frontiers in Aging Neuroscience

REVIEW
published: 15 November 2021
doi: 10.3389/fnagi.2021.755392

Brain Pathogenesis and Potential Therapeutic Strategies in Myotonic Dystrophy Type 1

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Myotonic dystrophy type 1 (DM1) is the most common muscular dystrophy that affects multiple systems including the muscle and heart. The mutant CTG expansion at the 3′-UTR of the *DMPK* gene causes the expression of toxic RNA that aggregate as nuclear foci. The foci then interfere with RNA-binding proteins, affecting hundreds of mis-spliced effector genes, leading to aberrant alternative splicing and loss of effector gene product functions, ultimately resulting in systemic disorders. In recent years, increasing clinical, imaging, and pathological evidence have indicated that DM1, though to a lesser extent, could also be recognized as true brain diseases, with more and more researchers dedicating to develop novel therapeutic tools dealing with it. In this review, we summarize the current advances in the pathogenesis and pathology of central nervous system (CNS) deficits in DM1, intervention measures currently being investigated are also highlighted, aiming to promote novel and cutting-edge therapeutic investigations.

Keywords: myotonic dystrophy type 1, central nervous system, pathology, mechanism, treatment

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Received: *08 August 2021*
Accepted: *20 October 2021*
Published: *15 November 2021*

Citation:
Liu J, Guo Z-N, Yan X-L, Yang Y and Huang S (2021) Brain Pathogenesis and Potential Therapeutic Strategies in Myotonic Dystrophy Type 1. Front. Aging Neurosci. 13:755392. doi: 10.3389/fnagi.2021.755392

INTRODUCTION

Myotonic dystrophies (DM1 and DM2) are inherited autosomal dominant skeletal muscle diseases that are characterized by progressive muscle weakness and myotonia, and involves multisystem engagement. DM1, also known as Steinert disease, is caused by the abnormal expansion of a CTG-trinucleotide repeat in the 3′-UTR of the dystrophia myotonic protein kinase (*DMPK*) gene (Brook et al., 1992; Fu et al., 1992; Mahadevan et al., 1992). In healthy individuals, there are approximately 5–38 CTG repeats in the *DMPK* gene, while DM1 patients harbor 50 to several thousands of repeats. CTG repeats tend to increase throughout aging. And as the number of repeats increase, disease severity escalates and age of onset decreases (Bird, 1993). As a progressively debilitating disease, DM1 tends to have an earlier onset and more severe phenotype from one generation to the next, while symptoms could be highly variable among patients (Udd and Krahe, 2012).

Conventionally, DM1 can be divided into five types: congenital, childhood-onset, juvenile-onset, adult-onset, and late-onset, with the adult-onset form being the most prevalent (De Antonio et al., 2016). In the past few years, several neurological symptoms, including cognitive impairment, behavioral impairment, and sensory-motor neural integration have attracted more

and more attention, indicating cerebral involvement (Meola and Sansone, 2007; Meola and Cardani, 2015). These central nervous system (CNS) deficits among DM1 individuals significantly increase the disease burden, not only affecting neuropsychological domains but also decreasing the whole quality of life. A large clinical longitudinal study of DM1 patients by Miller et al. (2021) demonstrated that cognitive deficits, hypersomnolence, and apathy are critical brain symptoms of adult-onset DM1 caused by the underlying molecular mechanisms. In contrast, depression and anxiety are secondary coping symptoms with chronic physical and emotional stress (Miller et al., 2021). In addition, Simoncini et al. (2020) proved that the severity and progression rate of neurological impairments are highly variable over time, possibly attributed to underlying neuropathology (Mazzoli et al., 2020). The cognitive impairment in DM1 patients can be severe. This varies significantly with the phenotype, including the typical intellectual disability and lower intelligence quotient (IQ) levels in the congenital phenotype (Angeard et al., 2007, 2011; Echenne et al., 2008; Ekström et al., 2008; Douniol et al., 2012), the reading and spelling impairment, autistic behavior, attention deficits, deficiency in the speed of processing and severe difficulties in social interactions in childhood-onset phenotype (Steyaert et al., 1997), and dysfunctional personality, visuospatial deficits, unawareness of disease symptoms and signs, impaired facial expression and emotion recognition, and later apathy in the adult-onset phenotype (Meola et al., 2003; Winblad et al., 2006; Sansone et al., 2007; Takeda et al., 2009; Kobayakawa et al., 2010, 2012; Sistiaga et al., 2010; Jean et al., 2014; Gallais et al., 2015). Compared with the congenital groups, the childhood group shown greater cognitive and adaptive development (Lindeblad et al., 2019). Fatigue and sleep disorders including excessive daytime sleepiness (EDS) are also prominent complaints in DM1 patients (Steyaert et al., 1997; Quera Salva et al., 2006). Since fatigue involves both central and peripheral performances, the sense of tiredness is primarily caused by CNS dysfunction (Angelini and Tasca, 2012). Till now, a variety of neuropsychological tests have been developed to evaluate the CNS involvement in DM1 (Okkersen et al., 2017a; Simoncini et al., 2020). **Tables 1**, **2** briefly summarizes the critical CNS symptoms in DM1 and the recent findings about CNS involvement measured by neuropsychological tests in DM1, respectively (Meola and Sansone, 2007; Subramony et al., 2020). In addition, multiple neuroimaging studies relying on structural and functional explorations suggest a wide range of brain abnormalities in DM1 (Okkersen et al., 2017b; Minnerop et al., 2018; Angelini and Pinzan, 2019), mainly involving white matter (WM) abnormalities, widespread gray matter (GM) atrophy and hypometabolism in the frontal lobes. The primary studies focused on neuroimaging abnormalities in DM1 have been shown in **Tables 3**, **4**. Furthermore, specific patterns of neuroimaging alterations and their correlations with other clinical parameters, such as clinical performances and neuropsychological test results have also been discovered, such as sleepiness might be associated with WM status in the superior longitudinal fasciculus and cingulum (Wozniak et al., 2014), and visuospatial impairment might be correlated with WM abnormalities and cortical atrophy (Cabada et al., 2017). Although the single structural or functional alterations seems to be critical for specific CNS dysfunctions, recent advance further revealed the abnormal functional connectivity patterns in DM1 brain and their effects on different personality traits (Serra et al., 2014, 2016a,b, 2020b). Besides, the main executive dysfunction and memory and visuo-spatial impairment were associated with the whole brain volume loss, but cannot be attributed to focal atrophy in any specific regions (Baldanzi et al., 2016b). Small but extensive WM damages in DM1 patients with normal-appearing WM beyond the signal changes detected with conventional MR imaging might be associated with the neuropsychological deficit (Anderson, 2013; Baldanzi et al., 2016b). This implying the critical effects of disrupted complex neuronal networks on cognitive impairments in DM1. Explorations on the complex neuronal networks and undetected lesions and their complex mechanisms contributing to clinical impairments might provide effective outcome measurements as well as effective therapeutic targets for DM1 CNS deficits. Despite a large amount of imaging and neuropsychological evidence of CNS involvement in DM1, the molecular mechanisms driving these deficits are largely unidentified, and targeted therapies aimed at ameliorating neurological deficits are scarce. This review summarizes the recent advances in the pathology and pathogenesis of CNS disorders in DM1 and the promising therapeutic strategies, hoping to provide new proposals for future investigations.

TABLE 1 | CNS symptom in DM1.

CNS symptom	Related symptoms
Cognitive change	Mental retardation Reduced IQ values MMSE scores decrease Memory deficits Visual-Spatial deficits Attentional deficits Speech and language delay and verbal memory deficits Impaired facial expression and emotion recognition Difficulty in social communication Brain fog
Behavioral abnormality	Executive dysfunction/aphasia Avoidance behavior Impulsivity Personality changes Apathy Anxiety Depression Anosognosia
Sleep disorder	EDS SDB Restless legs syndrome and PLMS REM sleep dysregulation Long nighttime sleep
Fatigue	

DM1, myotonic dystrophy type 1; CNS, central nervous system; IQ, intelligence quotient; MMSE, Mini Mental State Examination; EDS, excessive daytime sleepiness; SDB, sleep disorder breathing; PLMS, periodic limb movements of sleep; REM, rapid eye movement.

TABLE 2 | Neuropsychological tests in DM1.

References	Neuropsychological tests (alterations)	Participants	Main results
Tremblay et al., 2021	WASI-II (Intellectual abilities); FAB (Executive functioning); LARS (Apathy)	11 patients with DM1	Adults with childhood-onset DM1 present relative dependence in regard to IADLs, the level of which is, at least partially, associated with cognitive impairments
Cabada et al., 2021	Digit Span from TBR, Spatial Span from the WMS-III scale, and Letter-Number Sequencing from the WAIS-IV scale (Working memory); BVRT-Part C, Cubes from TBR (Visuospatial constructional ability); TMT-B (Alternating attention); TAVEC (Verbal memory); Word Accentuation Test-30 (Verbal IQ)	33 patients with DM1	DM1 patients have a significant deterioration in test performance that measures working memory and visuospatial skills, which are significantly associated with white matter lesion load
Lopez-Titla et al., 2021	MMSE and MOCA (Cognitive impairment); 19 CANTAB tests (Cognitive domains of attention, global memory, visual memory, and executive functions)	22 patients with DM1 vs. 22 healthy controls	Patients with DM1 have significant deficits in memory and problem-solving tasks WM integrity degradation at frontal, temporomedial, and parietal lobes could be associated with specific memory impairments in DM1
Woo et al., 2019	Wechsler Adult Intelligence Scale (Intelligence); Rey-Kim memory test (Memory); Executive Intelligence Test (Executive function)	19 patients with DM1	Verbal memory impairment significantly deteriorated in the juvenile-onset DM1 as compared to the adult-onset DM1
Breton et al., 2020	The digit symbol coding subscale of the WAIS-R (Processing speed); CVLT (Learning ability and verbal memory); Ruff 2 & 7 (Sustained and selective attention)	115 patients with adult-onset DM1	DNA methylation at the DMPK gene locus might be a predictor of DM1-related cognitive dysfunction
Romeo et al., 2010a	Raven's progressive Matrices (Non-verbal intelligence); Stroop and Fluency tests (Frontal executive functions); Wechsler Memory Scale and Corsi's Block tests (Memory and learning functions); Rey-Osterrieth Complex Figure (Visuo-spatial abilities)	50 patients with DM1 vs. 14 patients with DM2	There is a specific temporo-insular diffuse lesional pattern in DM1 There might be a possible correlation between cognitive impairment and diffuse frontal lesions Brain involvement might be different in DM1 and DM2, and severer CNS changes are observed in DM1
Meola et al., 2003	SCID-II personality scale (Personality); TMT (Serial ordering and alternation); WCST (Concept formation and set shifting); Stroop Test (Attentional control and response inhibition); TLT (Planning and problem solving)	21 patients with moderately severe DM1	Executive dysfunction and avoidant personality trait are associated with hypoperfusion in frontal and parieto-occipital regions of the brain
Sistiaga et al., 2010	WAIS-III (IQ, attention and working memory); WCST (Categorization and cognitive flexibility); Stroop Color and Word Test (Automatic response inhibition); Raven's Progressive Matrices (Visual deduction, semantic and phonetic verbal fluency); BJLOT (Visuospatial ability); RCF (Visual-motor organization and planning strategies); CalCAP (Maintained attention and simple and complex reaction time); RAVLT (Immediate and delayed memory); MCMI-II (Personality traits and psychopathology)	121 adult patients with DM1 vs. 54 healthy controls	CTG expansion size in DM1 is negatively related to many cognitive and personality deficits The cognitive impairment predominantly affects the frontoparietal lobe
Serra et al., 2014	Clinical interview and Minnesota Multiphasic Personality Inventory-2 (Personality assessment)	27 patients with DM1 vs. 16 matched healthy controls	A continuum of atypical personality profiles ranging from schizotypal personality traits to paranoid personality disorder is discovered in DM1 patients Alterations of functional connectivity of the brain may explain the atypical personality traits observed in DM1 patients
Bertrand et al., 2015	SCL-90-R (Psychological symptoms); NEO-FFI (Personality dimensions); Rosenberg Self-Esteem Scale (Self-esteem); ASIQ (Suicidal ideation); WAIS-R Full Scale IQ (Global intellectual functioning); WAIS-R Information score, WAIS-R Verbal IQ, and Boston Naming Test total score (Language abilities); WAIS-R Picture Completion, WAIS-R Block Design, WAIS-R Performance IQ, Hooper's test, TVPS subtests, and copy of the Rey-Osterrieth Complex Figure (Non-verbal abilities); WAIS-R Digit Span, Ruff 2 & 7 Speed and Accuracy, Stroop subtests, WAIS-R Similarities, Category and Letter verbal fluency, and Raven's progressive matrices (Attention/executive functions); CVLT and Rey-Osterrieth Complex Figure immediate recall, delayed recall, and recognition total scores (Memory)	200 patients with DM1	Psychological traits differ across DM1 phenotypes The presence of higher phobic anxiety and lower self-esteem are associated with lower education, a higher number of CTG repeats, more severe muscular impairment, and lower cognitive functioning
Kobayakawa et al., 2012	RMET and faux pas recognition (ToM)	9 patients with adult-onset DM1	Social cognitive impairment in patients with adult-onset DM1 is associated with ToM dysfunction
Baldanzi et al., 2016b	RAVLT-IR, RAVLT-DR, ROCF, Digit Span, and CBT (Immediate memory); TMT-A and TMT-B (Selective attention and cognitive flexibility); Stroop Test (Automatic response inhibition); FAS, FAB, Modified WCST (Frontal and executive functions); ROCF-copy (Spatial organization and visuo-constructional skills)	30 patients with DM1	Disrupted complex neuronal networks can underlie cognitive-behavioral dysfunctions in DM1

(Continued)

TABLE 2 | (Continued)

