Dystrophin orchestrates the epigenetic profile of muscle cells via miRNAs

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FUNCTION OF THE DYSTROPHIN GLYCOPROTEIN COMPLEX
Muscular dystrophies (MDs) are a group of fatal inherited diseases (~30), associated with progressive muscle wasting caused by muscle membrane fragility, abnormal metabolic control, increased oxidative and energetic stress and abnormal proliferation of satellite cells (Campbell, 1995; Cohn and Campbell, 2000; Constantin et al., 2006; Vercherat et al., 2009; Wallace and McNally, 2009). The most prevalent and severe Duchenne MD (DMD) and the milder Becker MD (BMD) both result from mutations in the Dystrophin (Dys) gene. Dys, the largest gene in the human genome (1.2 Mb, 79 exons), encodes a structural cytoplasmic protein that is the key component of the larger membrane-associated multiprotein dystrophin glycoprotein complex (DGC; Kunkel et al., 1986; Hoffman et al., 1987). The DGC classically consists of dystrophin, dystroglycans α and β, sarcoglycans α, β, γ, and δ, sarcospan, and other proteins, such as α-dystrobrevin, syntrophins α1, β1, β2, γ1, γ2, calveolin-3, Growth factor receptor–bound protein–2 (Grb2), and neuronal Nitric Oxide Synthase (nNOS) have been shown to be associated with the DGC (Durbeej and Campbell, 2002).

The DGC has multiple roles in muscle: mechanical stabilization of the muscle sarcolemma via anchoring the extracellular matrix (ECM) to the cytoskeleton, signal transduction between the internal and external environments of the muscle cell and provides a scaffold responsible for the membrane localization of signaling proteins (Ervasti and Sonnemann, 2008). The DGC, via Syntrophin (Syn) anchors a variety of signaling molecules to their functional sites at the membrane. For example, it localizes nNOS at the sarcolemma consequently regulating intramuscular generation of nitric oxide (NO; Wehling et al., 2001). nNOS signaling nitrosylates the histone deacetylases (HDACs) that regulate gene transcription in muscle progenitor cells by controlling the activity of myogenic (MyoD, Myf5, myogenin, and MRF4) and MEF2 family proteins (McKinsey et al., 2000; Puri et al., 2001). Upon myoblast differentiation, HDACs are displaced from the chromatin that then becomes hyperacetylated leading to transcriptional activation. Since Dys deficiency leads to downregulation of nNOS signaling (Brennan et al., 1995), it indirectly plays a role in control of the balance between acetylation and deacetylation of muscle differentiation genes and has an impact on the regenerative potential of muscle stem cells. It is not clear if the DGC is just a scaffold for Syn–nNOS or, since it has been shown that the DGC is also a signal-transducing module involved in cross talk between the internal and external environments of the muscle cell (Moore and Winder, 2010), it can also actively control epigenetic characteristics of muscle cells via the nNOS signaling pathway.

MUSCLE MAINTENANCE AND REGENERATION
Muscles can withstand rigorous mechanical stress and, if damaged, be repaired by the progeny of satellite cells (Figure 1). Satellite cells are quiescent muscle progenitor cells that reside along the basal lamina of the muscle fiber and proliferate only in response to specific signals, for example muscle injury (Charge and Rudnicki, 2004). For continuous and sufficient muscle regeneration, satellite cells must be easily activated to proliferate but also should return to quiescence to maintain their stem cell characteristics (Dhawan and Rando, 2005).

The progeny of satellite progenitor cells are primary myoblasts. These myoblasts proliferate to increase in number and upon
satellite cells are not lost in an untimely manner (Buckingham, 2006). To ensure that muscle is replenished as necessary and that satellite muscle cells or myocytes. This program must be tightly regulated.

myotubes then cluster into myofibers which again cluster to form muscle. Myoblasts later differentiate and fuse to form myotubes. Myotubes cluster into myofibers, the structures that muscle cells consist of.

**FIGURE 1** | Muscle damage can be repaired by the progeny of satellite cells. When muscle fibers need to be replaced, signals are sent to otherwise quiescent satellite cells, which activates their proliferation and generates proliferating myoblasts. Myoblasts later differentiate and fuse to form myotubes. Myotubes cluster into myofibers, the structures that muscle cells consist of.

activation differentiate and fuse to form myotubes. These myotubes then cluster into myofibers which again cluster to form muscle cells or myocytes. This program must be tightly regulated to ensure that muscle is replenished as necessary and that satellite cells are not lost in an untimely manner (Buckingham, 2006).

