Molecular Therapies for Myotonic Dystrophy Type 1

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Contributor: Germana Falcone , , Jonathan Isacco Battistini , Claudia Provenzano , Fabio Martelli , Beatrice Cardinali

Myotonic dystrophy type 1 (DM1) is the most common muscular dystrophy affecting many different body tissues, predominantly skeletal and cardiac muscles and the central nervous system. The expansion of CTG repeats in the DM1 protein-kinase (*DMPK*) gene is the genetic cause of the disease. The pathogenetic mechanisms are mainly mediated by the production of a toxic expanded CUG transcript from the *DMPK* gene. With the availability of new knowledge, disease models, and technical tools, much progress has been made in the discovery of altered pathways and in the potential of therapeutic intervention, making the path to the clinic a closer reality.

myotonic dystrophy trinucleotide-expansion disease DM1 mice antisense oligonucleotides

molecular therapy

gene editing

1. Introduction

Myotonic dystrophy type 1 (DM1) is caused by an unstable expanded CTG repeat located within the 3' untranslated region (3' UTR) of the *DMPK* gene. The molecular mechanisms of DM1 are mainly the consequence of accumulation of mutant *DMPK* transcripts into ribonuclear foci leading to the impairment of alternative splicing and normal gene expression. Cell and animal models of DM1 have been crucial to providing insight into disease mechanisms and to revealing new therapeutic targets.

2. Myotonic Dystrophy Type 1: Clinical Features and Pathogenetic Mechanisms

DM1 is the most common dystrophy in adults, having an estimated worldwide prevalence of 1:20,000, with a recent report of 4.76:10,000 for *DMPK* CTG expansion \geq 50 CTG repeats in a newborn screening program in New York State, USA ^[1]. Clinical features of DM1 (Steinert's disease, OMIM# 160900) include muscle weakness, dysphagia, neuromuscular respiratory insufficiency, cardiac complications and cognitive, intellectual or behavioral impairment as well as sleep disorders. In the most severe forms, life quality and expectancy are seriously compromised ^{[2][3][4]}. DM1 results from CTG-repeat expansions in the 3' UTR of the *DMPK* gene on chromosome 19 ^{[5][6]}. The disease severity and age of onset are broadly correlated with the number of CTG repeats, with the highest (over 750) in the congenital form, while in non-affected individuals the number of repeats is up to 35 ^[2]. The number of repeats is usually unstable and tends to increase in some body tissues during lifetime (somatic instability) as well as in successive generations, leading to the phenomenon called "anticipation", where children of DM1 patients have a higher repeat number and more severe phenotypes compared to their parents 2. Interestingly, in DM1 families with variant repeats, where GGC, CCG and CTC interruptions are present within the CTG-repeat array, the repeats are stabilized and the disease phenotypes are milder ^{[8][9]}. Several pathogenic mechanisms likely contribute to disease in DM1 (Figure 1) [4][10]. At the DNA level, epigenetic modifications may impact the development or severity of the phenotype in DM1 patients [11]. In DM1 patient-derived cells and in a DM1 mouse model, the hairpin-like structures of the repeats can induce chromatin changes, such as CpG methylation, resulting in haploinsufficiency of DMPK and neighboring genes, or cause replication-fork stalling during DNA duplication, leading to cell stress [12] [13][14]. Large experimental evidence supports the hypothesis of an RNA gain-of-function mechanism of the mutated DMPK transcript. CUG-containing RNAs sequester crucial nuclear factors of the muscleblind-like (MBNL) family into ribonuclear foci, thus preventing their normal functions that are mainly associated with the regulation of alternative splicing ^[15]. Splicing regulation is required for the proper development and maintenance of tissues in which the DMPK gene is highly expressed, such as in muscle and the nervous system [16]. The MBNL family and the CUGBP Elav-like family (CELF) are among the most important splicing regulators in skeletal and cardiac muscle, and act antagonistically on several pre-mRNA targets [17][18]. Nuclear retention of MBNL proteins in nuclear foci prevents pre-mRNA processing and export to the cytoplasm, leading to a decrease in protein translation, and the loss of functional MBNL1 is accompanied by CELF1 upregulation ^[19]. The increase in CELF1 levels is induced by protein-kinase-C (PKC)-mediated hyperphosphorylation, leading to protein stabilization ^[20]. Both sense and antisense repeated RNAs have been shown to contribute to the clinical phenotype of nucleotide-expansion diseases ^[21]. An antisense transcript emanating from the DMPK-adjacent SIX5 regulatory region spanning the CTG expansion was first identified in DM1 patient-derived cells. The transcript was shown to be converted into siRNAs, which are able to recruit DNA and histone methyltransferases, leading to heterochromatin formation ^[22]. Interestingly, in transgenic mice carrying the human DMPK locus, in addition to CUG-containing transcripts, CAGcontaining transcripts were also found to form distinct ribonuclear foci [23].



