MicroRNAs in Dystrophinopathy

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Contributor: Ahyoung Lee, Jiwon Moon, Jin Yu, Changwon Kho

Dystrophinopathies are a group of X-linked inheritance disorders characterized by loss of limbs, loss of respiratory and cardiac muscle strength, and destruction of nerve tissue. There are two main forms of dystrophinopathy: Duchenne muscular dystrophy (DMD), which develops in early childhood and presents with severe symptoms, and Becker muscular dystrophy (BMD), which develops late as a milder form.

Keywords: dystrophinopathy ; Duchenne muscular dystrophy ; microRNA ; biomarker

1. microRNAs Associated with Dystrophinopathy

1.1. Importance of miRNA

MiRNAs are small, non-coding RNAs of approximately 22 nucleotides in length [1]. miRNA genes can be included in other genes or can be located in the intron of host genes. Sometimes, miRNA genes are composed of polycistronic clusters and are expected to be co-expressed [2]. The production of mammalian miRNAs is a highly regulated process [1]. In the nucleus, miRNA is transcribed by RNA polymerase II/III to generate primary miRNA (pri-miRNA), which are modified with a 7-methylguanosine cap structure and polyadenylation. Pri-miRNA is usually more than one kilobase long and contains a double-strand area incompletely in the hairpin loop. Through the canonical Drosha/DGCR8 cleavage or non-canocical pathways, pri-miRNA is converted to a hairpin-like precursor miRNA (pre-miRNA) with a length of about 70–100 nt. This pre-miRNA is exported from the nucleus to the cytoplasm with the help of Exportin 5, and is further processed by the RNase called Dicer to generate mature miRNA of ~22 nt in length. Each pre-miRNA can release two mature miRNA strands (5p and 3p) containing different messenger RNA (mRNA)-targeting sequences. In general, only one single strand becomes a template loaded into the RISC (RNA-induced silencing complex) to control the fate of specific mRNAs. The mature miRNA functions by complementary base-pairing with the miRNA response elements (MRE) located in the target mRNA. The 3′-untranslational region (3′-UTR) often contains MREs [3]. As a result, it can interfere with the translation of the transcript or can cause the degradation of the mRNA target directly.

1.2. miRNAs as a DMD Biomarker

MiRNAs are expressed with tissue specificity. Eight miRNAs, namely miR-1, miR-133a, miR-133b, miR-206, miR-208a, miR-208b, miR-499a, and miR-499b, were identified as muscle-specific miRNAs [4][5][6][7]. Except for miR-206 (predominant in skeletal muscle) and miR-208a (predominant in cardiac muscle), they are expressed in both cardiac and skeletal muscle tissues. Three miR families, miR-1, miR-133, and miR-206, are among the most abundant in muscle cells, accounting for more than 25% of all miRNAs [6]. They are involved in skeletal muscle proliferation and differentiation [8][9].

Several microarray analyses have identified DMD-associated miRNAs [10][11][12]. For example, muscle-specific miRNAs were found to be differentially expressed in dystrophic muscle tissues in patients and in mdx mice, a well-established mouse model for Duchenne muscular dystrophy (DMD) research. The miRNAs, miR-1, miR-133, and miR-206, were decreased in the dystrophic muscles compared with healthy tissue. Moreover, a significant upregulation (~70-fold) of miR-31 inhibited the dystrophin expression by targeting the 3′-UTR of dystrophin in DMD muscles [13]. Importantly, several muscle-enriched miRNAs (miR-1, miR-133, miR-206, miR-208, and miR-499) were upregulated in the dystrophic sera, not only in animal models, but also in patients. In particular, the expression of miR-1 and miR-133, as a result of muscle degeneration, was highly elevated in the dystrophic serum of DMD patients (up to 100-fold in DMD and up to 30-fold in BMD versus healthy controls) [14].

Several non-muscle-specific miRNAs, including miR-30c, miR-181a, and miR-95, were also elevated in the serum or plasma of DMD patients [15][16].

1.3. microRNAs Associated with DMD Cardiomyopathy

miR-1: Several studies have demonstrated a pathophysiological role for miR-1 in heart disease. For example, an abnormal expression of miR-1 is involved in electrical remodeling, such as the development of arrhythmias. With respect to the underlying mechanism, miR-1 directly targets the key proteins that regulate potassium current (e.g., potassium ion channel and gap junction protein) [17] or proteins involved in muscle cell Ca^{2+} cycling (e.g., protein phosphatase PP2A) [18]. In addition, miR-1 is associated with mechanical remodeling, suggesting that it has anti-hypertrophic properties. A reduced miR-1 expression along with miR-133 has been reported in three different mouse models of cardiac hypertrophy [19]. Because miR-1 is transcribed as a bicistronic transcript, together with members of the miR-133 family, it raises the possibility of cooperation in cardiac hypertrophy. In addition, miR-1 overexpression was shown to attenuate agonist-induced cardiac hypertrophy in vitro and in vivo [20].