References	Neuropsychological tests (alterations)	Participants	Main results
Gallais et al., 2015	LARS (Apathy); Mini International Neuropsychiatric Interview (MDE); MMSE (Cognitive impairment); Stroop Test (Processing speed, attentional control, response inhibition); FAB (Executive abilities); KFSS (Fatigue)	38 patients with adult-onset DM1 vs. 19 patients with FSHD vs. 20 matched healthy controls	Apathy is more prevalent in DM1 than in FSHD, which is independent of the psychopathological domain, fatigue, age, and motor disability, but is associated with general cognitive status
Labayru et al., 2018	K-BIT (Overall cognitive functioning); Digit span subtest from the WAIS-III (Attention performance); POFA (Emotion recognition); The Faux Pas test (ToM); TECA (Empathy)	38 patients with DM1 vs. matched healthy controls	DM1 patients don't manifest specific impairments in ToM, while emotion recognition appears as a core deficit
Serra et al., 2020a	Emotion attribution test, social situations test, moral/conventional distinction test (Social cognition)	30 patients with DM1 vs. 25 healthy controls	Cortical thickness changes in DM1 patients are significantly associated with deficits in social cognition performances
Serra et al., 2016a	RMET and ToM-story test (ToM); WAIS-R (Global cognitive efficiency)	20 patients with DM1 vs. 18 healthy controls	Deficits in ToM are associated with specific patterns of abnormal connectivity between the left inferior temporal and frontocerebellar nodes in DM1 brains
Minnerop et al., 2011	c.I.T.S (Focused attention); c.I.T.I (Interference); TMT A (Psychomotoric speed); TMT B (Attention shift, mental flexibility); DSS (Daytime sleepiness); NeurocogFX (Choice reaction time, interference, verbal memory-recognition, figural memory-recognition); KFSS (Fatigue); PSQI (Sleep quality); Ullanlinna-Narcolepsy Scale (Narcolepsy)	22 patients with DM1 vs. 22 patients with DM2 vs. matched healthy controls	Depression in DM might be a reactive adjustment disorder rather than a direct consequence of structural brain damage DM1 presents with more prominent WM lesions than DM2, with prominent callosal body and limbic system affection. WM changes might dominated the extent of gray matter changes.
Rakocevic-Stojanovic et al., 2014	Hamilton rating scale (Depressive and anxiety); KFSS (Fatigue); DSS (EDS); ACE-R (Global cognitive status); RSPM and the Serbian version of WAIS-R (General intellectual level); RAVLT (Verbal memory); ROCF (Visuoconstructive abilities and visual memory); TMT-A (Speed and attention); WCST and TMT-B (Executive functions); BNT (Phonetic and semantic verbal fluency); CANTAB (Attention, visual memory, executive functions)	22 patients with juvenile-onset DM1 vs. 44 patients with adult-onset DM1	Patients with juvenile-onset DM1 scored lower than adult-onset DM1 patients regarding total INQoL score and all INQoL subdomains, except for myotonia. Different central manifestations strongly influence QoL in patients with both adult-onset DM1 and juvenile-onset DM1
Heatwole et al., 2018	MDHI, INQoL (QoL); SF-36v2 (Health impairment)	52 patients with DM1	The MDHI correlates well with objective metrics that reflect disease severity in DM1 Participants in DM1 clinical studies favored the MDHI over the INQoL and the SF-36v2 in multiple areas of perceived relevance, usability, and responsiveness
Peric et al., 2016	SF-36 (QoL)	84 patients with DM1	QoL improved in DM1 patients during a 5-year period despite the disease progression SF-36 should be used with caution as a patient-reported outcome measure in DM1 clinical trials
Peric et al., 2017b	INQoL (QoL)	67 patients with DM1	INQoL questionnaire scores improved in DM1 patients during a 6-year period INQoL score did not correlate with progression of muscle weakness
Symonds et al., 2017	MDHI (Health status); DM1-Activ, DM1 Activc, LIFE-H (Activities of daily living); INQoL (Health-related quality of life); ESS, DSS, CFS, FSS, FDSS (Sleep and fatigue)	/	Several patient-reported outcome assessments are suited to make valid measurements in DM1 populations
Heatwole et al., 2016	MDHI	70 patients with DM1	MDHI is a valid tool to measure disease burden in DM1 patients
Baldanzi et al., 2016a	TIB (Intellectual functioning); BDI-II, STAI-Y2 (Depressive and anxiety); AES (Apathy); RAVLT-IR, RAVLT-DR, ROCF-DR, ROCF-IR, CBT (Immediate memory); TMT-A and TMT-B (Selective attention and cognitive flexibility); Stroop Test (Automatic response inhibition); FAS, FAB, Modified WCST (Frontal and executive functions); ROCF (Spatial organization and visuo-constructional skills); Raven's progressive matrices (PM47) (Culture-free abstract reasoning); INQoL (Disease awareness)	65 patients with adult-onset DM1	Several cognitive functions, including executive and mnesic domains with visuo-spatial involvement, were affected in DM1 patients The reduced illness awareness occurs across different physical and life domains, and it appears more prominent in Activities and Independence domains The unawareness significantly related to the cognitive performance deficits, specifically in the domains of visuo-spatial memory, cognitive flexibility and conceptualization

ACE-R, Addenbrooke's Cognitive Examination-Revised; AES, Apathy Evaluation Scale; ASIQ, Adult Suicidal Ideation Questionnaire; BDI-II, Beck Depression Inventory-II; BJLOT, Benton Judgment of Line Orientation Test; BNT, Boston naming test; BVRT, Benton Visual Retention Test; CBT, Corsi Block-Tapping test; CFS, Chalder Fatigue Scale; c.I.T.S, subtest (symbol counting) of the Cerebraler Insuffizienztest; c.I.T.I, subtest (response inhibition) of the Cerebraler Insuffizienztest; CVLT, California Verbal Learning Test; CalCAP, California Computerized Assessment Package; CANTAB, Cambridge Neuropsychological Test Automated; DM, myotonic dystrophy; DSS, Daytime Sleepiness Scale; EDS, excessive daytime sleepiness; FDSS, the Fatigue and Daytime Sleepiness Scale; FSHD, facioscapulohumeral dystrophy; FAB, Frontal Assessment Battery; FAS, phonemic verbal fluency test; FSS, the Krupp Fatigue Severity Scale; IADLs, instrumental activities of daily living; INQoL, Individualized Neuromuscular Quality of Life questionnaire; IQ, Intellectual Quotient; KFSS, Krupp's Fatigue Severity Scale; K-BIT, Kaufman Brief Intelligence Test; LARS, Lille Apathy Rating Scale; LIFE-H, Assessment of Life Habits; MCMI, Millon Multiaxial Clinical Inventory; MDE, major depressive episodes; MDHI, Myotonic Dystrophy Health Index; MMSE, Mini Mental State Evaluation; MOCA, Montreal Cognitive Assessment; NEO-FFI, NEO Five-Factor Inventory; NeurocogFX, computerized neuropsychological screening test battery; POFA, Pictures of Facial Affect; PSQI, Pittsburgh Sleep Quality Index; RCF, Rey's Complex Figure; QoL, Quality of life; RMET, Reading the Mind in the Eyes Test; RAVLT-IR, Immediate Recall of the Rey Auditory Verbal Learning Test; RAVLT-DR, Delayed Recall of the Rey Auditory Verbal Learning Test; ROCF-IR, Immediate Recall of the Rey-Osterrieth Complex Figure test; ROCF-DR, Delayed Recall of the Rey-Osterrieth Complex Figure test; RSPM, Raven standard progressive matrices; STAI-Y2, State-Trait Anxiety Inventory-2; SCL-90-R, Symptom Checklist-90-Revised; TAVEC, Test de Aprendizaje Verbal España-Complutense; TBR, Test de Barcelona Revised; TECA, Test of Cognitive and Affective Empathy; TIB, Brief Intelligence Test; TLT, Tower of London Test; TMT, Trail-Making Test; ToM, theory of mind; TVPS, Test of Visual-Perceptual Skills; WAIS, Wechsler Adult Intelligence Scale; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WCST, Wisconsin Card Sorting Test.

TABLE 3 | Structural brain imaging in DM1.

References	Imaging tools	Participants	Imaging abnormalities	Possible correlations between imaging abnormalities and clinical symptoms
Walker et al., 1984	CT	22 adults with DM vs. 45 healthy controls	Increased ventricular surface areas Focal cerebral atrophy	
Glantz et al., 1988	0.5T MRI	14 patients with DM vs. 12 controls	Periventricular hyperintensities Ventricular enlargement	
Hashimoto et al., 1995	MRI	7 patients with adult-onset DM vs. 6 patients with CDM	The incidence of a small corpus callosum or ventricular enlargement is higher in CDM than in adult-onset DM	
Baldanzi et al., 2016b	3T MRI BPF VBM LL% and Fazekas scale	30 patients with DM1 vs. healthy controls	Widespread GM reduction Decreased FA and increased RD, MD and AD	Negative relationships are discovered between left temporal atrophy and verbal memory, between RD and mnesic and visuo-spatial cognitive domains, and between AD and verbal memory The involvement of normal appearance WM, beyond the signal changes detected with conventional MR imaging, is associated with neuropsychological deficit
Romeo et al., 2010a	MRI SPECT	50 patients with DM1 vs. 14 patients with DM2 vs. 44 healthy controls	Scattered supratentorial, bilateral, symmetrical focal or diffuse WMHLs A typical temporo-insular diffuse subcortical pattern Minimal hypoperfusion in the posterior cortex planes	
Weber et al., 2010	BPF VBM FDG-PET	20 patients with DM1 vs. 9 patients with DM2 vs. healthy controls	Global GM volume reduction A bilateral hippocampal volume reduction Frontal and parietal lobes volume reduction A frontotemporal hypometabolism	Hippocampal volume reduction is correlated to episodic memory deficits
Kobayakawa et al., 2010	MRI	9 patients with DM1 vs. 13 healthy controls	More severe lesions in the frontal, temporal, and insular white matters	Sensitivity to the emotion of disgust is negatively correlated with temporal lesions Sensitivity to anger is negatively correlated with frontal, temporal, and insular lesions
Minnerop et al., 2011	3T MRI VBM DTI	22 patients with DM1 vs. 22 patients with DM2 vs. 22 healthy controls	Extensive WM changes involved all cerebral lobes, brainstem, corpus callosum and limbic system, especially in frontal WM	Sleepiness is linked with FA values in the brainstem
Wozniak et al., 2013	DTI	16 patients with DM1 vs. 15 healthy controls	Diffusive WM abnormalities	WM abnormalities are associated with the degree of working memory impairment
Wozniak et al., 2011	DTI	8 patients with DM1 vs. 8 healthy controls	Abnormal WM integrity indices: FA, RD, MD, and AD	Whole cerebrum fractional anisotropy is correlated with full-scale intelligence and a measure of executive functioning
Franc et al., 2012	MRI	5 adults with CDM1 vs. 5 adults with adult onset DM1 vs. 5 adults with DM2 vs. 5 healthy controls	WM integrity reduction GM volumes reduction only in adult-onset DM1 patients	
Wozniak et al., 2014	3T MRI DTI	45 patients with DM1 vs. 44 healthy controls	Bilateral disturbances in WM integrity	DTI metrics are correlated with cognitive functioning, particularly working memory and processing speed WM integrity is correlated with the muscular impairment Sleepiness is associated with WM status in the superior longitudinal fasciculus and cingulum
Caso et al., 2014	MRI VBM	51 patients with DM1 vs. 34 healthy controls	WM hyperintensities Regional GM atrophy WM tract microstructural damage	WMHs and microstructural damage are correlated with cognitive deficits
Schneider-Gold et al., 2015	3T MRI VBM	12 patients with juvenile or classical DM1 vs. 16 adults with DM2 vs. 33 healthy controls	Ventricular enlargement Supratentorial GM and WM atrophy WM reduction in the splenium of the corpus callosum and in left-hemispheric WM adjacent to the pre- and post-central gyrus	Morphological changes is related to reduced flexibility of thinking and atrophy of the left secondary visual cortex
Serra et al., 2015	3T-MRI BPF VBM	10 patients with DM1 vs. 16 healthy controls	Widespread GM atrophy and WM integrity	Extent of GM and WM damage is correlated with CTG triplet expansion and cognition

(Continued)

TABLE 3 | (Continued)