In order for a cell to be a myocyte it must express specific transcription factors, including Mef2, MyoD, and myogenin among others (Sabourin and Rudnicki, 2000). Before myoblasts express these factors they are in a proliferative state that requires repression of terminal differentiation genes and cell cycle inhibitors. In order for differentiation of myoblasts to occur, proliferation must halt. This requires the coordinated agreement of cell cycle inhibition and initiation of muscle specific gene expression.

In dystrophic patients, Dys insufficiency causes the muscle sarcolemma to become fragile leading to damage that cannot be easily repaired due to inadequate response of satellite cells. This results in chronic inflammation of muscle tissue by penetration of immune cells and eventually leads to the replacement of myofibers with adipose and fibrotic tissue (Porter et al., 2002).

Age-dependent muscle degeneration in MD patients is associated with defects in multiple processes that occur in different cell types such as activation of satellite cell proliferation, progenitor cell maintenance, myoblast differentiation, muscle cell homeostasis, immune cell recruitment, etc. These processes are also required during normal muscle development and growth and the transcriptional circuitry and signaling pathways controlling these events have been extensively studied using many model organisms. In this review we will discuss how recent studies have also revealed a new level of regulation of muscle gene expression that is mediated by miRNAs. Since miRNAs have great potential for therapeutics, understanding their basic biology and specific functions in healthy and diseased muscle tissue is of great importance.

**THE Dys–Syn–nNOS PATHWAY AND miRNA LEVELS ARE RECIPROCALLY REGULATED**

The DGC through the Dys–Syn–nNOS pathway regulates the expression of miRNAs required for muscle tissue maintenance and regeneration (Cacchiarelli et al., 2010; Figure 2). Indeed, it has been found that mRNA levels are altered in the human DMD pathology, which correlates with mis-expressed miRNAs (Eisenberg et al., 2007). Specifically nNOS signaling controls modification of HDAC2, which in normal situations prevents binding to promoter regions that would lead to transcriptional activation. When Dys is absent this signaling is disturbed, which also results in miRNA dysregulation (Figure 3). Interestingly it was found that most of the mis-expressed miRNAs found in DMD patients are returned to normal expression levels when HDACs were inhibited by restoring NO signaling (Cacchiarelli et al., 2010). This is in accord with a previous study that showed that class I HDAC inhibitors and NO-inhibited HDACs effectively ameliorate MD in mouse models (Colussi et al., 2008).

Not only does the DGC play a role in miRNA regulation, but it is also regulated via miRNAs. For example, miR-222 regulates the Dys–Syn–nNOS pathway possibly by targeting the 3′-UTR of β1-Syntrophin (De Arcangelis et al., 2010). Since Syntrophins bind to Dys and act as a scaffold for nNOS, miR-222 could control the timing of NO signaling during differentiation. miR-222 has the same seed sequence as miR-221, both are controlled by the Ras–MAPK pathway and are downregulated upon differentiation of myoblasts (Cardinali et al., 2009). Additionally, miR-221 and miR-222 promote cell cycle progression by down-regulating the cyclin-dependent kinase inhibitors p27 (Cdkn1b/Kip1) and p57 (Cdkn1c/Kip2) that are essential for the maintenance of the proliferative state (le Sage et al., 2007; Medina et al., 2008). Since both miR-221 and miR-222 are significantly upregulated in MDs (Eisenberg et al., 2007; Greco et al., 2009; De Arcangelis et al., 2010), the cell cycle kinetics of muscle progenitor cells could also be affected.