Figure 1. DM1 pathogenetic mechanisms and therapeutic strategies. The actions of molecular therapies for DM1 at different pathogenetic levels are illustrated: (1) at DMPK gene, drugs can inhibit CTG-repeat transcription and induce repeat contraction; ZFN, TALEN or CRISPR/Cas9 nucleases can modify gene sequence by inducing CTG-repeat contractions or deletions, or by inserting premature polyadenylation signals; (2) mutated DMPK mRNA can be functionally inactivated by drugs inducing degradation or binding to CUG repeats; (3) MBNL can be released from CUG repeats by disruption of MBNL:CUG interaction through competitive binding, and CELF levels can be regulated by protein kinase C and glycogen synthase kinase 3β; (4) altered signaling pathways downstream of DMPK transcript can be rescued by modulation of splicing and miRNAs; circRNAs and RAN translation could also be targets of future therapies.

Other mechanisms involved in DM1 pathogenesis are repeat-associated non-ATG (RAN) translation (reviewed in ^[24]), which results in the production of toxic protein aggregates containing polyglutamine from antisense CAG-repeated transcripts ^{[25][26]}, microRNA (miRNA) dysregulation ^{[27][28][29][30]}, and upregulation of circular RNA (circRNA) expression ^{[31][32][33]}. In addition to the ones described above, other signaling cascades are affected by the toxic *DMPK* RNA and may play important roles in DM1 pathogenesis. For example, MBNL and CELF regulators, besides being key splicing regulators, are likely involved in cytoplasmic pathogenetic processes altering proteostasis and sarcomere structure (reviewed in ^[34]). Omics studies have added new information to the previous

knowledge, revealing several alterations in gene expression, alternative splicing, CpG methylation and proteins levels that potentially contribute to DM1 pathogenesis. In perspective, these new approaches can be crucial to evaluate the degree of therapeutic rescue and the off-target effects of drug candidates (reviewed in ^[35]).

3. DM1 Cell and Animal Models

In vitro models of DM1 have greatly contributed to clarifying the pathogenetic mechanisms of the disease. Among these, there are engineered cell lines with CTG repeats of different lengths inserted in minigenes ^{[36][37]}, DM patient-derived primary myoblasts, immortalized myoblasts or MYOD1-converted fibroblasts ^{[38][39][40][41]}, and embryonic stem cells ^[42]. Additionally, induced pluripotent stem cells (iPSCs) and iPSC-derived distinct cell types were used to study tissue-specific DM1 pathological alterations ^{[43][44][45][46]}. Recently, the first 3D in vitro human-muscle model of DM1 was developed by encapsulating patient-derived MYOD1-converted fibroblasts in hydrogels ^[47]. All of these cell models reproduce molecular alterations typical of DM1 and have been very useful for discovering crucial molecules and cellular pathways involved in the disease and for testing therapeutic strategies.

Drosophila models have also been used by several groups to study DM1. Interrupted CTG repeats of various lengths driven by either constitutive or inducible promoters were expressed in flies and DM1-related molecular as well as phenotypic alterations were observed in flies carrying more than 480 repeats [48][49][50]. Although DM1 modeling is complicated by the multifaceted impact of the DM1 mutation, many DM1 mouse models have been generated over time through the silencing of the Dmpk gene or the Mbnl family genes; alternatively, mouse models expressing CELF proteins or toxic CTG repeats in various tissues were produced, in order to mimic the different aspects of the disease and to discover therapeutic molecules (Table 1). It is unclear whether the DMPK haploinsufficiency observed in DM1 patients may affect functions of the tissues in which the gene is normally highly expressed, such as muscles and the central nervous system (CNS). To address this question, different Dmpk-knockout (KO) mouse models have been generated and characterized through the years with different results. Initial reports on *Dmpk*-KO mice described cardiac conduction defects ^[51] and mild myopathy ^[52]. Since these mice models were characterized by a mixed genetic background possibly leading to confounding effects, more recently a Dmpk-KO model backcrossed to two different pure genetic backgrounds was generated. This model did not confirm the previous observations, but showed that Dmpk gene deletion does not compromise cardiac or skeletal-muscle function ^[53]. Additionally, *DMPK* transcript silencing through antisense oligonucleotides (ASOs) was well tolerated in mice, rats and monkeys [54]. These findings suggest that reduction in DMPK expression should not be a prominent cause of the disease. Given the crucial regulatory role of MBNL proteins in DM1, different Mbnl KO models were generated to elucidate the role of each MBNL protein in the disease. Mbnl1 and Mbnl2 loss of function resulted in muscular and CNS symptom manifestation, respectively [55] ^{[56][57]}, while *MbnI3* KO caused a progressive delay in muscle regeneration and embryonic muscle differentiation abnormalities, in agreement with their expression profiles during development [58]. Mice with double Mbnl1/Mbnl2 KO or Mbnl1/Mbnl3 KO exhibited more severe phenotypes compared with the single KO ^[60] and the triple *Mbnl1/2/3* KO in muscle tissues recapitulated the severe phenotype observed in congenital DM1, in both newborn and adult mice [61], supporting the idea of a prominent role of MBNL proteins and alternative