References	Imaging tools	Participants	Imaging abnormalities	Possible correlations between imaging abnormalities and clinical symptoms
Baldanzi et al., 2016b	3T-MRI BPF VBM	30 patients with DM1 vs. 30 healthy controls	Widespread GM atrophy Decreased FA and increased RD, MD, and AD	BPF value is correlated with visuo-spatial and executive impairment Negative relationship between left temporal atrophy and verbal memory, between RD and amnesic and visuo-spatial cognitive domains, and between AD and verbal memory
Zanigni et al., 2016	DTI MRI VBM	24 adults with DM1 vs. 25 healthy controls	Widespread WM DTI abnormalities GM volume reduction	
Cabada et al., 2017	MRI DTI	42 patients with DM1 vs. 42 healthy controls	WML load Cortical and corpus callosum atrophy Diffuse WM DTI abnormalities	Visuospatial impairment is correlated with WM abnormalities and cortical atrophy Daytime sleepiness is associated with WML and ventral diencephalon and pallidum volume loss
Sugiyama et al., 2017	VBM	28 patients with DM1 vs. 28 healthy controls	Extensive GM atrophy, including cortical and subcortical structures Increased connectivity in the left fusiform gyrus and decreased connectivity in the right striatum	Increased connectivity in the left fusiform gyrus and decreased connectivity in the right striatum are associated with impairment in face perception and theory of mind, and schizotypal-paranoid personality traits
Labayru et al., 2019	MRI DTI VBM	31 patients with DM1 vs. 57 healthy controls	Global GM and WM volume reduction FA reduction	Higher ratings on muscular impairment and longer CTG expansion sizes predict a greater volume decrease in GM and lower FA values
van der Plas et al., 2019	3T MRI	79 patients with DM1 vs. 58 healthy controls	Smaller ICV Smaller volume in frontal GM and WM, parietal GM, corpus callosum, thalamus, putamen, and accumbens Larger volumes of the hippocampus and amygdala	Some morphological differences are associated with cognitive deficits and EDS
Serra et al., 2020a	3T MRI	31 patients with DM1 vs. 25 healthy controls	Thickness reduction in the right premotor cortex, angular gyrus, precuneus, and inferior parietal lobule	Cortical thickness are associated with social cognition performances
Cabada et al., 2020	MRI VBM DTI	33 patients with DM1	Increased WML Ventricular enlargement Decreased volume of the left thalamus, caudates, putamen, and hippocampus Global cortical volume decrease Mean diffusivity increase and fractional anisotropy decrease in WM	Working memory and visuospatial skills deterioration are significantly associated with WML load and mean diffusivity increase Progressive WM and GM involvement
Langbehn et al., 2021	3T MRI	59 patients with adult-onset DM1 vs. 68 healthy controls	Pathological increased volume of the hippocampus	Enlarged hippocampal volume is inversely associated with cognitive dysfunction
Leddy et al., 2021	Conventional and qMT MRI	28 patients with DM1 vs. 29 patients with MS vs. 15 healthy controls	Higher prevalence of anterior temporal lobe lesions, but none in the cerebellum and brainstem Characteristic demyelination (significantly reduced F values) A similar WM lesion distribution compare with that typical of relapsing remitting MS	

DM, myotonic dystrophy; MRI, magnetic resonance imaging; CDM, congenital DM; SPECT, single photon emission computed tomography; GM, gray matter; WM, white matter; WMHL, WM hyperintense lesions; BPF, brain parenchymal fraction; VBM, voxel-based morphometry; FDG-PET, fluorodeoxyglucose positron emission tomography; DTI, diffusion tensor imaging; FA, fractional anisotropy; RD, radial diffusivity; MD, mean diffusivity; AD, axial diffusivity; WMH, WM hyperintensities; WML, WM lesion; ICV, intracranial volume; EDS, excessive daytime somnolence; qMT, quantitative magnetization transfer; MS, multiple sclerosis.

MOLECULAR MECHANISMS

The pathogenesis of DM1 has been mainly attributed to the gain-of-function of toxic RNA (Pettersson et al., 2015). Specifically, the mutant CTG repeat at the 3′-UTR of the *DMPK* gene causes toxic RNA expression that accumulate in the nucleus called "nuclear foci," which interferes with RNA-binding proteins (Miller et al., 2000; Fardaei et al., 2002), leading to the sequestration of muscleblind-like (MBNL) proteins and upregulation of CUGBP/Elav-like family (CELF) proteins. These

TABLE 4 | Functional brain imaging in DM1.

References	Imaging tools	Participants	Imaging abnormalities	Possible correlations between imaging abnormalities and clinical symptoms
Toth et al., 2015	fMRI	8 DM1 patients with grip myotonia vs. 8 DM1 patients without grip myotonia		Myotonia is related to cortical function in high-order motor control areas
Serra et al., 2014	RS-fMRI	27 patients with DM1 vs. 16 health controls		DMN functional connectivity in the bilateral posterior cingulate and left parietal nodes are associated with schizotypal-paranoid traits
Serra et al., 2016a	RS-fMRI	20 patients with DM1 vs. 18 healthy controls	Specific patterns of abnormal connectivity between the left inferior temporal and fronto-cerebellar nodes	Specific patterns of abnormal connectivity are associated with atypical personality profiles and ToM deficits
Serra et al., 2016b	RS-fMRI	31 patients with DM1 vs. 26 healthy controls	Reduced connectivity in a large frontoparietal network Peculiar patterns of frontal disconnection Increased parietal-cerebellar connectivity	Reduced connectivity in a large frontoparietal network is correlated with isolated impairment in visuospatial reasoning The balance between loss of connectivity and compensatory mechanisms is correlated with the paradoxical mismatch between structural brain damage and minimal cognitive deficits
Serra et al., 2020b	RS-fMRI	32 patients with DM1 vs. 26 healthy controls	Increased functional connectivity between VTA and the left supramarginal and superior temporal gyri	Deficit of decision-making is related to increased connectivity between VTA and brain areas critically involved in the reward/punishment system and social cognition
Renard et al., 2016	FDG-PET	24 patients with DM1 vs. 24 healthy controls	Reduced FDG-uptake especially in Brodmann area 8	Reduced FDG-uptake in Brodmann area 8 is correlated to CTG-repeat numbers
Peric et al., 2017a	FDG-PET	16 patients with DM1 vs. 13 patients with DM2	Prominent glucose hypometabolism in prefrontal, temporal, and pericentral regions	Right frontotemporal hypometabolism is associated with executive dysfunction
Romeo et al., 2010b	PET/SPECT	58 patients with DM1 subjected to SPECT and 17 patients with DM1 subjected to PET	Reduced CBF and perfusion and abnormal glucose metabolism, more pronounced in the left hemisphere, the frontal lobe and the cortex	
Meola et al., 2003	SPECT	21 patients with moderately severe DM1	Frontal and parieto-occipital hypoperfusion	Specific cognitive and behavioral profile (avoidant trait personality disorder) is associated with hypoperfusion in frontal and parieto-occipital regions of the brain
Chang et al., 1998	MRS	14 patients with DM vs. 24 healthy controls	Elevated levels of myoinositol, total creatine, and choline-containing compounds	Creatine and myoinositol levels are proportional to the number of trinucleotide (CTG)n repeats
Akiguchi et al., 1999	MRS	21 patients with DM vs. 16 healthy controls	Lower ratio of N-acetylaspartate to creatine and phosphocreatine Lower ratio of N-acetylaspartate to choline-containing compounds	
Krogias et al., 2015	TCS	17 patients with DM1 vs. 14 patients with DM2 vs. 31 healthy controls	Third ventricle enlargement	Mesencephalic raphe echogenicity is related with EDS
Peric et al., 2014b	TCS	66 patients with DM1 vs. 55 health controls	Increased third ventricle width Brainstem raphe hypoechogenicity Substantia nigra both hypoechogenicity and hyperechogenicity	

DM, myotonic dystrophy; fMRI, functional MRI; RS-fMRI, resting-state fMRI; ToM, theory of mind; VTA, ventral tegmental area; FDG-PET, fluorodeoxyglucose positron emission tomography; MRS, magnetic resonance spectroscopy; TCS, transcranial sonography.

alterations subsequently affected hundreds of mis-spliced effector genes, resulting in aberrant expression of embryonic splice isoforms and loss of these gene product functions, accounting for the multisystemic phenotype (Udd and Krahe, 2012; Chau and Kalsotra, 2015). In recent years, other factors, such as repeat-associated non-AUG (RAN) translation, which can contribute to the formation of toxic homopolymeric (e.g., polyQ) polypeptides, aberrant polyadenylation, activation of protein kinase C (PKC)-dependent signaling pathway, and microRNA deregulation have also been reported to play important roles in DM1 (Chau and Kalsotra, 2015). Regarding CNS, alternative splicing dysregulation has been frequently reported (Caillet-Boudin et al., 2014). Meanwhile, the widespread distributions of mutant *DMPK* mRNA accumulated in nuclear foci in neurons, astrocytes, oligodendrocytes, as well as in human DM1 induced pluripotent stem cell (iPSC)-derived neural stem cells (NSCs) have been reported (Jiang et al., 2004; Hernández-Hernández et al., 2013a; Xia et al., 2013; Sicot et al., 2017). In animal models, different splicing defects and their associated CNS symptoms were also studied (**Figure 1**). Except for these, emerging pathogenic events independent of splicing defects have also been discovered in the brain of DM1 patients (Marteyn et al., 2011; Hernández-Hernández et al., 2013b). Some CNS symptoms are non-linearly dependent on patient age and CTG repeat length, suggesting the complex and multifactorial mechanisms driving neurological deficits (Heatwole et al., 2012).

This section concludes the current advance about CNS pathogenesis, hoping to better understand the complex nature of the DM1 CNS disorders.

Loss Function of Muscleblind-Like Proteins

Three MBNL paralogs are expressed in mammals, MBNL1, MBNL2, and MBNL3, which can be involved in regulating alternative splicing, mRNA stability, translation and so on (Charizanis et al., 2012; Wang et al., 2012). A large amount of previous studies have revealed the critical role of MBNL proteins in muscle or heart-related disorders, while in recent years, a close relationship between the loss-of-function of MBNL and DM1 brain-related phenotypes were also detected (Matynia et al., 2010; Charizanis et al., 2012; Goodwin et al., 2015), especially MBNL2. Nowadays, hundreds of dysregulated splicing factors, including in *Cacna1d* (McKinney et al., 2009), *Tanc2* (Han et al., 2010), *Ndrg4* (Yamamoto et al., 2011), and *GRIN1* (Shimizu et al., 2000) have been detected in the brain of *Mbnl* 2–/– mice, most of which were similarly dysregulated in DM1 patients, indicating a critical role of the *Mbnl2* loss in DM1 brain pathology (Charizanis et al., 2012). Further, *Mbnl2*–/– mice which are exposed to sleep deprivation also developed several CNS features including impaired long-term potentiation (LTP), deficits in spatial memory, reduced synaptic NMDAR response and impaired hippocampal synaptic plasticity (Charizanis et al., 2012), which were similar to the DM1 phenotype. In 2018, one study described prolonged and enhanced responsiveness to intracortical train stimulation in *Mbnl2*–/– mice, partially attributed to abnormal glutamate neurotransmission (Chen et al., 2018). Particularly, these abnormalities have also been observed in DM1 patients (Meola and Sansone, 2007; Takado et al., 2015).

Several studies also reported a potential role of MBNL1 protein in CNS disorders. For example, cognitive and behavioral abnormalities have been discovered in *Mbnl1*–/– mice (Matynia et al., 2010). In cultured primary hippocampal neurons and EpA960/CaMKII-Cre mice (a brain-specific DM1 model carrying 960 *DMPK* CTG repeats in the postnatal brain), expanded CUG repeats led to deubiquitination of cytoplasmic MBNL1, subsequent nuclear translocation, and morphological defects. These effects can be ameliorated by inhibiting the degradation of lysine 63-linked polyubiquitin chains or by promoting MBNL1 ubiquitination (Wang P. Y. et al., 2018). In 2020, cell studies shown that gain-of-function of MBNL1 could reverse the proliferation defect of skeletal muscle satellite cells in DM1 by inhibiting autophagy *via* the mTOR pathway (Song et al., 2020). Moreover, functional characterization of neuronal cells derived from human embryonic stem (ES) cells reported a reduced proliferative capacity and increased autophagy associated with alterations of the mTOR signaling pathway, while gain-of-function of MBNL1 rescued the phenotype (Denis et al., 2013), suggesting that MBNL1 loss might influence brain pathology by regulating the mTOR signaling pathway. Some important splicing defects have also been detected in the brain of *Mbnl1*–/– mice, in genes such as *Sorbs1*, *Dclk1*, and *Camk2d* (Suenaga et al., 2012). However, the extent of alternative splicing defects in the brain of *Mbnl1*–/– mice was much less than that observed in DM1. A number of alternative exons, such as *GRIN1* exon 4, *APP* exon 7, and *Tau* exons 3 and 9, which have already been reported to be mis-spliced in the brains of DM1 patients, were unaltered in *Mbnl1*–/– mice, thus indicating a limited contribution of MBNL1 to DM1 CNS defects (Suenaga et al., 2012).

In addition, it's worth noting that the combined loss of MBNL1 and MBNL2 has shown infant/immature structural phenotypes in mutant brains, similar to that of DM1 patients (Goodwin et al., 2015). Besides, single gene knockout may also contribute to the compensatory upregulation of the remaining *Mbnl* genes (Lee et al., 2013). In *Mbnl1*–/– mice, the expression of MBNL2 could be upregulated, which subsequently targets transcripts that are normally regulated by MBNL1 (Lee et al., 2013). These findings indicate a collaborative role of MBNL1 and MBNL2 involved in DM1 CNS.

Gain of CUGBP/Elav-Like Family Activities

The human CELF family has six members, all of which are involved in alternative splicing regulation (Ladd et al., 2001, 2004). Among these, the upregulations of CELF1 and CELF2 have been observed in the brain of DM1 patients (Dhaenens et al., 2011).

CELF1 has been identified as a (CUG)n repeat-binding protein (Timchenko et al., 1996). Unlike MBNL1, it is increased in DM1 patients mainly through PKC-mediated phosphorylation to stabilize the protein (Kuyumcu-Martinez et al., 2007), or through decreased levels of miR-23a/b (Kalsotra et al., 2014). In opposite, the increasing expression of CELF2 is not related to protein hyperphosphorylation, indicating other potential regulatory mechanisms. CELF1 and CELF2 can influence various transcripts (Ladd, 2013) in the DM1 brain, such as different exons of *Tau* and *NMDAR1* exon 5 (Leroy et al., 2006a,b). Tau proteins can promote neurite outgrowth, organize axonal microtubules, and participate in kinesin-dependent axonal transport (Andreadis, 2012). NMDARs are key components of glutamate-mediated excitatory signaling, which can contribute to excitatory synaptic transmission and synaptic plasticity, thought to be the basis of learning and memory (Zorumski and Izumi, 2012). It has been discovered that four exons (2, 3, 6, and 10) of *Tau* isoforms could respond to one or more CELF proteins in DM1 (Leroy et al., 2006a,b; Dhaenens et al., 2011). CELF2 can regulate alternative exon 5 transcripts of *NMDAR1* to change neuronal excitation in rat brain (Zhang et al., 2002), while CELF1 is inefficient. Aside from alternative splicing regulation, CELF proteins can also participate in regulating mRNA adenylation status, stability, and translation in various cell types (Dasgupta and Ladd, 2012), indicating its potential cytoplasmic functions in the brain.