Another miRNA that is known to regulate muscle terminal differentiation genes is miR-31, which directly targets the 3′-UTR or Dys consequently inactivating the Dys–Syn–nNOS pathway (Cacchiarelli et al., 2011). In normal muscle, miR-31 activity is detected in early myoblasts to suppress precocious expression of late differentiation markers, while in dystrophic muscles miR-31 levels are elevated probably due to activation of the regenerative program in differentiating satellite cells and myoblasts. Increased miR-31 levels in these cells subsequently reduce the amount of Dys, the lack of which correlates with a differentiation delay (Greco et al., 2009; Cacchiarelli et al., 2011). Importantly, in dystrophic
FIGURE 2 | The Dys–Syn–nNOS pathway and miRNAs coordinate the muscle differentiation program. Dys–Syn–nNOS signaling regulates the epigenetic profile of muscle cells via nitrosylation of HDAC2 that influences gene expression by altering the acetylation status of histones. miR-221 and miR-222 share the same seed sequence and both target cell cycle inhibitors, p27 and p57. miR-222 also targets β1-Syn implying an impact on nNOS signaling. miR-31 temporally targets terminal differentiation genes including Dys. miR-1 and miR-133 are transcriptionally controlled by the nitrosylation state of HDAC2, which is regulated by nNOS. miR-133 targets SRF during proliferation, which in a self regulatory manner promotes expression of miR-1. miR-31, miR-1 targets G6PD and HDAC4 during differentiation, and since HDAC4 regulates the transcription of muscle differentiation genes, Dys–Syn–nNOS signaling indirectly promotes differentiation. In a self-promoting regulatory loop, the expression of muscle differentiation genes results in miR-1 expression. miR-29 is also transcriptionally controlled by the nitrosylation state of HDAC2. Additional regulation of miR-29 comes from YY1, a member of NF-κB signaling. The skeletal muscle specific miRNA, miR-206 is also upregulated by muscle gene expression and aids in cell cycle inhibition by targeting DNA Polα1 and Pax7. Utrophin is another target of miR-206 providing another link between it and the DGC.

miRNAs BALANCE THE EPIGENETIC NETWORK OF DYSTROPHIC MUSCLE

miR-1 is evolutionarily conserved from invertebrates to vertebrates and via targeting another histone deacetylase, HDAC4 (Chen et al., 2006) it can modulate epigenetic profiles of muscle genes. Multiple HDAC4 transcriptionally regulated genes promote muscle differentiation, including Mef2 (Lu et al., 2000; McKinsey et al., 2000; Chen et al., 2006). Insights from research in Drosophila showed that miR-1 is necessary for post-mitotic growth but not establishment of muscles (Sokol and Ambros, 2005). miR-1 expression is regulated initially by Twist, a mesoderm fate determining transcription factor, then in later stages by Mef2 (Sokol and Ambros, 2005), a central regulator of myogenesis. This puts miR-1 in a positive feedback loop where its expression is initiated and promoted by the muscle differentiation program (myogenic factors and Dys–Syn–nNOS signaling) and then, miR-1 acts to reassure terminal differentiation through downregulation of HDAC4, a repressor of myogenic genes.

In mdx mouse and human DMD patients, when Dys is absent and NO signaling is perturbed, miR-1 is downregulated in differentiating myoblasts (McCarthy and Esser, 2007; Greco et al., 2009; Cacchiarelli et al., 2010). Myofibers generated under such conditions are not robust and can be lost as part of the disease pathology. Transcriptomic analysis carried out on the dystrophic mouse revealed an altered gene expression profile that might affect proper myofiber differentiation (Ghahramani Seno et al., 2010). Additionally, miR-1 targets Glucose-6-phosphate dehydrogenase (G6PD) that controls oxidative stress by maintaining levels of oxidized and reduced glutathione, a major antioxidant (Cacchiarelli et al., 2010). Since dystrophic muscle is sensitive to different stresses and has altered levels of reactive oxygen/nitrogen species (Martins et al., 2008; Shkryl et al., 2009; Kucherenko et al., 2011; Marrone et al., 2011), finding new ways to protect against oxidative stress is of a great significance. Importantly, miRNAs have been shown in many organisms to be involved in stress response (Biggar and Storey, 2011; Dorn, 2011).

Once muscle differentiation genes start to be expressed they in turn can regulate expression of miRNAs. miR-1 and miR-133 are transcribed together from a single primary transcript (Chen et al., 2006).
In dystrophic muscle the epigenetic network of muscle differentiation is disrupted. When Dys is absent, Dys–Syn–nNOS signaling is disrupted inhibiting nitrosylation of HDAC2. Consequently, levels of miR-133/miR-1 and miR-29, all of which are repressed by non-nitrosylated HDAC2, are down. The regulatory roles of miR-133/miR-1 are disturbed leading to inhibition of muscle differentiation gene expression and an increase in oxidative cellular stress. Muscle tissue generated under imbalanced conditions will contribute to the progression of adipogenesis. The decrease in miR-29 levels correlates with an increase in the amount of Collagen and Elastin that are indicative of fat and fibrotic tissue. Due to reasons that are not quite clear at this time, levels of miR-206 and miR-31 are increased altering the equilibrium between the proliferation and differentiation states. miRNAs circled in green are upregulated and miRNAs circled in red are down regulated, bold letters indicate upregulated protein levels, gray circles with diagonal lines and gray lines indicate deficiencies.
et al., 2010). This indicates that miR-206 is not regulated by the Dys–Syn–nNOS pathway; however, miR-206 contributes to the imbalance of the regeneration program in dystrophic muscle.

