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Review

Molecular mechanisms of muscle atrophy in myotonic dystrophies☆

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ABSTRACT

Myotonic dystrophy type 1 (DM1) and myotonic dystrophy type 2 (DM2) are multisystemic diseases that primarily affect skeletal muscle, causing myotonia, muscle atrophy, and muscle weakness. DM1 and DM2 pathologies are caused by expansion of CTG and CCTG repeats in non-coding regions of the genes encoding myotonic dystrophy protein kinase (DMPK) and zinc finger protein 9 (ZNF9) respectively. These expansions cause DM pathologies through accumulation of mutant RNAs that alter RNA metabolism in patients' tissues by targeting RNA-binding proteins such as CUG-binding protein 1 (CUGBP1) and Muscle blind-like protein 1 (MBNL1). Despite overwhelming evidence showing the critical role of RNA-binding proteins in DM1 and DM2 pathologies, the downstream pathways by which these RNA-binding proteins cause muscle wasting and muscle weakness are not well understood. This review discusses the molecular pathways by which DM1 and DM2 mutations might cause muscle atrophy and describes progress toward the development of therapeutic interventions for muscle wasting and weakness in DM1 and DM2.

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1. Introduction

Myotonic dystrophy type 1 (DM1) and myotonic dystrophy type 2 (DM2) are complex multisystemic diseases that affect many tissues but primarily cause defects in skeletal muscle (Harper, 2001; Ricker et al., 1995). In both diseases the severity of the clinical manifestations, including skeletal muscle pathology, varies between patients. There are four main clinical forms of DM1 that differ in the severity of the muscle phenotype and the age of onset. The most severe form of DM1 is a congenital form that affects newborn children. Skeletal muscle of patients with congenital DM1 shows a delay in development with severe muscle weakness, characterized by reduced muscle tone (hypotonia) (Amack and Mahadevan, 2004; Reardon et al., 1993). The childhood-onset form of DM1 is characterized by cognitive and behavioral abnormalities. Patients with the asymptomatic form of DM1 do not have muscle symptoms, whereas patients with adult onset of DM1 develop a progressive myotonia, muscle wasting, and weakness.

DM2 is a late-onset disease that mostly affects proximal muscles, causing muscle weakness, muscle pain, and myotonia. There is no congenital form of DM2. Whereas DM1 is characterized by severe muscle atrophy, DM2 is a much milder disease. Both diseases are associated with cardiac defects, endocrine abnormalities, neurological dysfunctions, and cataracts (Harper, 2001; Ricker et al., 1995). Histological studies of skeletal muscle sections from patients

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with DM1 and DM2 show atrophic fibers, variability of myofiber size, ring fibers, and an increase in central nuclei. Different fiber types are atrophic in DM1 and DM2: there is an increase in atrophic type 1 (slow twitch) fibers in DM1, whereas type 2 fibers are atrophic in DM2 (Vihola et al., 2003).

DM1 is caused by a polymorphic CTG triplet repeat expansion within the 3′ untranslated region (UTR) of the *DMPK* gene on chromosome 19q (Brook et al., 1992; Fu et al., 1992). In unaffected individuals these CTG expansions vary in length from 5 to 35 repeats, but in patients with DM1 the number of CTG repeats is increased to the range of 50 to several thousand repeats. The severity of the clinical phenotype in different patients with DM1 is dependent on the number of CTG repeats.

DM2 is caused by unstable expansion of CCTG tetranucleotide repeats in intron 1 of the gene encoding ZNF9 (also known as *C*ellular *N*ucleic Acid-*b*inding *P*rotein, CNBP) (Liquori et al., 2001). In unaffected individuals, the length of these CCTG repeats does not exceed 26 repeats; however, patients with DM2 have very long expansions of up to several thousand repeats. In contrast to the positive correlation between phenotype severity and the number of CTG repeats in patients with DM1, in DM2 there is no a clear relationship between the length of the CCTG repeats and the severity of disease. Although both DM1 and DM2 are multisystemic diseases, the most devastating symptoms in both diseases that significantly affect the quality of life are skeletal muscle atrophy and muscle weakness.

Studies of the molecular mechanisms by which polymorphic expansions of CTG and CCTG repeats cause the muscle pathology of DM1 and DM2 revealed the critical role of RNA CUG and CCUG repeats. Because the CTG and CCTG expansions are both located in non-coding regions of the disease genes they do not disrupt the major protein product. However, CTG repeat expansion might produce short peptides through AUG-independent translation (Zu et al., 2011). Importantly, the mutant RNAs containing CUG and CCUG repeats have increased stability and reduced turnover (Jones et al., 2011), which is likely responsible for the accumulation of non-degraded mutant RNA within patients' cells. It is well established that the accumulation of these mutant RNAs is toxic to RNA metabolism because the CUG and CCUG repeats bind RNA-binding proteins, thus interfering with their normal activities (Schoser and Timchenko, 2010).