A Novel Splicing Regulator—RBFOX Proteins

RBFOX proteins are sequence-specific RNA binding proteins which can regulate alternative splicing in multiple tissues, such as skeletal muscle, heart, and brain (Gehman et al., 2011;

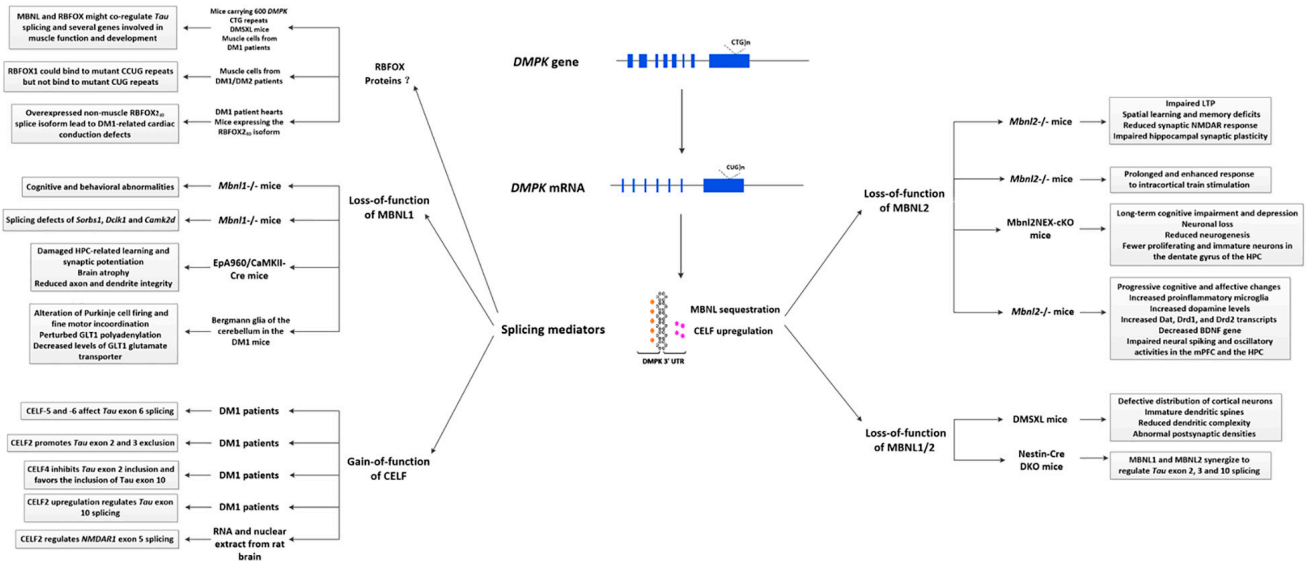

FIGURE 1 | Primary splicing defects described in the DM1 brain. Splicing defects are generally considered the primary cause of DM1 pathology, similar to those in the brain. Specifically, the mutant *DMPK* gene transcripts into expanded CUG RNA, which folds into a hairpin-like structure in the nucleus called "nuclear foci." These nuclear foci then bind and regulate RNA-binding proteins, affecting alternative splicing, eventually causing a wide range of pathogenic changes. Most splicing defects involved in brain pathology are mediated by the sequestration of MBNL proteins and upregulation of CELF proteins. In animal studies, it has been shown that loss-of-function of MBNL1 might be related to cognitive and behavioral abnormalities, learning abnormalities, alteration of Purkinje cell firing and fine motor incoordination, and perturbed GLT1 levels. Besides, it also contributes to alternative splicing alterations of several genes, such as *Sorbs1*, *Dclk1*, and *Camk2d*. Loss-of-function of MBNL2 could be associated with sleep alterations, spatial learning and memory deficits, impaired synaptic NMDAR response and hippocampal synaptic plasticity, neuronal loss, reduced neurogenesis, cognitive and affective changes and so on. Meanwhile, synergistic effects of MBNL1 and MBNL2 can regulate *Tau* exon 2, 3, and 10 splicing, while a combination loss of MBNL1/2 might be related to abnormal sleepiness, defective distribution of cortical neurons, immature dendritic spines, reduced dendritic complexity, and abnormal PSDs. In DM1 patients, it has been shown that gain-of-function of several CELF proteins can regulate *Tau* exon 2, 3, 6, and 10 splicing, and CELF2 can regulate *NMDAR1* exon 5 splicing. A novel splicing regulator, RBFOX protein has recently been considered a new player in DM1 pathogenesis, *via* a competitive or cooperative interaction with MBNL1. Additionally, the non-muscle RBFOX2$_{40}$ splice isoform in DM1 heart may also contribute to cardiac conduction defects. DM1, myotonic dystrophy type 1; CELF, CUGBP/Elav-like family; MBNL, muscleblind-like; GLT1, glutamate transporter 1; LTP, long-term potentiation; mPFC, medial prefrontal cortex; HPC, hippocampus; BNDF, brain derived-neurotrophic factor.

Singh et al., 2014; Conboy, 2017; Jacko et al., 2018). Nowadays, it has been discovered that RBFOX1 is involved in the regulation of synapses and autism-related genes in the cytoplasm of neurons (Wang et al., 2016). Klinck et al. (2014) reported that MBNL1 and RBFOX1 protein could co-regulate the splicing of a series genes involved in muscle function and development, some of which are also mis-spliced in DM1 tissues. And the decreased RBFOX1 may amplify the mis-splicing changes caused by the loss-of-function of MBNL1. At the same time, they found that the ectopic expression of RBFOX1 partially rescued the mis-splicing of *Tau* exon 2 in glioblastoma cells. Since the MBNL proteins have been shown to regulate the splicing of *Tau* exon 2 in DM1 brains, it is therefore interesting to postulate that cooperation of MBNL and RBFOX1 might regulate *Tau* splicing in DM1 brains. Nevertheless, Sellier's researches proposed different results, that RBFOX1 could bind to expanded CUG RNA repeats, competing with MBNL1 and reducing the sequestration of MBNL1 in DM2 muscle cells, which suggest a partly competitive relationship between RBFOX1 and MBNL1 (Sellier et al., 2018). Misra et al. (2020) found a new non-muscle RBFOX2$_{40}$ splice isoform which is overexpressed in DM1 patient hearts. Particularly, mice expressing the RBFOX2$_{40}$ isoform in hearts also performed DM1-related cardiac conduction dysfunctions (Misra et al., 2020), which may due to its promotion of the production of pathogenic ion channel splice variants. All of these results provide a novel idea explaining the splicing dysregulation in DM1, though their possible roles in CNS dysfunctions still need further exploration.

Effector Genes Alterations Due to Splicing Defects

Nowadays, hundreds of spliced effector genes changes have been discovered in the DM1 brain (Jiang et al., 2004; de León and Cisneros, 2008; Suenaga et al., 2012; Hernández-Hernández et al., 2013a; Otero et al., 2021). Jiang et al. (2004) screened 45 exons (in 31 genes) spliced in the brain of DM1 patients, wherein four of them changed in the ratio of exon inclusion/exclusion splice products, including decreased inclusion of *APP* exon 7, *Tau* exons 2 and 10, and increased inclusion of *NMDAR1* receptor exon 5. Interestingly, the sequences encoding *APP* exons 7 and 8 are excluded in neurons, but are included in astrocytes, indicating the splicing defects in astrocytes. In 2021, *via* detecting transcriptome alterations in frontal cortex of DM autopsy samples, Otero et al. (2021) reported 130 high-confidence splicing changes, which occur in ion channels, neurotransmitter receptors, and synaptic scaffolds, while mis-splicing of *GRIP1* might change

kinesin association. In frontal cortex samples, downregulated genes tend to express in neurons, while upregulated genes tended to express preferentially in endothelial and microglial, which suggest neuroinflammatory responses. In DMSXL mice (carrying ∼1,000–1,800 *DMPK* CTG repeats with multisystemic transgene expression), the mis-splicing patterns of *GRIN1* exon 21, *Ldb3* exon 11, and *Mbnl2* exon 7 in frontal cortex, as well as *GRIN1* exon 5, *Ldb3* exon 11, *APP* exon 8, and *Frx1* exons 15/16 in brainstem have been detected (Hernández-Hernández et al., 2013a), and *GRIN1* and *Tau* mis-splicing appear to be involved in synaptic dysfunction. In the brain of *Mbnl1*–/– mice, 14 mis-spliced events have been observed using splicing-sensitive microarray, including *Sorbs1* exons 6 and 25, *Spag9* exon 31, *Dclk1* exon 19, *APP* exon 7 and 8, *GRIN1* exon 4, and so on (Suenaga et al., 2012).

Heterogeneity in Splicing Defects in Different Brain Regions

Recently, the heterogeneity of splicing defects in the DM1 brain also attracted increasing attention. In *Mbnl* knockdown mice, it has been identified that abnormal alternative splicing in the cerebellum are fewer than in other brain regions (Charizanis et al., 2012; Suenaga et al., 2012). The inclusion of *Mbnl1* exon 5 and *Mbnl2* exons 5 and 8 were higher in most brain areas, except in the cerebellum for *Mbnl2* exons 5 and 8. Besides, RNA foci preferentially accumulate in the frontal cortex and certain areas of the brainstem of DM1 transgenic mice (Huguet et al., 2012; Hernández-Hernández et al., 2013a), and seem to be more abundant in cortical astrocytes than in neurons (Hernández-Hernández et al., 2013a). Using autopsied brain tissues of DM1 patients, researchers further observed varying degrees of mis-splicing among the cerebellar cell layers (Furuta et al., 2018). LASER capture microdissection revealed splicing defects in the molecular layer of the cerebellum, but not in the granular layer (Furuta et al., 2018). Similarly, one study reported that mis-splicing in WM is less apparent than in GM of the DM1 brain, which may be attributed to the inability to transfer the abnormal/fetal splicing isoform to the axon (Nishi et al., 2020). Future analysis of the mis-splicing diversity in the DM1 brain may favor a precise therapy targeting specific sites.

Translational RNA Differences

Though sharing with a common pathogenetic mechanism, alternative splicing defects, further findings suggested a new perspective influencing the performances of DM patients. According to the results of Salvatori et al. (2009) the molecular and biochemical differences of troponin T and the insulin receptor between DM1 and DM2 due to different translational patterns and distribution patterns might partially explain the apparent differences on their clinical phenotypes. This phenomenon promotes the exploration of DM1 pathogenesis at the translation level.

Somatic Expansion

Recently, an important aspect of the pathogenesis of DM1 regarding to somatic expansion has attracted increasing attention. It has been demonstrated that the length of modal allele in blood DNA samples of DM1 patients increased over time, driven primarily by the inherited progenitor allele length (ePAL), age-at-sampling, and age-at-onset (Morales et al., 2020). Since the DNA mismatch repair proteins MSH2, MSH3, and MSH6, are considered critical players in CTG repeat expansion, and their decreased expressions inhibit the expansion (Dragileva et al., 2009; Tomé et al., 2009), they provide a new insight into the mechanism of CTG repeat instability in DM1. Tomé et al. (2009) reported that MSH2 ATPase domain mutation could influence somatic instability in DM1 transgenic mice. Compared with fibroblasts, MSH2, MSH3, and MSH6, were highly expressed in DM1 patient-derived iPSC, accompanied with longer CTG repeat, while MSH2 silencing inhibited CTG repeat expansion (Du et al., 2013). Flower et al. (2019) reported that the altered MSH3 levels caused by MSH3 3a repeat allele decreased somatic expansion and changed the DM1 phenotype. Thus, regulation of MSH3 might represent a new roadmap for potential target therapy of DM1.

CELLULAR PROCESSES ALTERATIONS

Synaptic Dysfunction

Synaptic protein dysfunction is an important feature demonstrated in the DM1 brain. RAB3A is an abundant synaptic vesicle protein that regulates neurotransmission by interacting with other synaptic proteins. The upregulation of RAB3A causes spontaneous exocytosis, and plays important roles in spatial learning, sleep control, and synaptic plasticity (Sudhof, 2004). Synapsin I (SYN1) can regulate synaptic vesicle release in a phosphorylation-dependent manner, and its hyperphosphorylation determines short-term synaptic plasticity alterations (Rosahl et al., 1993). Hernández-Hernández et al. (2013a) reported RAB3A upregulation and SYN1 hyperphosphorylation in DMSXL mice, transfected cells, and DM1 patient samples, which were related to altered spontaneous neurosecretion in cell culture, electrophysiological and behavioral deficits in mice, and possibly contributed to the neuropsychological manifestations in DM1 patients. Then, Jimenez-Marin et al. (2021) demonstrated that transcriptional signatures of synaptic vesicle genes at least partially explain the mechanisms of DM1 neurodegeneration. Nowadays, a close relationship between splicing regulator alterations and synaptic protein dysfunctions has been found, possibly contributing to DM1 neurological phenotypes (Hernández-Hernández et al., 2013b). For example, loss-of-function of MBNL1 in DMSXL mice brain mediated the upregulation of RAB3A levels and determined the length of neuronal dendrites and axons (Hernández-Hernández et al., 2013b). The overexpression of CELF1 or CELF2 in neuronal-like PC12 cells containing expanded CUG transcripts mediated SYN1 hyperphosphorylation (Hernández-Hernández et al., 2013b). And other splicing alterations, such as *GRIN1* and *Tau* splicing defects, might also contribute to synaptic dysfunction in DM1 (Hernández-Hernández et al., 2013b). However, although influenced by different splicing regulators, these synaptic protein

alterations seem to be independent of mis-splicing of their coding transcripts, suggesting that DM1 neuropathogenesis have far-reaching implications beyond the disruption of splicing programs.