miRNAs REGULATE TISSUE REPLACEMENT IN COMPROMISED DYSTROPHIC MUSCLE

Even though different types of MDs have specific mechanisms of muscle degeneration, inflammation is a hallmark symptom of dystrophic muscle. Accordingly, an increase in miR-222 and miR-223 levels in dystrophic muscle is believed to be due to inflammation (Eisenberg et al., 2007; Greco et al., 2009). Inflammation is associated with fat and fibrotic replacement of muscle fibers and degeneration (Porter et al., 2002). To elucidate the differences seen in different types of muscular disorders a comprehensive study was carried out in which muscle specimens were analyzed representing 10 different human conditions (Eisenberg et al., 2007). What was learned from this study is that (1) there is a large amount of variation in miRNA levels in disease states, (2) there are shared misregulated miRNAs across muscular disorders (miR-146b and miR-miR-221) and (3) only a small number of miRNAs are unique to an individual disorder such as DMD (miR-95, miR-30d, miR-486, miR-331, miR-193b, miR-30a_5p, miR-30e_5p, and miR-26a).

Previously it was thought that improper fate determination of satellite cell progeny generated extra fibrotic tissue in dystrophic muscle (Shefer et al., 2004; Brack et al., 2007). Fibrosis therefore ought to occur at the expense of muscle regeneration. However, recently it has been shown that in addition to satellite muscle progenitor cells, there are also mesenchymal progenitor cells living among myofibers that give rise to adipocytes and fibroblasts which generate fat/fibrotic tissue (Joe et al., 2010; Uezumi et al., 2010). These cells have been termed fibro/adipogenic progenitors (Natarajan et al., 2010). What is amazing about these cells is that they are activated during muscle regeneration similar to satellite cells, but in a non-autonomous manner receive signals from the surrounding muscle environment. If muscle regeneration is producing normal healthy muscle fibers then adipogenesis is inhibited. However, if muscle regeneration is compromised then adipogenesis proceeds and fibrotic tissue will arise in the interstitial space between myofibers (Figure 4). Certain proteins are indicative of fibrotic tissue such as collagen and elastin. Recently it has been shown that their mRNAs are targeted by the miR-29 family, which helps to modify ECM organization (van Rooij et al., 2008). miR-29 is an enhancer of differentiation and is repressed by NF-κB and is a member of the Polycomb group that acts as a transcriptional silencer (Wang et al., 2008). During myogenesis expression of miR-29 is upregulated by SRF and Mef2, and in a self regulatory manner, miR-29 suppresses YY1 and HDAC4 by targeting their 3′-UTRs (Wang et al., 2008; Li et al., 2009). Interestingly, the expression of miR-29 is also controlled by the Dys–Syn–nNOS pathway where, similar to miR-1, nitrosylation of HDAC2 allows for its transcription (Cacchiarelli et al., 2010). In mdx mouse and human DMD patients there is therefore an expected decrease in miR-29 levels which promotes an increase in fibrotic tissue (Eisenberg et al., 2007; Greco et al., 2009; Cacchiarelli et al., 2010).

All of these findings lead to the conclusion that in dystrophic muscle the alteration in miRNA levels is the result of an imbalanced regeneration program, where not only activation of satellite cell proliferation but also myoblast differentiation are impaired (Figure 3). The overall result is that damaged muscle fibers do not properly regenerate resulting in fat and fibrotic tissue replacement with accompanying inflammation. Each of these processes is accompanied by misregulation of certain miRNAs that can be considered in a multistep treatment of these fatal neuromuscular disorders.