splicing dysregulation in DM1 pathogenesis. To determine the role of CELF proteins in DM1 pathogenesis, mouse models overexpressing CELF1 and CELF2 in skeletal and/or cardiac muscle were generated ^{[62][63][64][65]}. Overexpression of CELF1 was shown to reproduce DM1-associated histopathological and functional changes ^[63]. Notably, CELF1/2 overexpressing mouse models have revealed a strong pattern of antagonistic regulation of mRNA levels by CELF and MBNL proteins through competitive binding to 3' UTR regions ^[64] (**Table 1**A).

Table 1. DM1 mouse models used for studying pathogenetic mechanisms and/or molecular therapies.

(A) Knockout and Overexpressing Models							
Mouse Model	Generation Strategy	DM1-Like Features	Limitations	Research Application	Ref		
DMPK ^{-/-}	<i>Dmpk</i> KO via replacement of 5'-UTR and exons 1-7 with hygromycin cassette	Late-onset mild myopathy and altered Ca ⁺⁺ homeostasis	Mild phenotype; possible confounding insertional effects on flanking genes; mixed genetic background	Relevance of absence of DMPK protein to DM1 phenotype	(<u>52)(66)</u>		
DMPK ^{-/-}	<i>Dmpk</i> KO via replacement of 5'-UTR and exons 1-7 with neomycin cassette	Late-onset mild myopathy; decreased force generation; altered Na ⁺ currents in skeletal muscles; cardiac conduction defects	Mild phenotype; possible confounding insertional effects on flanking genes; mixed genetic background	Relevance of absence of DMPK protein to DM1 phenotype	(<u>51)(67)</u>		
DMPK ^{-/-}	<i>Dmpk</i> KO via replacement of 5'-UTR and exons 1-7 with hygromycin cassette	No phenotype	Failure to replicate the DM1 phenotype	Relevance of absence of DMPK protein to DM1 phenotype	[<u>53]</u>		
Mbnl1 ^{ΔE3/ΔE3}	<i>Mbnl1</i> KO via targeted deletion of <i>Mbnl1</i> exon 3	Mild myotonia and myopathy (centralized nuclei, split fibers); heart conduction defects; progressive cataracts; AS alterations	Mild muscle phenotype; mild brain alterations; limited spliceopathy	Evaluation of MBNL1 splicing regulation to DM1 phenotype	(<u>56)(57)</u>		
Mbnl2 ^{ΔE2/ΔE2}	Mbnl2 KO via targeted deletion of Mbnl2 exon 2	Development of several CNS	Failure to replicate the DM1	Evaluation of MBNL2 splicing	[55]		