In addition, other synaptic-related abnormalities have also been identified in the DM1 brain. Lee et al. (2019) found distribution defects of cortical neurons, abnormal dendritic morphology and complexity and postsynaptic densities in the *Mbnl1/2*–/– mice. A time-course study using EpA960/CaMKII-Cre mice revealed that hippocampus (HPC)-related learning and synaptic potentiation were damaged before structural alterations occurred in the brain, followed by brain atrophy associated with progressively reduced axon and dendrite integrity. Notably, cytoplasmic MBNL1 level on dendrites decreased before dendrite degeneration, whereas MBNL2 expression reduction and MBNL-mediated alternative splicing defects were evident after degeneration (Wang et al., 2017), suggesting that MBNL1 reduction might contribute to synaptic transmission dysfunction in the DM1 brain.

The Defective Neuroglial Interactions

A recent study shows that compared to neurons, cortical astrocytes contain more ribonuclear foci in DM1 transgenic mice (carrying 45 kb of human genomic DNA cloned from a DM1 patient) (Hernández-Hernández et al., 2013a). Meanwhile, RNA sequencing discovered more frequent splicing deficits in glia of DMSXL mice (Oude Ophuis et al., 2009; González-Barriga et al., 2021), suggesting a non-negligible presence of neuroglial damage in DM1. Glutamate transporter 1 (GLT1) is a glial-specific glutamate transporter that can recapture excitatory glutamate from the synaptic cleft and protect it from neurotoxicity caused by glutamate overstimulation (Bellamy, 2006). In the Bergmann glia of the cerebellum in DMSXL mice, scientists found glutamate excitotoxicity associated with decreased GLT1 (Sicot et al., 2017). In astrocytes of DMSXL mice, downregulation of GLT1 increased glutamate neurotoxicity and caused neuronal damage, while the upregulation of GLT1 corrected Purkinje cell firing and motor incoordination (Sicot et al., 2017). These studies indicated that the loss-of-function of GLT1 and defective neuroglial interactions might play critical roles in inducing DM1 brain disorders.

Nowadays, studies have identified that the expression of GLT1 is regulated by RNA transcription, splicing and stability, post-translational modifications, and protein activity (Kim et al., 2011). Specifically, loss-of-function of MBNL1 can perturb GLT1 polyadenylation, thus decreasing the levels of GLT1 glutamate transporter, while MBNL2 inactivation did not affect GLT1 levels, but contributed to the compensating increase in MBNL1 protein (Batra et al., 2014; Mohan et al., 2014). In the future, restoring GLT1 protein and glutamate neurotransmission by regulating MBNL proteins might be promising approaches to reverse the defective neuroglial interactions in DM1. Besides, in an inducible glial cell model of DM1 derived from human retinal Müller glial cells (MIO-M1) expressing 648 CUG repeats [MIO-M1 CTG(648)], scientists identified that the activation of inflammatory pathways and immune responses could partially explain DM1 CNS defects associated with defective glia (Azotla-Vilchis et al., 2021; González-Barriga et al., 2021). In glial cells of DMSXL mice, expanded CUG RNA affected preferentially differentiation-associated molecular events, which open new avenues in studying DM1 brain pathology with cell type resolution (González-Barriga et al., 2021).

Altered Brain Insulin Signaling

Previous studies have observed the insulin resistance (IR) phenotype in DM1 patients (Moxley et al., 1978), which could be attributed to the mis-splicing of the insulin receptor gene. While recently, altered insulin signaling in the brain has also been proposed, thus provides potential alternative explanations for the DM1 neuropathogenesis (Nieuwenhuis et al., 2019). For example, animals with impaired insulin receptor signaling have shown reduced motivation, which could translate to apathy in humans (Dagenhardt et al., 2017), a critical symptom in adult DM1 patients (Gallais et al., 2015). In patients with obsessive-compulsive disorder, altered brain insulin signaling has been observed (van de Vondervoort et al., 2016). Besides, cognitive deficits, especially visuospatial and verbal memory deficits (Kullmann et al., 2016), depressive symptoms (Minier et al., 2018; van der Velden et al., 2019) and decreased behavioral flexibility (van de Vondervoort et al., 2019), have also been shown to be associated with brain IR. Moreover, a recent review pointed out the effects of insulin signaling on tauopathy and Aβ metabolism (Gonçalves et al., 2019). And several neuroimaging studies have discovered a decrease in glucose uptake in the brain of DM1 patients (Fiorelli et al., 1992; Peric et al., 2017a), however, it remains unclear whether altered insulin signaling is involved.

Neurochemical Changes

A series of neurochemical changes were also found in DM1, which may account for specific symptoms. For example, the loss of serotonin (5-HT)-containing neurons in the dorsal raphe nucleus (DRN) and the superior central nucleus (SCN) of DM1 patients is associated with hypersomnia (Ono et al., 1998). And the alteration of serotonergic raphe structures might be involved in the pathogenesis of hypersomnia (Peric et al., 2014b; Krogias et al., 2015; Krogias and Walter, 2016). The hypoechogenicity of nucleus raphe might be correlated with EDS and depression in DM patients (Peric et al., 2014b). The extent of WM hyperintensities might be correlated with fatigue (Minnerop et al., 2011). Using conditional *Mbnl2*NEX-cKO mice (a tissue-specific knockout mouse model lacking the *Mbnl2* gene in forebrain glutamatergic neurons), long-term cognitive impairment and depression were found (Ramon-Duaso et al., 2020). This might be associated with significant neuronal loss, reduced neurogenesis, and fewer proliferating and immature neurons in the dentate gyrus of the HPC. Additionally, in *Mbnl2*–/– mice, increased proinflammatory microglia, dopamine levels as well as Dat, Drd1, and Drd2 transcripts levels, decreased expression of the brain derived-neurotrophic factor (BDNF) gene, and impaired neural spiking and oscillatory activities in the medial prefrontal cortex (mPFC) and the HPC have been found, accompanied with progressive cognitive and affective changes (Ramon-Duaso et al., 2019). Similar abnormalities have also been observed in the mPFC and HPC of DM1 patients with severe depression and cognitive impairment (Romeo et al., 2010b).

Currently, chronic treatment with methylphenidate (MPH) has been shown to reverse the behavioral abnormalities, reduce proinflammatory microglia and Dat level, and increase BDNF and Nrf2 mRNA expressions in *Mbnl2–/–* mice. This makes it a promising drug candidate to treat CNS dysfunctions in DM1 patients (Ramon-Duaso et al., 2019). However, this intervention also impaired glutamate uptake and increased glutamate levels in juvenile rats (Schmitz et al., 2016, 2017), querying whether MPH therapy would increase glutamate neurotoxicity and induce the defective neuroglial interactions.

In addition, dysregulation of cerebrospinal fluid (CSF) homeostasis was observed in early onset DM1. A study introducing *DMPK* CTG expansions into the mouse found that mis-splicing significantly affected brain choroid plexus epithelial cells (Nutter et al., 2019). Besides, increased levels of total-Tau, IgG, γ-globulin, and myelin basic protein (MBP), as well as decreased levels of Aß1-42 and orexin-A were found in the CSF of DM1 patients (Hirase and Araki, 1984; Martínez-Rodríguez et al., 2003; Winblad et al., 2008; Peric et al., 2014a). Orexins are hypothalamic peptides that play critical roles in sleep/wake regulation (Sakurai, 2014). A possible correlation between an altered CSF orexin-A levels and EDS in systemic lupus erythematosus (SLE) patients with hypothalamic lesions and patients with frontotemporal dementia (FTD) have been reported (Çoban et al., 2013; Suzuki et al., 2018). Notably, significantly lower orexin-A levels were also detected in the CSF of 6 DM1 patients affected by EDS (Martínez-Rodríguez et al., 2003), thus providing potential explanations for DM1 sleep disorders. Furthermore, in 2015, a decreased level of BDNF, a neurotrophin participate in learning and memory, was detected in the serum of DM1 patients. Since it can cross the brain-blood barrier (BBB), it might be considered a promising biomarker of CNS defects (Comim et al., 2015).

Neuropathological Defects in Early Developmental Processes

To determine the expression patterns of DMPK with age, Langbehn et al. (2021) analyzed the brain from 99 donors with DM1 ranging from 5 postconceptional weeks to 80 years old. They found that peak expression of wildtype *DMPK* coincides with a time of dynamic brain development, thus indicating that the abnormalities in DM1 brain *DMPK* expression may affect early brain development. Besides, direct injection of $(CUG)_{91}$ repeat-containing mRNA into single-cell embryos of zebrafish induced CNS toxicity during early development, resulting in morphological abnormalities, behavioral abnormalities, and extensive transcriptional alterations, while co-injection of zebrafish *Mbnl2* RNA suppressed this toxicity and reversed the associated behavioral and transcriptional abnormalities (Todd et al., 2014). In addition, defects in the genes involved in dysfunctional neurite outgrowth and synaptogenesis at the neuromuscular junction were also observed in neuronal progeny derived from DM1 mutant human ES cells, which are associated with the decreased expression of two genes that belong to the *SLITRK* family, *SLITRK2* and *SLITRK4* (Marteyn et al., 2011). Transfection of *SLITRK2* and *SLITRK4* into cultured DM1 cells restored neurite length to control levels. However, it is interesting that *DMPK* mutation and dysregulation of splicing by MBNL1 do not appear to be involved in SLITRK misexpression or neurite outgrowth, suggesting other new molecular mechanisms involved in DM1 abnormal neurodevelopment (Marteyn et al., 2011).

PATHOLOGICAL FEATURES

Tau Pathology

In the DM1 brain, dysregulation of alternative splicing could lead to pathologic Tau proteins accumulations and the formation of neurofibrillary tangles (NFTs) (Caillet-Boudin et al., 2014), which are mainly located in the HPC, entorhinal cortex, and most of the temporal areas, called Tau pathology. Nowadays, Tau pathology has been confirmed a critical histopathological characteristic in the brain of DM1 patients (Caillet-Boudin et al., 2014), and could interfere with axonal transport and neurosecretion (Caillet-Boudin et al., 2014). Although there is no direct evidence, current research suggests that this pathology may be related to cognitive dysfunctions in DM1.

In the adult brain, *Tau* gene could encode six *Tau* isoforms through alternative splicing of exons 2, 3, and 10, whereas in DM1, all of these exons are absent, thus promoting fetal expression of the 3-repeat *Tau* isoform (Sergeant et al., 2001; Jiang et al., 2004). Interestingly, a recent study in a congenital DM1 patient with intellectual disability also suggested the existence of a 4-repeat tau dominant pathology (Mizuno et al., 2018). Originally, cell studies identified that long CUG repeats-mediated loss-of-function of MBNL1 could be responsible for the changes in *Tau* splicing (Dhaenens et al., 2008). While in 2014, researchers discovered that both MBNL1 and MBNL2 have an enhancer activity of *Tau* exon 2 inclusion, and only the interaction of MBNL1 and MBNL2 can fully reverse the splicing defect of *Tau* exon 2 induced by the mutant CUG repeats, similar to that observed in DM1 (Carpentier et al., 2014). Then in 2015, a further study examining the *Tau* splicing using Nestin-Cre DKO mice (a *Mbnl1/2–/–* mouse model) suggested that both MBNL1 and MBNL2 synergize to regulate *Tau* exon 2, 3, and 10 splicing (Goodwin et al., 2015). These findings proved that the regulation of MBNL1/2 and their interactions are highly essential in DM1 Tau pathology. Except MBNL proteins, CELF proteins also serve as potential regulators of *Tau* splicing. Four exons (2, 3, 6, and 10) of *Tau* isoforms have been discovered to respond to one or more CELF proteins (Leroy et al., 2006a,b). Among them, *Tau* exon 10 responds specifically to CELF2 upregulation (Dhaenens et al., 2011). *Tau* exon 6 splicing is regulated by CELF5 and CELF6 (Leroy et al., 2006b). Notably, the heterogeneous distribution of Tau protein in the DM1 brain has also been reported, which may affect its splicing regulation patterns.

Other than Tau pathology, several kinds of protein and nucleotide deposits have also been observed in the brain of DM1 patients (Weijs et al., 2021), including Lewy bodies (LBs), neuronal intranuclear eosinophilic inclusion bodies, intracytoplasmic inclusion bodies, increased Marinesco bodies,

gliosis (Itoh et al., 2010; Jinnai et al., 2013), skein-like ubiquitin-positive inclusions and granulovacuolar degeneration (GVD), which suggest neurodegeneration in the DM1 brain (Itoh et al., 2010; Yamazaki et al., 2011; Nakamori et al., 2012).

RNAopathy and Spliceopathy

In the DM1 brain, the mutant *DMPK* RNA accumulates as nuclear foci in extensive areas, which contributes to abnormal alternative splicing (Miller et al., 2000; Fardaei et al., 2002). The nuclear foci are widely distributed throughout the brain of DM1 patients, including cortex, WM in subcortical and callosal areas, HPC, thalamus, brainstem, and cerebellum, and presented in various cell types, such as neurons, astrocytes, oligodendrocytes, Purkinje cells and human DM1 iPSC or ES-cell-derived NSCs (Jiang et al., 2004; Denis et al., 2013; Hernández-Hernández et al., 2013a). Their distributions varied from different genetic features, histological features and clinical features in each person (Jiang et al., 2004). Abnormal alternative splicing has been considered the critical pathogenesis of DM1. Changes in RNA-binding proteins, such as MBNL and CELF proteins, can lead to splicing defects of a variety of pre-mRNAs and misexpressions of different protein isoforms. Nowadays, the interaction between RNAopathy, spliceopathy, and Tau pathology have accounted for essential parts of DM1 neuropathology (Caillet-Boudin et al., 2014).