The major RNA-binding proteins that mediate the pathologic effects of mutant CUG and CCUG repeats are MBNL1 and CUGBP1 (a member of the *C*UGBP and *E*mbryonic *L*ethal abnormal vision-like *F*amily of proteins, CELF) (Mankodi et al., 2000; Miller et al., 2000; Philips et al., 1998; Timchenko, 1999; Timchenko et al., 1996a,b). Several reports have suggested that ZNF9, a protein with DNA- and RNA-binding activities (Calcaterra et al., 2010), is also involved in DM2 pathology (Chen et al., 2007; Huichalaf et al., 2009; Raheem et al., 2010; Sammons et al., 2010). Recent data showed that the mutant CUG repeats might impair RNA-binding proteins (such as CUGBP1) through disruption of signaling pathways mediated by PKC and GSK3β kinases (Jones et al., 2012; Kuyumcu-Martinez et al., 2007). Alteration of activities of RNA-binding proteins in DM leads to myotonia, muscle atrophy, and weakness in skeletal muscle and has toxic effects in other tissues. In this review, we will focus on the molecular pathways associated with muscle atrophy in DM1 and in DM2 and discuss how molecular advances have been translated into the development of therapeutic approaches for DM.

2. Muscle atrophy in DM1 is caused by expanded RNA CUG repeats

Several mouse models have been generated for examination of the molecular basis of DM1 pathology. A major group of DM1 mouse models addresses the role of the accumulation of long CUG repeats in DM1 muscle pathology (Mankodi et al., 2000; Orengo et al., 2008; Seznec et al., 2001). In these mouse models, CUG repeats are expressed within the entire *DMPK* gene (Seznec et al., 2001), in the 3′ UTR of *DMPK* mRNA (Orengo et al., 2008), or in the 3′ UTR of mRNA unrelated to *DMPK* (Mankodi et al., 2000). The second group of DM1 mouse models includes models designed to elucidate the role of RNA-binding proteins targeted by mutant CUG repeats in DM1 (CUGBP1 and MBNL1) through overexpression of CUGBP1 and deletion of MBNL1 (Ho et al., 2005; Kanadia et al., 2003; Timchenko et al., 2004; Ward et al., 2010). The first transgenic mouse model that demonstrated the crucial role of CUG RNA in DM1 muscle pathology expressed an array of pure CUG repeats (250 repeats) in the 3′ UTR of the gene encoding skeletal muscle actin (HSA^{LR} mice) (Mankodi et al., 2000). These mice developed myotonia and skeletal muscle myopathy, which was characterized by an increase in central nuclei, variability of myofiber size, and nuclear chains, similar to the muscle histopathology in patients with DM1. Whereas initial studies did not reveal overt muscle atrophy in adult (up to 6 months of age) HSA^{LR} mice (Mankodi et al., 2000), recent analysis showed that the total number of myofibers is reduced in *gastrocnemius* of six-month-old HSA^{LR} mice in at least some mouse lines of this model (*e.g.*, line LR20b) (Jones et al., 2012). The reduction in the total number of fibers in *gastrocnemius* of six-month-old HSA^{LR} mice is accompanied by a strong variability in myofiber size with an increase in both small and enlarged fibers (Jones et al., 2012). This analysis showed that the expression of long CUG repeats in DM1 causes muscle atrophy. Consistent with the reduction in fiber number, HSA^{LR} mice are characterized by reduced grip strength (Jones et al., 2012), mimicking the reduced handgrip strength in patients with DM1 (Tang et al., 2012). It is not yet known whether fiber loss in HSA^{LR} *gastrocnemius* progresses with age. It is important to note that the number of fibers in *tibialis anterior* in the six-month-old HSA^{LR} mice was not changed (Jones et al., 2012). Moreover, approximately 20% of HSA^{LR} mice have normal grip strength (Jones et al., 2012). Other reports show that muscle force is impaired in extensor digitorum longus of the five-month-old HSA^{LR} mice, but not in soleus or diaphragm (Moyer et al., 2011). Elucidation of the reasons for the variability of the symptoms in HSA^{LR} muscle requires further investigations. It would be important to characterize phenotype in all muscle groups in these mice using the same approaches. The length of CTG repeats and the levels of expression of CUG RNA in different muscle groups in HSA^{LR} mice should be determined to correlate muscle phenotype with the length of CTG repeats and with the levels of CUG-containing transcripts.

A similar effect of mutant CUG repeats on muscle pathology was observed in a DM1 mouse model that expresses the entire human *DMPK* gene containing an array of 300 expanded CTG repeats (DM300 mice) (Seznec et al., 2001). Skeletal muscle of these mice is characterized by myotonia, increased number of fibers with central nuclei, increased variability in fiber size, and focal areas of regeneration–degeneration that express the neonatal myosin heavy chain. In addition to these abnormalities, DM300 transgenic mice have an increased number of atrophic fibers with specific atrophy of type 1 fibers (Seznec et al., 2001). Consistent with the muscle atrophy, whole body weight was reduced in these mice even at a young age (Seznec et al., 2001). The same mice with an increased length of CTG expansion (DM550) developed progressive age-dependent muscle weakness and wasting associated with reduced muscle mass and fiber diameter (Vignaud et al., 2010).

The most striking muscle wasting was observed in the DM1 inducible mouse model expressing a mutant 3′ UTR of *DMPK* containing a long CUG expansion (960 repeats) under the control of a skeletal muscle promoter (Orengo et al., 2008). In addition to myopathic abnormalities typical of DM1 muscle pathology, expression of the mutant 3′ UTR of *DMPK* in these mice caused severe

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