		alterations (REM sleep propensity, deficit in spatial memory, decreased synaptic plasticity), AS alterations	muscular phenotype	regulation to DM1 phenotype	
Mbnl3 ^{∆E2}	<i>Mbnl3</i> KO via targeted deletion of <i>Mbnl3</i> exon 2 (X-linked)	Progressive delay in muscle regeneration; abnormalities in embryonic muscle differentiation leading to neonatal hypotonia	Possible compensation by MBNL3 truncated isoform or other MBNI family members	Evaluation of MBNL3 contribution to DM1 phenotype	<u>(58)</u>
Mbnl1 ^{ΔE3/ΔE3} ; Mbnl2 ^{C/C} ; Myo-Cre ^{+/-}	<i>Mbnl1</i> KO; skeletal-muscle specific Cre- mediated <i>Mbnl2</i> KO	Small size at birth and skeletal abnormalities; myopathy and severe motor deficits; AS alterations also in brain tissues	High neonatal mortality and reduced lifespan	Evaluation of MBNL1 and MBNL2 contribution to DM1 muscular phenotype	[<u>60]</u>
Mbnl1 ^{∆E3/∆E3} ; Mbnl3 ^{∆E2}	<i>Mbnl1</i> and <i>Mbnl3</i> KO via targeted deletion of <i>Mbnl1</i> exon 3 and <i>Mbnl3</i> exon 2	Myotonia and myopathy; reduction in muscle strength; chloride currents alteration; AS alterations; translation defects	AS alterations similar to <i>Mbnl1</i> single knock out; lack of brain alterations	Evaluation of MBNL1 and MBNL3 contribution to DM1 phenotype	<u>[59]</u>
Mbnl1 ^{ΔE3/ΔE3} ; Mbnl2 ^{C/C} ; Mbnl3 ^C ; Myo-Cre ^{+/-}	<i>Mbnl1</i> KO; muscle-specific Cre- mediated <i>Mbnl2</i> and <i>Mbnl3</i> KO	Severe congenital myopathy and spliceopathy, severe respiratory difficulties and muscle wasting in adults; gene expression changes	High neonatal mortality and reduced lifespan	Evaluation of all MBNL proteins loss contribution to DM1 muscular phenotype	[<u>61</u>]
MCKCUGBP1	Insertion of human <i>CELF1</i> transgene under striated-muscle-specific MCK mouse promoter	Chains of central nuclei in myofibers, increased NADH	Neonatal lethality in mice expressing high levels of CELF1	Contribution of CELF1 overexpression to	[<u>62]</u>

		reactivity, degenerating fibers and AS alterations		DM1 muscular phenotype		
TRECUGBP1	Insertion of Tet-responsive human <i>CELF1</i> transgene; heart-specific rtTA expression	Left ventricular systolic dysfunction and dilatation, AS alterations	DM1-like phenotype limited to heart defects	Contribution of CELF1 overexpression to DM1 heart phenotype	[<u>63</u>]	
TRECUGBP1	Insertion of Tet-responsive human <i>CELF1</i> transgene; skeletal- muscle-specific rtTA expression	Myofibers containing central nuclei, decreased muscle weight, impaired muscle function, AS alterations	DM1-like phenotype limited to skeletal-muscle defects	Contribution of CELF1 overexpression to DM1 skeletal- muscle phenotype	[65]	
TRECUGBP2	Insertion of Tet-responsive human <i>CELF2</i> transgene; heart-specific rtTA expression	No observed heart pathology; AS alterations similar to those observed in TRECUBP1 mice	Mild heart phenotype	Contribution of CELF2 overexpression to DM1 heart phenotype	[<u>64]</u>	
	(B) Trar	nsgenic Models with	Repeat Expansion			
Mouse Model	Generation Strategy	(CTG)n	DM1-Like Features	Limitations	Research Application	Ref
DM200	Insertion of a Tet-responsive expanded <i>DMPK</i> transgene where <i>DMPK</i> coding region is replaced by GFP	200	Ribonuclear foci; MBNL1 sequestration; AS alterations; myotonia, progressive cardiac conduction abnormalities	Splicing alterations in the heart have not been described	Study of DM1 phenotype associated with toxic CUG repeats; modeling muscle regeneration; test of therapeutic strategies	(<u>68</u>) (<u>69</u>) (<u>70</u>)
DM300	Insertion of a 45Kb human genomic fragment containing <i>DMWD</i> , <i>DMPK</i> and <i>SIX5</i> genes from a DM1 patient	~300	Ribonuclear foci (skeletal muscle, heart and brain); myotonia; muscle atrophy; morphological abnormalities; changes in the distribution of MAPT/Tau protein isoform; defect in	High mortality; mild splicing alterations; intergenerational instability of CTG- repeat numbers	Evaluation of <i>DMPK</i> transcript toxicity in different tissues	[<u>71</u>] [72]