Other Pathological Features

Other neuropathological features of DM1 include neuronal loss in different areas, such as the superficial layer of the frontal and parietal cortices, the occipital cortex, the medullary arcuate nuclei, the anterior and dorsomedial thalamic nuclei, the midbrain, and pontine reticular formation, which may be related to cortical atrophy (Culebras et al., 1973; Ono et al., 1995, 1998; Mizukami et al., 1999). The cell loss of specific areas might also contribute to the cognitive and behavioral abnormalities in DM1 patients (Rosman and Kakulas, 1966; Ono et al., 1996; Mizukami et al., 1999). In the post mortem brain and spinal cord of DM1 patients with congenital or childhood onset with intellectual deficiency, heterotopic neurons have been found, suggesting abnormal neurodevelopment (Ogata et al., 1998). Degenerative WM changes were also reported in DM1 patients, including myelin and axonal loss, expansion of perivascular spaces, gliosis, and hyalinization of capillaries in deep and subcortical WM (Itoh et al., 2010). However, most studies exploring the microscopic brain pathology in DM1 patients, as well as their relationships with neuroimaging features and splicing changes are case reports or small-scale researches. Clearly, larger follow-up studies are eagerly needed to improve the understandings of pathological alterations in DM1.

DEVELOPMENTAL OR NEURODEGENERATIVE?

Multiple studies have identified a wide range of CNS alterations in DM1 patients. However, the varied characteristics between DM1 patients, such as CTG triplet expansion size, duration time, and age, significantly influence the cerebral performances. In several studies based on cross-sectional analyses, progressive GM loss and increased rate of cortex volume loss correlated with age have been reported (Weber et al., 2010; Minnerop et al., 2011; Caso et al., 2014; Serra et al., 2015; Zanigni et al., 2016; Cabada et al., 2017). A longitudinal study evaluating MRI in DM1 patients also revealed that the WM degeneration and ventricular enlargement progressed over time, though it varied between different individuals (Conforti et al., 2016). However, other studies did not find significant associations between WMHL and age or a significant increase of WML during disease progression (Meola and Sansone, 2007; Itoh et al., 2010; Bajrami et al., 2017; Cabada et al., 2017). Moreover, studies by Antonini et al. (2004) demonstrated a significantly reduced GM volume which was negatively correlated with age in DM1 patients, whereas WM volume was shown not to be correlated with cortical atrophy or age. Thus, further longitudinal evaluations are still need to assess spatiotemporal imaging changes. Regarding clinical features, Sansone et al. (2007) noted a progression in frontal cognitive impairment (attentional) in both DM1 and DM2 patients. Studies by Winblad and Gallais reported a cognitive decline in adult-onset DM1 is positively related to the earlier onset and longer duration of the disease (Winblad et al., 2016; Gallais et al., 2017). Moreover, a close relationship between CNS defects and CTG expansion size has also been discovered. For example, the impaired facial emotion recognition is significantly related to CTG repeat size (Winblad et al., 2006). The extent of GM and WM damage could be correlated with CTG expansion (Serra et al., 2015). And longer CTG expansion sizes could indicate a larger decrease in GM volume (Labayru et al., 2019). Further studies are needed to determine the progressive pattern of CNS dysfunctions.

Whether the progressive cerebral involvement in DM1 patients is due to a developmental or a neurodegenerative process is still an open question (Axford and Pearson, 2013). A variety of neurodegenerative pathological features, including NFTs, LBs and WM abnormalities, as well as a progressive cognitive decline reported by a limited number of longitudinal studies have been found in DM1 patients, which support that DM1 is in part a neurodegenerative process. However, another view supports that the progressive CNS dysfunction may be responsible for cognitive impairment, rather than neurodegenerative changes, since the distinct brain alteration patterns different from neurodegenerative features might also be associated with cognitive impairments in DM1 (Axford and Pearson, 2013; van der Plas et al., 2019; Labayru et al., 2020; Langbehn et al., 2021). A newly emerged opinion proposes that DM1 could be considered a progeroid disease (an early and accelerated aging process) (Sansone et al., 2007; Modoni et al., 2008; Caso et al., 2014; Winblad et al., 2016; Gallais et al., 2017; Solovyeva et al., 2021), as typical symptoms related to aging, such as cognitive decline, occur in the early years. However, a recent study shown an interesting contrast, that the presentation of simple tasks is hugely decreased while that of complex tasks are mostly retained in DM1, which is different from normal aging (Gallais et al., 2017). Further, it's worth noting that in the

congenital/childhood-onset DM1 patients, typical molecular and clinical deficits are observed during early developmental processes, which indicate an influence of DM1 on early brain development.

By the way, there are also some limited studies comparing the different characteristics between different phenotypes of DM1 (based on age-onset). In the congenital/childhood-onset DM1 patients, typical clinical deficits including intellectual disability and behavioral abnormalities are frequently reported, without further decline over these ages (Dhaenens et al., 2011; Caillet-Boudin et al., 2014; Fernandez-Gomez et al., 2019; Lindeblad et al., 2019). In addition, compared with adult-onset DM1 patients, verbal intelligence and memory was significantly deteriorated in juvenile-onset DM1 patients, reflecting a more pronounced developmental process in the juvenile type (Woo et al., 2019). However, in contrast, other studies demonstrated that adult-onset DM1 patients presented with more pronounced decrease of quality of life than juvenile-onset DM1 patients in almost all domains (Rakocevic-Stojanovic et al., 2014). A cross sectional study identified a significant cognitive impairment progression by aging in the majority of the cognitive domains in adult-onset DM1 patients (Baldanzi et al., 2016a), suggesting the existence of progressive degeneration. However, verbal memory abilities were relatively preserved, suggesting different changing patterns involved in memory and cognitive deficits (Baldanzi et al., 2016a). Regarding to neuroimaging observations, Caso et al. (2014) observed a more severe damage of GM in adult-onset DM1 patients than in juvenile-onset DM1 patients, supporting a degenerative origin of GM abnormalities. Conversely, the severe and distributed WM microstructural damage detected in both types might support a developmental change of microstructural WM damage. In 2020, the first longitudinal study of structural brain involvement in pediatric and adult/late-onset DM1 shown that the brain volume loss over time in both groups was not significant compared with their healthy controls, thus supporting the probable occurrence of the neurodevelopmental process. However, these findings cannot completely rule out the existence of the neurodegenerative process, since patients were not yet in their 60's at follow-up (Labayru et al., 2020). In the future, additional studies with larger-sample and longitudinal observations are still needed to further clarify the feature of DM1 brain damages.

THERAPEUTIC STRATEGIES OF DM1

Management of Neurological Defects

To date, there are no specific therapeutic agents available to reverse neurological defects in DM1. Modalities for management mainly rely on supportive care, including sleep hygiene improvement, cognitive−behavioral therapy, aerobic exercise training, and careful use of stimulant drugs. Sleep−related disorders have been recognized as primary symptoms of CNS involvement in DM1. Early recognition and treatment of sleep disorder breathing with nocturnal non-invasive mechanical ventilation have served as important countermeasures to deal with these problems (Pincherle et al., 2012). In a large clinical cohort study, scientists found that patients who insist on home mechanical ventilation for $\geq$5 h/24 h shown significantly higher survival rates than those who use it less (Seijger et al., 2021), and their tolerance and adherence were remarkably high. Besides, the biggest multicenter, randomized clinical trial in DM1 named the Observational Prolonged Trial in Myotonic Dystrophy Type 1 to Improve Quality of Life-Standards, a Target Identification Collaboration (OPTIMISTIC) revealed that cognitive behavioral therapy significantly improved the ability for activity and social participation at 10 months in severely fatigued patients with DM1 (NCT02118779) (Okkersen et al., 2018). Compared with usual care, cognitive behavioral therapy plus aerobic exercise training also increased the physical activity in DM1 patients (OPTIMISTIC) (van Engelen, 2015), indicating this therapy as a promising interventions for severe fatigue in DM1. Stimulant drugs also shown the potential to treat EDS. In 2007, the American Academy of Sleep Medicine (AASM) declared that MPH might be an effective tool for treating DM1-related EDS (Morgenthaler et al., 2007). However, a Cochrane review on well-designed psychostimulant trials in patients with DM1 and EDS pointed out the lack of evidence to support its routine use (Annane et al., 2002). Some clinical studies reported that modafinil might improve hypersomnia and fatigue without significantly increasing activity levels in DM1 (Hilton-Jones et al., 2012; Laberge et al., 2013). However, respiratory insufficiency (due to abnormal central drive and respiratory muscle weakness) and sleep fragmentation related to central or obstructive apnea must be excluded (Harper et al., 2002). Except for treating sleep-related disorders, in *Mbnl2*–/– mice, mirtazapine, a kind of antidepressant, has been discovered to reverse cognitive impairments and depression, as well as reduce microglia and neuronal loss (Ramon-Duaso et al., 2020). Moreover, metformin treatment reversed the metabolic and mitochondrial dysfunction and the accelerated aging process, such as impaired proliferation, in fibroblasts derived from DM1 patients (García-Puga et al., 2020). And its beneficial effects on muscle function have been confirmed in several clinical trials (Bassez et al., 2018). Since basic science reports have proposed the important role of abnormal insulin signaling in the brain (Nieuwenhuis et al., 2019), it indicates another possible therapeutic mechanism for metformin in DM1 brain. Furthermore, therapies *via* modulating glutamate levels and dopaminergic function have also emerged to attract more and more attention (Sicot et al., 2017; Serra et al., 2020b), which provide new insights for future DM1 CNS treatment.

Great progress of molecular therapies has been made in DM1, however, before we can move these treatments into clinical trials, there is also a great need to identify feasible outcome measures to evaluate the effectiveness of these therapies by characterizing the component of CNS deficits in DM1. Currently, the main outcome measures actually used to study CNS involvements in DM1 patients are represented by a variety of patient questionnaires and clinical neuropsychological tests which can assess cognitive and behavioral dysfunctions, and computerized neuroimaging techniques which can assess neuroimaging alterations (summarized in **Tables 2**–**4**). Besides, given the high heterogeneity of symptoms in DM1 patients,

several patient-reported outcome measures are also developed, such as DM1 activity and participation scale for clinical use (DM1-ActivC), and the fatigue and daytime sleepiness scale (FDSS) (Hermans et al., 2013, 2015), which have shown valid measurements in DM1 populations (Angelini and Siciliano, 2020). Notably, due to the increasing risk and higher severity of COVID-19 in DM1 patients, and the difficulty in contacting a doctor during the COVID-19 epidemic, the Italian Association for Glycogenosis (AIG) developed telemedicine equipment, the AIGkit application (AIGkit app), which allows patients to receive constant remote monitoring by using dedicated questionnaires and getting personalized treatment (Symonds et al., 2017). A review by Simoncini et al. (2020) comprehensively summarized the clinical instruments available for cognitive and behavioral measures and neuroimaging assessment in DM1 brain. In the future, additional investigations are warranted to improve the reliability of these available measures, as well as to discover the new outcome markers.

Potential Therapeutic Strategies

With significant advances in understanding the molecular pathogenesis of DM1, several approaches targeting disease mechanisms have been developed, such as antisense oligonucleotide (ASO)-based therapy, small-molecule therapy, genome editing, non-coding RNAs (ncRNAs)-based therapy, and iPSC technique, which target different steps in the pathological process of DM1 (Mulders et al., 2010; Magaña and Cisneros, 2011). Focusing on the most upstream target should block the initiation of the toxic cascade and correct more defects in tissues. Since most therapeutic efforts of DM1 mainly focused on the myocardium and skeletal muscle, and only few studies described their effects on the neurological defects, we briefly introduce their roles in the treatment of DM1 and their therapeutic potential in CNS deficits, hoping to provide references for DM1 CNS treatment. **Figure 2** specifically introduced the current management measures as well as promising therapeutic strategies expected to be applied to DM1 CNS disorders.

Antisense Oligonucleotides

Antisense oligonucleotide is one of the important approaches which can target toxic RNA. It consists of a strand of nucleotides that can bind to a specific pre-mRNA/mRNA sequence and then alters protein synthesis through several mechanisms. In DM1, ASOs can interfere with the interaction between MBNL1 protein and toxic RNA, mainly by targeting the CUG repeat to reduce mutant transcripts, or by RNase-H-mediated degradation of expanded transcription (Klein et al., 2015). Other alterative mechanisms including inhibiting mRNA translation or altering RNA stability (Bennett and Swayze, 2010; Schoch and Miller, 2017).

Till now, various kinds of ASOs have shown efficacy *in vitro* and *in vivo* DM1 treatments. In 2003, scientists produced a retrovirus that expressed a 149-base pair (bp) antisense RNA, complementary to the $(CUG)_{13}$ repeats and the proceeding 110-bp region (Furling et al., 2003). Injection of this ASO into human DM1 myoblasts significantly decreased toxic RNA and normalized CELF1 levels, eventually ameliorating the delay of muscle fusion and IR (Furling et al., 2003). However, this approach also reduced the level of normal *DMPK* transcripts and proteins. Since the unmodified ASOs are unstable and could easily be degraded, several chemical modifications to ASOs were developed to increase their stability and affinity for the target mRNA (Bennett et al., 2017; Khorkova and Wahlestedt, 2017). The first and the most widely used generation of modification was the phosphorothioate (PS) backbone modification (Bennett et al., 2017; Schoch and Miller, 2017), usually together with sugar modifications such as 2′-O-methyl (2′-O-Me) and 2′-O-methoxyethyl (2′-MOE). In 2009, a fully 2′-O-Me-PS-modified ASO, complementary to CUG repeats, called CAG7, was developed for DM1. Administration of this ASO in muscle tissue of DM500 mice (a DM1 model carrying > 300 *DMPK* CTG repeats) and HSA^{LR}20b mice (a DM1 model expressing human skeletal actin transcripts containing ∼250 *DMPK* CTG repeats) silenced the expression of mutant RNA and decreased the formation of nuclear foci in a selective and (CUG)n-length-dependent manner (Mulders et al., 2009). Subsequently, morpholino ASO was discovered, which can bind to the toxic RNA and inhibit its interactions with proteins as well as disrupt CUG-exp-MBNL1 complexes. CAG25 was the first morpholino ASO to be used in DM1. Injection of CAG25 into muscle fibers of HSA^{LR} mice by intramuscular injection followed by *in vivo* electroporation significantly reversed myotonia within 4–5 weeks, accompanied with the increased translation of the mutant RNA (Wheeler et al., 2009). Since morpholino ASO does not induce cleavage of target mRNA, they do not affect normal *DMPK* transcripts and proteins (Summerton, 1999).

