy potentially by inhibiting the translation of MuRF1 and MAFBx mRNAs [83]
	miR-486	Overexpression of miR-486 rescues atrophy in a model of chronic kidney disease by targeting FoxO1 and PTEN, which are required for MuRF1 and MAFBx gene expression [37, 84]
Hypertrophy	miR-206	Inhibition of miR-206 promotes myotube hypertrophy through de-repression of HDAC4 [86]
	miR-486	Increased myotube size in vitro and helps maintain skeletal muscle mass in vivo [38]
	miR-1, miR-133	Levels of miR-1 and miR-133 are reduced in response to functional overload [87]

TABLE 4

Role of noncoding RNAs in muscular dystrophy.

Disease	Non-coding RNA	Regulation
DMD	miR-146b, miR-221, miR-222, and miR-181d	Upregulated in muscle biopsies from DMD patients [89]
	miR-486	Decreased in human muscles from DMD patients [36, 89] and in <i>mdx</i> muscles [36, 95]; Ameliorates myopathy in <i>mdx</i> mice through the DOCK3/PTEN/Akt pathway [95]
	miR-29 a/b	Repressed in human muscles from DMD patients [89] and in skeletal muscle of <i>mdx</i> mice [94]. Overexpression of miR-29 mimic promotes regeneration and inhibits fibrosis in the dystrophic muscles of <i>mdx</i> mice [94]
	miR-1, miR-133, miR-206	Upregulated in the serum of DMD patients [96]. Only miR-206 is upregulated in newly formed myofibers of <i>mdx</i> mice [25]
	miR-31	Elevated in both muscles biopsies from DMD patients and skeletal muscles of <i>mdx</i> mice. Targets Dystrophin mRNA [96].
	miR-199a	Upregulated in dystrophic muscles of <i>mdx</i> mice. Targets Wnt pathway [97].
	lnc-31	Upregulated in skeletal muscles of <i>mdx</i> mice and DMD patients [59].
	linc-MD1	Repressed in myoblasts derived from muscles of DMD patients. Overexpression of linc-MD1 increases MALM1 and MEF2C and promotes differentiation in DMD myoblasts [27]
FSHD	miR-146b, miR-221, miR-222, miR-146a, and miR-29a/b	Upregulated in muscle biopsies from FSHD patients [89]
	DBE-T	Upregulated in FSHD patients' muscle or in FSHD-like conditions. Increases expression of FSHD candidate genes [99]