			glucose metabolism			
DMSXL	Insertion of a 45Kb human genomic fragment containing <i>DMWD</i> , <i>DMPK</i> and <i>SIX5</i> genes from a DM1 patient	>1000	Ribonuclear foci; MBNL1 sequestration; AS alterations; deficits in motor performance; behavioral abnormalities; synaptic dysfunction; inhibition of exploratory activity and cerebellar glial dysfunction	High mortality; severe body-weight reduction; interindividual variability; decreased transgene expression with aging; mild muscular phenotype	Evaluation of <i>DMPK</i> transcript toxicity in different tissues and in multiple brain cell types; test of therapeutic strategies	[23] [73] [74]
HSA ^{LR}	Insertion of the human skeletal actin (HSA) gene including CTG repeats in the 3' UTR	~250	Ribonuclear foci; AS alterations; myotonia and muscle histopathology abnormalities (increase in central nuclei and variability in fiber size) after six months of age	Limited to skeletal muscle; does not contain <i>DMPK</i> gene sequence; absence of muscle weakness	Investigation of expanded-CUG- repeat toxicity in muscle fibers; test of therapeutic strategies	ر ب ال <u>گی</u> ا ال
LC15 LR [<u>76</u>]	[<mark>77]</mark> Insertion of CTG expanded <i>DMPK</i> 3' UTR downstream Luciferase gene driven by CMV-βA promoter	250–400	Ribonuclear foci, AS alteration and MBNL2 upregulation in the heart; reduced Na ⁺ and K ⁺ channel activity; ventricular arrhythmias	DM1-like phenotype limited to heart defects [75][78][79][80][81	Evaluation of biophysical mechanisms reproducing DM1- like [[824]@gcardiograph abnormalities	[[[[]]]]]]]]]]]]]]]]
EpA960/ α-MHC-Cre	Insertion of CTG expanded <i>DMPK</i> exon 15 transgene containing Cre-responsive loxP sequences; heart-specific myosin Cre expression	960 (CTCGA- interrupted)	Ribonuclear foci; MBNL1 sequestration; CELF1 protein upregulation; AS alterations; cardiomyopathy, arrhythmias; systolic and	Does not reproduce CTG-repeat continuity; mouse model no longer available	Evaluation of <i>DMPK</i> transcript toxicity and CELF1 overexpression in heart tissue	[<u>78]</u>]

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			diastolic dysfunction				logy,
EpA960/ HSA-Cre	Insertion of CTG expanded <i>DMPK</i> exon 15 transgene containing Cre-responsive loxP sequence; skeletal-muscle-specific Cre expression	960 (CTCGA- interrupted)	Ribonuclear foci; MBNL1 sequestration; CELF1 protein upregulation; AS defects; myotonia and progressive muscle wasting, deficits in muscle performance and histopathological abnormalities	Does not reproduce CTG-repeat continuity; mouse model no longer available	Evaluation of <i>DMPK</i> transcript toxicity and CELF1 overexpression in skeletal tissue	[<u>79</u>]	r, K.; sion of ember. ;
EpA960/ CamKII-Cre	Insertion of CTG expanded <i>DMPK</i> exon 15 transgene containing Cre-responsive loxP sequence; brain-specific Cre expression	960 (CTCGA- interrupted)	Ribonuclear foci; MBNL1 sequestration; AS alterations; learning disability; neurotransmission dysfunction; brain atrophy and aging	Does not reproduce CTG-repeat continuity; mouse model no longer available	Identify mechanisms involved in CTG- dependent neuronal degeneration	[<u>80</u>]	peat in al and
TREDT960I/ α-MHC-rtTA	Insertion of Tet-responsive expanded <i>DMPK</i> exons 11–15 transgene; heart-specific rtTA expression	960 (CTCGA- interrupted)	Ribonuclear foci; MBNL1 sequestration; CELF1 protein upregulation; AS alterations ; arrhythmias	Does not reproduce CTG-repeat continuity	Study of alteration of ion transport and action potential in cardiomyocytes expressing toxic CUG	[<u>81</u>] [<u>82</u>]	յth of . Hum.
TREDT960I/ MDAF-rtTA	Insertion of Tet-responsive expanded <i>DMPK</i> exons 11–15 transgene; skeletal-muscle-specific rtTA expression	960 (CTCGA- interrupted)	Ribonuclear foci; MBNL1 sequestration; CELF1 protein upregulation; AS alterations; muscle wasting and myopathy	Does not reproduce CTG-repeat continuity	Study the mechanisms of CUG-repeat- induced muscle tissue loss	[<u>83</u>]	ckton,

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Abbreviations: AS = alternative splicing; ChP = brain choroid plexus; CMVβA = cytomegalovirus enhancer/β-actin; 14. Brouwer, J.R.; Huguet, A.; Nicole, A.; Munnich, A.; Gourdon, G. Transcriptionally Repressive GFP = green fluorescent protein; KO = knockout; MDAF = expression vector carrying regulatory sequences for the Chromatin Remodelling and CpG Methylation in the Presence of Expanded CTG-Repeats at the rat myosin light chain 1/3 gene; MHC = myosin heavy chain; Myo = myogenin; NADH = nicotinamide adenine DM1 Locus. J. Nucleic Acids 2013, 2013, 567435. dinucleotide; polyA = polyadenylation; rtTA = reverse tet transactivator.

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