To date, it is still a question whether *DMPK* knout-out will indeed cause DM1 phenotype. Some studies reported that both *DMPK*± and *DMPK*-/- mice shown abnormal cardiac conduction (Berul et al., 1999, 2000), and homozygous deletion also exhibited skeletal myopathy and muscle weakness (Reddy et al., 1996), while other findings countered that the administration of *DMPK*-targeting ASOs with heterozygous deletion did not influence the normal cardiac or muscle function in mice, thereby supporting the feasibility and safety of ASOs usage in DM1 (Carrell et al., 2016). In the future, more relevant experiments are needed to reach a conclusion.

Since nuclear-retained CUG repeats are sensitive to antisense silencing, and RNase H are essentially ubiquitous expressed in nuclear (Suzuki et al., 2010), the recruitment of diverse gapmer-based ASOs shown promising futures *via* mediating RNase H cleavage and decay of the target RNA (Walder and Walder, 1988; Wheeler et al., 2012; Nguyen and Yokota, 2020). In HSA^{LR} mice, subcutaneous injection of gapmer ASOs significantly degraded expanded CUG transcripts as well as lncRNAs in skeletal muscle, reversing MBNL1 sequestration, myotonia, and mis-splicing without apparent off-target effects (Schoch and Miller, 2017). This strategy is also more attractive since it's highly specific to expanded CUG repeats compared with normal-size repeats, and could maintain effects for 1 year after the treatment. Besides, BNANC gapmers targeting the DMPK 3′ UTR specifically knockdown the expanded CUG RNA and reversed the mis-splicing and RNA foci accumulation without inducing caspase activation (Manning et al., 2017). Moreover,

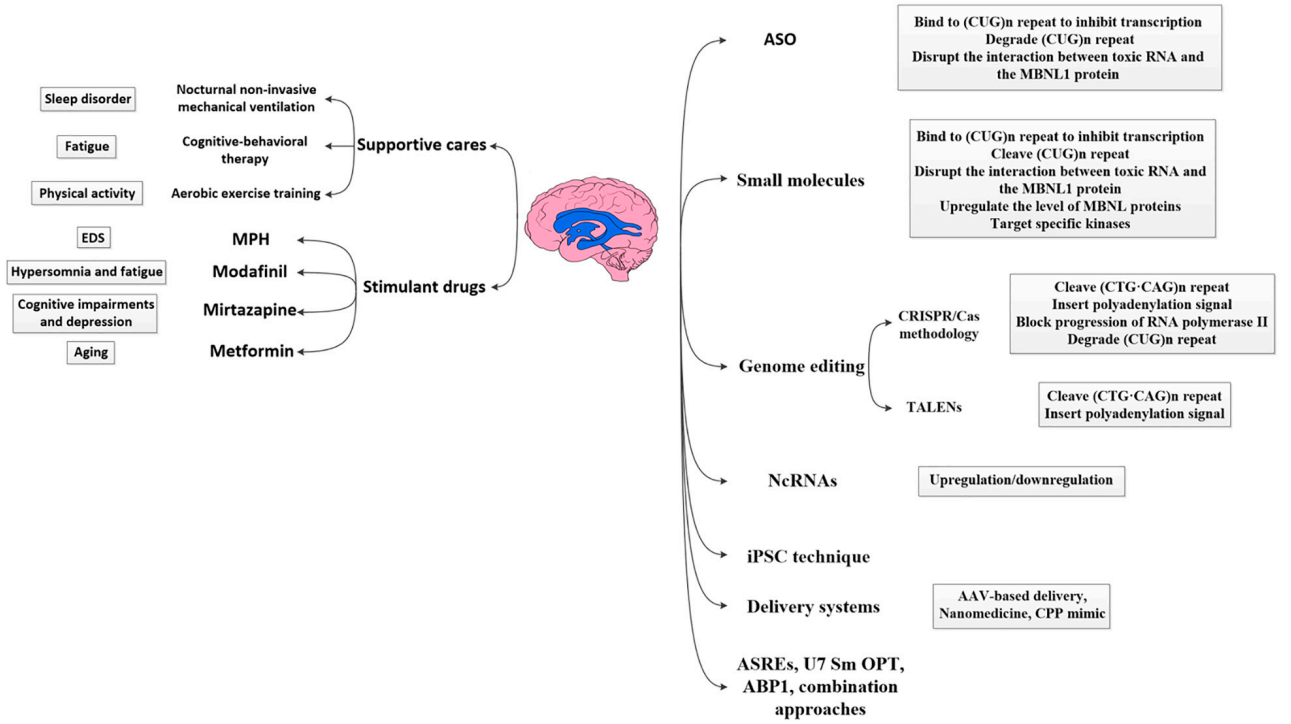

FIGURE 2 | Current and future therapeutic strategies applied to DM1 CNS disorders. The therapeutic strategies for DM1 CNS disorders can be divided into available management measures and future promising strategies. Available modalities for management mainly rely on supportive care, including nocturnal non-invasive mechanical ventilation, cognitive–behavioral therapy, aerobic exercise training, and careful use of stimulant drugs such as MPH, modafinil, mirtazapine, and metformin. Future potential therapeutic strategies currently investigated include ASO-based therapy, small-molecule therapy, genome editing, ncRNAs-based therapy, iPSC technique and so on, which target different levels in the pathological process of DM1 (i.e., DNA level, RNA level, and protein level). Besides, the application of various effective delivery systems also improved the transportation efficiency and promoted the wide distribution of drugs. DM1, myotonic dystrophy type 1; MPH, methylphenidate; EDS, excessive daytime sleepiness; NcRNA, non-coding RNAs; iPSC, induced pluripotent stem cell; AAV, adeno-associated viral vector; ASREs, artificial site-specific RNA endonucleases; CPP, cell-penetrating peptide; ABP1, D-amino acid hexapeptide; ASO, antisense oligonucleotide; CRISPR-Cas9, clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated system 9; TALEN, transcription activator-like effector nucleases; MBNL, muscleblind-like.

the combinative application of gapmer and CAG25 morpholino produced synergistic effects to reduce expanded CUG repeats by 80% and almost eliminate RNA foci in DM1 cell culture, and get a smaller CUG repeats reduction in skeletal muscle of DM1 mice by half (Lee et al., 2012). However, the competition between gapmer and CAG25 in targeting the CUG repeats might limit their effects.

Other chemical modifications of ASOs also significantly optimized its characteristics. For example, the establishment of modified human U7 small nuclear RNAs (hU7-snRNAs), which contain a poly-CAG antisense sequence targeting the mutant CUG repeats, specifically degraded toxic RNA transcripts without influencing the products of wild-type DMPK alleles (Francois et al., 2011). Since the instability of expanded CTG repeats is a critical characteristic of DM1, which could be enhanced by RNA repeats, recent work shown that early intervention with CAG-repeat ASOs can not only reduce RNA toxicity but also stabilize CTG:CAG repeats at subpathogenic lengths in both DM1 human cells and transgenic mice model (Nakamori et al., 2011). One study using a 2′-4′-constrained ethyl-modified (cEt) ASO (ISIS 486178) effectively decreased *DMPK* mRNA levels in multiple organs of DMSXL mice or cynomolgus monkeys (Pandey et al., 2015). This ASO also exhibits a high level of RNA binding affinity and *in vivo* potency, without any association with muscle or cardiac toxicity. Furthermore, the systemic treatment with ASO (ISIS 486178) targeted to the non-CUG sequence within the 3′-UTR of *DMPK* also specifically rescued DM1 phenotypes of myotonia and cardiac conduction defects in DM200 mice [a DM1 model carrying a GFP-DMPK 3′-UTR (CTG) 200 transgene] (Jauvin et al., 2017; Yadava et al., 2020). In order to overcome the low efficiency of ASOs due to its wide distribution, Klein et al. (2019) developed an arginine-rich 466 cell-penetrating peptide (CPP). Compared with previous ASO strategies, this Pip6a-conjugated morpholino phosphorodiamidate oligomer (PMO) significantly increased ASO delivery into striated muscles after systemic administration in HSA^{LR} mice. Only low-dose treatment with Pip6a-PMO-CAG

sufficiently rescued splicing defects and myotonia in mice (Klein et al., 2019). Hsieh et al. (2018) designed a short miniPEG-γ peptide with terminal pyrenees, which also exhibited high affinity and sequence specificity to toxic RNA repeats and successfully disrupted the CUG-exp–MBNL1 complex. With the new discovery of the imbalance in the splice isoform profile of *DMPK* in DM1 (Groenen et al., 2000; Wansink et al., 2003), two chemically modified ASOs were developed to prompt exon skipping from mRNA and degrade the CUG repeat from pre-mRNA in fibroblasts of DM1 patients. Disappointingly, neither strategy was as successful as predicted, but they did improve the DM1-related molecular phenotypes (Stepniak-Konieczna et al., 2020). It's worth noting that a newly selected ASO called ISIS-DMPKRx (ISIS 598769) gapmer-type candidate has been evaluated in a Phase 1/2a clinical trial for the treatment of DM1 (Lim et al., 2017), for it can bind to a specific 3′-UTR gene sequence outside the CUG repeat and degrade toxic RNA (NCT023412011). Though it presented great safety and tolerance, IONIS proposed an inefficient effect on the functional and biological endpoints set in the trial since no sufficient drug could reach the muscles.

Though a variety of modifications have improved pharmacokinetic and pharmacodynamic properties of ASOs, the systemic and tissue-targeted implementation of ASOs are still challenging due to their poor intracellular uptake in some tissues (particularly skeletal muscle, heart and brain) (Muntoni and Wood, 2011). To overcome this disadvantages, different administration routes were developed to increase the tissue specificity. Nowadays, the delivery of ASOs to a single muscle by intramuscular injection have been frequently used in DM1 pre-clinical trials. Given the multi-organ or systemic features of DM1, systemic delivery *via* intraperitoneal, subcutaneous, or intravenous administration results in a rapid and widespread absorption of ASOs to various peripheral tissues (Yin et al., 2008; Hua et al., 2011). Since the highly charged ASOs cannot cross the BBB (Smith et al., 2006), intraventricular or intrathecal injections were invented to directly introduce ASOs into the CSF or parenchyma, which highly increased the delivery efficiency and ensured adequate distribution of drugs in the CNS (Miller et al., 2013; Chiriboga et al., 2016). However, though intrathecal delivery is currently shown safe and well-tolerated, it's relatively invasive compared with other administrations. Identification of easier ASO delivery routes to the CNS such as intranasal administration may be an important step to promote their translation to human clinical trials. In addition, assisted delivery systems such as CPPs (Lebleu et al., 2008; Lehto et al., 2012; Boisguérin et al., 2015), nanoparticles (Wang et al., 2015) and adeno-associated virus (AAV) vectors (Danos, 2008), also increase the efficacy of ASOs, which would be introduced below.

Small Molecules

Recently, small-molecule-related strategies have received increasing attention in the treatment of DM1. Compared to other strategies, small molecules have many benefits, including low manufacturing cost, better oral delivery with shorter half-lives, longer shelf lives than other biologics, and sufficient biodistribution to affect multiple systems. Since a number of small molecules are existing drugs that explored for new applications, it also reduces the development time and potential risks of toxicity. However, despite the multiple advantages, most small molecules currently established can only target downstream processes to reduce toxic RNA or alter protein levels but cannot correct gene mutations. Meanwhile, their instability *in vivo* also limit their uses.

The mechanisms of molecular therapies can be divided into four aspects: inhibiting transcription of mutant RNA, cleaving CUG repeats, disrupting the interaction between toxic RNA and the MBNL1 protein, or targeting downstream pathways (Mulders et al., 2010; López-Morató et al., 2018; Reddy et al., 2019a). Cell and animal studies have indicated that pentamidine and a series of methylene linker analogs could exert beneficial effects by binding the CTG repeat DNA to inhibit transcription (Coonrod et al., 2013). One study using a DM1 HeLa cell model screened out that multiple microtubule inhibitors can target the toxic CUG RNA to reduce $r(CUG)_{480}$ levels and then rescue mis-splicing to some extent, wherein the clinical microtubule inhibitor colchicine could even make positive effects in HSA^{LR} mice and primary DM1 patient-derived cells (Reddy et al., 2019b). This strategy provides a new avenue for DM1 research and suggests an alternative method of repeat-selective screening. A new molecule, JM642, was reported to have the capacity to bind to the expanded r(CUG) repeat and disrupt ribonuclear foci in the C2C12 DM1 cells and HSA^{LR} mice, finally rescuing mis-splicing (Nakatani et al., 2020). Moreover, several potential therapeutic molecules focus on cleaving the aberrant CUG repeats from disease-affected cells. For example, cugamycin is a small molecule that has been confirmed to selectively bind expanded CUG repeat conjugated to a bleomycin A5-cleaving module to cleave expanded CUG repeat. And deglycobleomycin, an analog in which the carbohydrate domain of bleomycin A5 is removed, significantly improves its selectivity by reducing DNA damage as well as maintaining the cleave ability (Angelbello et al., 2020). The major small-molecule compounds identified in DM1 therapy have been summarized in **Table 5**.