NEW OPTIONS FOR miRNAs IN MUSCULAR DYSTROPHY THERAPIES

As discussed above, miRNA dysregulation contributes to a variety of MD pathologies and the miRNA regulatory network is disturbed in dystrophic muscle. In order to return the diseased tissue to normal mode, multiple processes have to be adjusted, and miRNAs are important functional units controlling different aspects of muscle regeneration and maintenance. In addition, miRNAs...
have been shown to be perfect players in fine-tuning different developmental processes: stem cell division and maintenance, differentiation, cell cycle control, etc (Shcherbata et al., 2006; Inui et al., 2010). Therefore re-establishing the normal miRNA levels may allow for improvement of misregulated protein synthesis. The proteomic fingerprint can be altered by variation of miRNA levels, which can be achieved in a positive or a negative manner. miRNAs can be inhibited in vivo silencing via use of chemically modified antisense nucleotides locked nucleic acids (LNA; Kumar et al., 1998), 2′-O-methyl-RNA oligonucleotides (2′-O-me-RNA; Matera and Ward, 1993), microRNA sponges (Ebert et al., 2007), or cholesterol conjugated RNA analogs (antagomirs; Krutzfeldt et al., 2005). Inversely miRNA levels can be increased by in vivo injection or viral delivery resulting in reduced expression of upregulated disease genes (Fasanaro et al., 2010; Pfeifer and Lehmann, 2010).

An exemplary result of miRNA targeting in DMD therapy comes from Cacciaciarielli et al. (2011). In mdx mice symptoms of muscle degeneration can be reversed by the introduction of viral vectors that allow for transcriptional exon skipping that removes a non-sense mutation in the Dys gene. However, these therapies have not been able to restore full muscle function due to low Dys levels. Dys is a target for miR-31 and any replacement of Dys via genetic manipulation could potentially be inhibited by the presence of this miRNA. The authors were able to significantly increase Dys levels in exon skipping treated DMD myoblasts by downregulation of miR-31 using a miR-31 sponge and an anti-miR-31 LNA oligonucleotide. These results set a precedent for the use of miRNAs as therapeutic targets to alleviate muscular dystrophy. It is unknown at this time if there are other mRNA targets of miR-31, alteration of which would give rise to deleterious side effects of this treatment.

Fibrotic degeneration, which is characteristic in mdx mice, was also successfully decreased by increasing miR-29 levels (Cacciarielli et al., 2010). Electroporation of mdx muscles with miR-29 had a therapeutic effect resulting in significant reduction of collagen deposition and an increase in both collagen and elastin miRNAs. These data prove that miRNAs are crucial regulators of the ECM that can possibly regulate the signals sent from the muscle environment to fibro/adipogenic progenitors, and targeting/promoting such miRNAs could inhibit fibrosis allowing for more successful muscle regeneration.

Though it seems obvious from the discussion presented thus far that Dys–Syn–nNOS signaling plays a key role in balancing the epigenetic network of muscle regeneration, it must be considered that therapies restoring NO signaling alone may not be fully curative. Patients with the milder BMD in some cases are missing the domain of Dys essential for Dys–Syn–nNOS signaling (Wells et al., 2003; Lai et al., 2009). Since these patients do not succumb to their illness, the malfunction of nNOS signaling is still compatible with life. Key muscle regenerative miRNAs regulated by nNOS signaling are probable therapeutic targets; however other isolated miRNAs should be given attention for disease treatment too. Screening for misregulated miRNAs has been done by several groups in dystrophic animal models and DMD patients which allowed to compile a comprehensive list of differentially regulated miRNAs that can be clustered into three functional categories: regeneration, degeneration, and inflammation (Eisenberg et al., 2007; Greco et al., 2009).

Regenerative miRNAs are upregulated during embryonic development and post ischemic regeneration (Greco et al., 2009; Suh and Blelloch, 2011), supporting their role in proliferation and differentiation of muscle cell progenitors. This indicates that functional tissue replacement is based on satellite cell populations, and for miRNA-based therapies to be effective progenitor cell maintenance and division should be taken into consideration. Muscle satellite cells are quiescent until they become proliferative upon response to muscle damage or heavy use. It will be of interest to determine what role miRNAs have in the initial activation of satellite cells, since it has been shown that miRNA signatures differ from self-renewing to quiescent stem cells and from proliferative to differentiating progenitor cells (Arnold et al., 2011).

Initially it was believed that the role of the DGC was to simply provide structural support at costameres and without this support the muscle cell would tear and waste away. However, that is obviously not the only avenue with which disease progresses. The DGC is right in the middle of the muscle differentiation program, since without the Dys–Syn–nNOS pathway muscle maintenance and regeneration is disrupted. This means that formed myotubes are compromised and contribute to tissue replacement by fat and fibrosis. The plethora of miRNAs implicated in the DMD pathology present a substantial and complex level of regulation that opens diverse avenues for future research and therapies.

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