miR-133: MiR-133 has been implicated in myocardial remodeling. Similar to miR-1, miR-133 overexpression suppresses cardiac cell hypertrophy [19]. In contrast, miR-133 inhibition induces cardiac hypertrophy by targeting cytoskeletal and myofibrillar rearrangement-related proteins (e.g., RhoA and CDC42) [19]. Decreased miR-133 promotes the progression of cardiac fibrosis. Several central mediators in tissue fibrosis, such as TGF-β1 (transforming growth factor-β1), CTGF (connective tissue growth factor), and COL1A1 (collagen type 1-alpha 1), have been identified as direct targets of miR-133 [21][22][23]. The accumulation of these miR-133 target molecules contributes to collagen deposition and fibrosis. Interestingly, miR-133 can be directly regulated by other noncoding RNA, such as linc-MD1. A muscle-specific long non-coding RNA (lncRNA), linc-MD1, binds to miR-133a and acts as a competitor RNA for targets of miR-133, including MAML1 (Mastermind-like 1) and MEF2C (Myocyte Enhancer Factor 2C) transcription factors [24]. The expression of linc-MD1 is diminished in Duchenne patient myoblasts. Although the role of lncRNAs in DMD pathogenesis is still unclear, understanding the lncRNAs−miRNAs−mRNAs network is important to explore the molecular mechanism of DMD.

miR-208a: The miR-208 family, which contains miR-208a/b and miR-499, contributes significantly to cardiac hypertrophy and arrhythmias. These three miRNAs are located in the introns of the genes encoding myosin heavy chain isoforms, which regulate the expression of sarcomeric contractile proteins [7][25]. Transgenic mouse studies have shown that miR-208a, a heart-enriched miRNA, is associated with hypertrophic cardiomyocyte growth and the upregulation of hypertrophy-related genes by targeting THRAP1 (thyroid hormone receptor-associated protein 1) and myostatin 2 [25]. Cardiac conduction abnormalities have also been reported in both miR-208a deletion mice and miR-208 overexpressing mice [5][25]. In addition, miR-208a null mice exhibited a reduction in cardiac contractility [13]. As miR-208a can be released from heart muscle cells into the serum and plasma in response to cardiac pathogenesis, several studies have evaluated their diagnostic value. For example, the sensitivity and specificity of circulating miR-208a were reported in patients with myocardial damage [26], severe COVID-19 [27], and heart failure with reduced ejection fraction [28].

miR-339-5p: It was recently shown that miR-339-5p is upregulated and released by exosomes from DMD patient-induced pluripotent stem cell-derived cardiomyocytes (DMD-iCMs). Downregulation of miR-339-5p directly modulated stress-response genes and reduced cardiomyocyte death in DMD-iCMs. These data indicate a pathological role of elevated miR-339-5p in DMD cardiomyocytes [29].

Serum miRNAs in disease carriers: Even without skeletal muscle symptoms, heart symptoms often occur in female DMD/BMD carriers for the asymptomatic form with mild abnormalities to progressive heart failure [30] and dilated cardiomyopathy [31], which may require heart transplantation [32]. Therefore, early detection of heart disease in female carriers is important. Changes in the miRNA levels associated with heart and/or skeletal muscle pathologies, including cardiac hypertrophy (e.g., miR-22 and miR-26a), fibrosis (e.g., miR-26a, miR-222, and miR-378a-5p), muscle cell death (e.g., miR-342), and regulation of skeletal muscle mass (e.g., miR-378 and miR-29c) regulators have been detected in the biofluids of disease carriers [33][34][35]. Interestingly, a significant downregulation of miR-29c was only found in the blood of female DMD carriers with cardiac symptoms detected by cardiovascular magnetic resonance [33]. It is worth determining whether this miR-29c downregulation is female-specific and whether its expression is comparable to healthy controls before cardiomyopathy in men with DMD.

2. microRNAs with Therapeutic Potential

2.1. Restoration of Dystrophin or Utrophin Expression

miR-31: MiR-31 is expressed in regenerating fibers, which are activated at the onset of DMD in both mouse and human muscles [13]. DMD myoblasts with accumulated miR-31 exhibit a lower differentiation potential and miR-31 has been shown to target dystrophin mRNA [13]. Importantly, the inhibition of miR-31 function may improve the therapeutic efficacy of restoring the dystrophin expression. In human DMD myoblasts, miR-31 inhibition increased dystrophin synthesis with

exon 51 skipping [13]. In the skeletal muscle, miR-31 also regulates myogenesis by inhibiting MYF5 (myogenic factor 5), an activator of muscular satellite cells, which are identical to myogenic stem cells [36]. Thus, miR-31 inhibition represents a therapeutic strategy to improve DMD muscle function by improving dystrophin synthesis and muscle differentiation. Furthermore, miR-31 has a role in cardiac remodeling. For example, atrial miR-31 inhibition contributes to electrical remodeling, such as the termination of atrial fibrillation, by the restoring dystrophin and nNOS (neuronal nitric oxide synthetase) levels [37]. The cardioprotective effects of miR-31 silencing have also been reported in rats with myocardial infarction [38]. Mechanistically, miR-31 represses TNNT2 (troponin T2), E2F6 (E2F Transcription Factor 6), NR3C2 (Nuclear Receptor Subfamily 3 Group C Member 2), and TIMP4 (Metalloproteinase inhibitor 4) by binding to their respective target 3′-UTR sequences.

miR-206: Skeletal muscle-specific miR-206 is considered a new target for DMD therapy because of its ability to regulate the expression of utrophin. In humans, utrophin is nearly 80% identical to dystrophin [39] and it is naturally increased in the sarcolemma of dystrophic skeletal muscles as a compensatory mechanism for dystrophin deficiency in mice [40][41] and humans [42]. In mdx mice, downregulation of miR-206 resulted in a higher utrophin expression and an improvement in the dystrophic phenotype [43]. In addition to miR-206, the suppression of utrophin by several miRNAs, including let-7c, miR-150, miR-196b, miR-296-5p, and miR-133b, was demonstrated [44][45]. A therapeutic strategy to enhance utrophin production could be applicable to BMD patients, as well as all DMDs, regardless of the type of dystrophin mutation. Currently, several drugs that stabilize the utrophin−glycoprotein complex, including TVN-102 (recombinant human biglycan) and rhAKM111 (recombinant human protein laminin-111), have been developed for utrophin therapy [46]. Meanwhile, miR-206 has been characterized as a cardioprotective molecule. It is upregulated in response to stress and promotes the survival of heart muscle cells in vitro and in vivo [47].

2.2. Inhibition of Pathogenic Muscle Remodeling: Anti-Fibrosis

miR-21: MiR-21 is upregulated in DMD fibroblasts, the major collagen-producing cells, and is correlated with the expression of pro-fibrotic genes [48]. Histological evaluations have shown that the inhibition of miR-21 reduces diaphragmatic fibrosis in mdx mice. In addition, in the diaphragm where miR-21 was overexpressed, the soluble collagen content was reduced compared with the control group [48]. MiR-21 is also tightly linked to cardiac fibrosis. Elevated miR-21 promotes cell transition from cardiac fibroblasts to myofibroblasts, resulting in pathogenic heart modeling [49]. MiR-21 is considered a potential therapeutic target for the treatment of cardiomyopathies [50]. With respect to fibrosis, Regulus therapeutics is currently conducting a phase 2 clinical trial jointly with Sanofi Genzyme to evaluate the safety and efficacy of anti-miR-21 oligonucleotides (RG-012) in Alport patients (ClinicalTrials.gov Identifier: NCT02855268).

miR-29: MiR-29 has pro-myogenic activity and anti-fibrotic properties in DMD. Downregulation of all three members of the miR-29 family, miR-29a, miR-29b, and miR-29c, were detected in dystrophic mouse muscles, including the limb muscles, diaphragm, and heart [51]. A reduced miR-29a and miR-29c expression has also been found in human DMD myoblasts [48]. Systemic delivery of miR-29 mimics into mdx mice promotes diaphragm muscle regeneration and inhibits the development of fibrosis in the diaphragm by directly repressing extracellular matrix components, such as microfibrillar-associated protein 5 and collagen [51]. The overexpression of miR-29c reduces muscle fibrosis in dystrophin and utrophin double-knockout mice [52]. The co-overexpression of miR-29 in DMD mice with micro-dystrophin restores fibrosis and muscle function to a similar levels to that of normal mice, suggesting a possible combination treatment strategy [52]. The therapeutic effects of miR-29 have been extensively studied in multiple organ fibrosis, including the heart [53]. Currently, the oligonucleotide mimic of miR-29b (Remlasten or MRG-201) is in phase 2 clinical trials for cutaneous fibrosis (ClinicalTrials.gov Identifier: NCT03601052).

2.3. Restoration of Abnormal Calcium Homeostasis

miR-1: RyR stabilization may prevent Ca^{2+} leakage from the SR, thereby reducing intracellular Ca^{2+} accumulation. For example, pharmacological stabilization of the RyR Ca^{2+} release channel attenuates the disease phenotype in mdx mice [54]. In addition, treatment with RyR stabilizing molecules increased the efficacy of exon-skipping drugs in DMD cell culture models [55]. With respect to microRNAs, elevated miR-1 can hyperactivate the RyR2 channel by inhibiting the PP2A regulatory subunit B56α, which is a scaffold for the RyR2 complex [18].

miR-25: Overall, the SERCA pump overexpression has shown beneficial effects in dystrophic mice. Importantly, severe dilated cardiomyopathy was ameliorated by SERCA2a gene transfer in aged mdx mice [56]. Several miRNAs, including miR-25, have been identified that target SERCA2a mRNA. The therapeutic potential of inhibiting miR-25 has also been evaluated in a mouse model of heart failure [57]; however, the expression profile and muscle-related function of miR-25 in DMD have not been reported. Clinical studies of SERCA2a gene therapy have been conducted for heart failure [58][59], which may serve as an important basis for designing DMD and DMD cardiomyopathy therapies. Moreover, given the

therapeutic implications of targeting Ca^{2+} cycling, in-depth studies of specific miRNAs that regulate Ca^{2+} mishandling in DMD are warranted. In particular, research on miRNAs that regulate calcium metabolism in heart disease is being actively conducted [60].

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