Some promising small molecules have even been tested in clinical trials. For example, AMO-02/tideglusib, a GSK-3β enzyme inhibitor, has been investigated for congenital DM by restoring the expression of CELF1 (Jones et al., 2012; Wang et al., 2019), which improved postnatal survival, weight, and neuromotor activity. Till now, a Phase II clinical trial of tideglusib on patients with congenital and juvenile-onset DM1 has already finished, and most participants presented with improved CNS and clinical neuromuscular performances (Horrigan et al., 2020). And a Phase II/III clinical trial on patients with congenital-onset DM1 is ongoing. In addition, MYD-0124 (erythromycin) and ERX-963 have been shown to bind to the CUG hairpin with high selectivity, reduce nuclear foci and reverse mis-splicing in DM1 vitro and vivo models. A Phase II clinical trial on adult patients with DM1 is currently underway to investigate the clinical effects of erythromycin after oral administration (Jenquin et al., 2019). Other molecules evaluated in clinical trials for specific disease symptoms (e.g., insulin resistance phenotype, myotonia, myalgia, or daytime sleepiness) include metformin, mexiletine, ranolazine, cannabinoids,

TABLE 5 | Small molecules in DM1 treatments.

References	Small molecules	Mechanisms	DM1 models	Effects
Inhibit transcription				
Coonrod et al., 2013	Heptamidine	Interact with the CTG DNA	DM1 HSA^{LR} mice	Reduce CUG repeats Rescue mis-splicing
	Pentamidine and its analogs	Interact with the CTG DNA	DM1 HeLa cells	Rescue mis-splicing Rescue myotonia
Siboni et al., 2015b	Actinomycin D	Interact with the CTG DNA Block progression of the RNA polymerase	DM1 HeLa cells DM1 patient-derived fibroblasts DM1 HSA^{LR} mice	Reduce CUG repeats Reduce ribonuclear foci Rescue mis-splicing
Siboni et al., 2015a	Pentamidine and heptamidine	Inhibit transcription or reduce the stability of the transcript or bind to CUG RNA to displace MBNL proteins	DM1 HeLa cells DM1 HSA^{LR} mice	Reduce CUG RNA levels Reduce ribonuclear foci Rescue mis-splicing
Reddy et al., 2019b	Microtubule inhibitors	Transcriptional interference during failed repair of the expanded CTG repeat	DM1 HeLa cells	Reduce CUG repeats Rescue mis-splicing
	Colchicine	Transcriptional interference during failed repair of the expanded CTG repeat	DM1 HSA^{LR} mice DM1 patient-derived myotubes	Reduce CUG repeats Reduce ribonuclear foci Rescue mis-splicing
Degrade the CUG repeat RNA				
Angelbello et al., 2019	Cugamycin	Cleave the CUG repeat RNA	DM1 patient-derived myotubes DM1 HSA^{LR} mice	Rescue mis-splicing
Angelbello et al., 2020	A small-molecule-deglycobleomycin conjugate	Cleave the CUG repeat RNA	DM1 patient-derived myotubes DM1 C2C12 cells	Reduce CUG repeats with reduced DNA damage Reduce ribonuclear foci Rescue mis-splicing
Disrupt the MBNL–CUG RNA interaction				
Chakraborty et al., 2018	Daunorubicin	Bind to the CUG repeat RNA to displace MBNL1 protein	DM1 patient-derived myoblast cells DM1 patient-derived skin fibroblasts DM1 drosophila-derived cardiomyocytes	Rescue cardiac dysfunction Increase survival Reduce ribonuclear foci Rescue mis-splicing
Hoskins et al., 2014	Dilomofungin	Bind to the CUG repeat RNA to displace MBNL1 protein	C2C12 cells transfected with pLC16	Rescue mis-splicing Increase CUG repeats in nuclear foci
Nakamori et al., 2016	Erythromycin	Bind to the CUG repeat RNA to displace MBNL1 protein	DM1 C2C12 cells DM1 patient-derived fibroblasts DM1 HSA^{LR} mice	Reduce ribonuclear foci Rescue mis-splicing Rescue myotonia
Nakatani et al., 2020	JM642	Bind to the CUG repeat RNA to displace MBNL1 protein	DM1 C2C12 cells DM1 HSA^{LR} mice	Reduce ribonuclear foci Rescue mis-splicing
Warf et al., 2009	Pentamidine	Bind to the CUG repeat RNA to displace MBNL1 protein	DM1 HeLa cells DM1 HEK293 cells DM1 HSA^{LR} mice	Reduce ribonuclear foci Rescue mis-splicing Release MBNL1 from foci
	Neomycin B	Bind to the CUG repeat RNA to displace MBNL2 protein	DM1 HeLa cells	Disrupt the MBNL1–CUG RNA interaction without rescue mis-splicing of any of the tested targets
Childs-Disney et al., 2013	A thiophene-containing compound 1	Bind to MBNL1 protein to inhibits its interaction with RNA	DM1 HeLa cells DM1 C2C12 cells DM1 HEK 293T cells DM1 patient-derived fibroblasts	Improve DM1-associated translational defects Induce splicing defect
	A substituted naphthyridine compound 2	Bind to the CUG repeat RNA to displace MBNL1 protein	DM1 HeLa cells DM1 C2C12 cell DM1 HEK 293T cells	Improve DM1-associated translational defects Improve splicing defects
Luu et al., 2016	Two bisamidinium ligands-linked heterodimer	Bind to the CUG repeat RNA to displace MBNL1 protein	DM1 HeLa cells DM1 drosophila	Reduce ribonuclear foci Rescue mis-splicing Improve eye degeneration and larval crawling defect in drosophila
Ofori et al., 2012	Molecules with benzo[g]quinoline substructure	Bind to the CUG repeat RNA to displace MBNL1 protein	DM1 C2C12 cells DM1 HSA^{LR} mice	Release nuclear CUG-RNA retention Rescue mis-splicing
García-López et al., 2011	D-amino acid hexapeptide	Bind to the CUG repeat RNA to shift duplex it to a single-stranded form	DM1 HSA^{LR} mice DM1 drosophila	Reduce ribonuclear foci Rescue mis-splicing Reverse muscle histopathology

(Continued)

TABLE 5 | (Continued)

References	Small molecules	Mechanisms	DM1 models	Effects
Target downstream proteins				
Wang et al., 2019	Tideglusib	Inhibit GSK3β activity	DM1 HSA^{LR} mice DM1 DMSXL mice CDM1 and DM1 patient-derived myoblasts	Normalize CELF1 activity Reduce CUG repeats Normalize CELF1- and MBNL1-regulated mRNA targets Improve postnatal survival and growth and neuromotor activity
Wojciechowska et al., 2014	C16 and C51	Inhibit ATP-binding site-specific kinase	DM1 patient-derived fibroblasts and myoblasts	Normalize CELF1 activity Reduce the size and number of ribonuclear foci Displace MBNL1 from foci Rescue mis-splicing
Zhang et al., 2017	ISOX and vorinostat	Upregulate MBNL1 protein levels	HeLa cell DM1 patient-derived fibroblasts	Increase MBNL1 protein levels Rescue mis-splicing
Wei et al., 2013	Lithium and TDZD-8	Inhibit GSK3β activity	DM1 HSA^{LR} mice	Normalize CELF1 and cyclin D3 activity Improve DM1 muscle function and histology
Chen et al., 2016	Phenylbutazone	Enhance MBNL1 transcription Attenuate binding of MBNL1 to expanded CUG RNA	DM1 C2C12 cells DM1 HSA^{LR} mice	Increase MBNL1 protein levels Rescue mis-splicing Disrupt MBNL1-CUG RNA interaction Improve DM1 wheel-running activity and muscle histopathology in mice
Wang et al., 2009	Ro-31-8220	Inhibit PKC activity	Tamoxifen-inducible heart-specific DM1 mice	Inhibit PKC-mediated elevation of CELF1 Increase survival Ameliorate the cardiac conduction defects and contraction abnormalities Rescue mis-splicing
Ketley et al., 2014	Ro 31-8220	Target unknown kinase	DM1 patient-derived myoblasts Embryos of zebrafish model	Eliminate nuclear foci Reduce MBNL1 protein in the nucleus Normalize CELF1 activity independent of PKC activity Rescue mis-splicing Rescue the mutant phenotype in zebrafish
Bargiela et al., 2019	Chloroquine	Upregulate MBNL1 and 2 protein levels	DM1 drosophila DM1 HSA^{LR} mice DM1 patient-derived myoblasts	Increase MBNL1 and 2 protein levels Rescue mis-splicing Restore locomotion in drosophila Restore muscle function and histopathology in mice
Yadava et al., 2015	P2D10	Anti-TWEAK activity	Transgenic DM1 mice	Block TWEAK/Fn14 signaling Improve muscle histopathology and functional outcomes
Brockhoff et al., 2017	AICAR	Activate AMPK activity	DM1 HSA^{LR} mice DM1 patient-derived myoblasts	Reduce ribonuclear foci Rescue mis-splicing Reduce myotonia in mice
	Rapamycin	Inhibit mTORC1 activity	DM1 HSA^{LR} mice DM1 patient-derived myoblasts	Improve muscle function *via* splicing-independent mechanisms
Oana et al., 2013	Manumycin A	Inhibit H-Ras farnesyltransferase activity	DM1 C2C12 cells DM1 HSA^{LR} mice	Rescue mis-splicing in mice
Mixed mechanisms				
Jenquin et al., 2018	Furamidine	Inhibit transcription Upregulate MBNL protein levels	DM1 HeLa cells DM1 patient-derived myotubes DM1 HSA^{LR} mice	Reduce CUG repeats Rescue mis-splicing Rescue gene expression Increase MBNL1 and MBNL2 proteins Disrupt the MBNL–CUG complex
Jenquin et al., 2019	A combination of erythromycin and furamidine	Inhibit transcription Disrupt the MBNL–CUG RNA interaction Upregulate MBNL protein levels	DM1 patient-derived myotubes DM1 HSA^{LR} mice	Reduce CUG repeats Rescue mis-splicing Rescue gene expression Increase MBNL1 and MBNL2 proteins Rescue myotonia in mice

DM1, myotonic dystrophy type 1; CDM1, congenital DM1; MBNL, muscleblind-like; CELF, CUGBP/Elav-like family; GSK3β, Glycogen synthase kinase-3β; PKC, Protein kinase C; mTORC1, mTOR complex 1; Fn14, fibroblast growth factor-inducible 14.

pitolisant, Caffeine, and theobromine formulation MYODM™ (Kouki et al., 2005; Logigian et al., 2010; Laustriat et al., 2015; Bassez et al., 2018; Vita et al., 2019; Heatwole et al., 2021; reviewed in Pascual-Gilabert et al., 2021).

Genome Editing

Compared with ASO therapy, the development of genome editing provides an opportunity for permanent corrections of gene mutation, which mainly includes clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated system (Cas) methodology and transcription activator-like effector nucleases (TALENs) (Richard, 2015; Lee et al., 2016; Long et al., 2016; Nelson et al., 2017; Raaijmakers et al., 2019).

The CRISPR/Cas methodology can be used to target a specific genomic locus in the genome of eukaryotes (Knott and Doudna, 2018). Specifically, the Cas endonuclease is complexed with a small guide RNA (sgRNA) to target a specific genomic locus. Upon binding, the Cas protein generates a double-strand DNA (ds DNA) break by cleaving the DNA in both strands, thereby correcting the genetic defect (Raaijmakers et al., 2019). The main advantage of this strategy is to eliminate the disease defect at the DNA level, so the mutant transcripts and downstream dysregulations are not produced.

So far, the effects of CRISPR/Cas methodology have been validated. In 2017, one study reported that dual cleavage at either side of the CTG expansion can lead to complete and precise excision of the repeat tract from *DMPK* alleles in DM500 cells (myoblasts carrying 500 *DMPK* CTG repeats), myoblasts of DM1 patients, and unaffected individuals. And it also prevented damage to genes in the DM1 locus (van Agtmaal et al., 2017). Then, a CRISPR-Cas9 system from Staphylococcus aureus (Sa) was developed to cleave the CTG repeats in the human *DMPK* locus. A single intramuscular injection of recombinant AAV (rAAV) vectors expressing CRISPR-SaCas9 and selected sgRNAs has been shown to successfully delete the mutant CTG repeats in muscle fibers and reduce the RNA foci in myonuclei of DMSXL mice (Lo Scrudato et al., 2019).

Except for targeting the mutant DNA, RNA-targeting Cas9 (RCas9) systems which can bind to single-stranded RNA were also investigated (Strutt et al., 2018). Batra et al. (2017) found that through delivering a truncated RCas9 system in human DM1 cells, the toxic mRNAs were highly eliminated and aberrant splicing was corrected. This approach also has fewer side effects, since it does not affect normal transcripts. However, the delivery of RCas9 would gradually decay in the genome, which means the requirement of repeat treatments. Other scientists also proposed methods to prevent expanded transcription by inserting a homology-directed polyadenylation signal into the *DMPK* gene (Wang Y. et al., 2018), or recruiting catalytically deficient Cas9 (dCas9) to the repeat effectively to block progression of RNA polymerase II (Pinto et al., 2017). A recent review by Raaijmakers et al. (2019) carefully elaborated CRISPR/Cas-mediated approaches that target the causative mutation in the DNA and the RNA that cause DM1.

In recent years, some novel Cas-associated strategies have gradually emerged. For example, CRISPR-Cas13a is an RNA guided RNase. Zhang et al. (2020) using Leptotrichia shahii (Lsh) Cas13a in DM1 patient-derived myoblasts successfully degraded the expanded CUG RNA and reversed several important mis-splicing events. CRISPR/Cas9-associated base editing (BE) technology is a new therapy that do not rely on a dsDNA break at target sites but directly mediate the conversion of base pairs, and thus reduce the deletions or insertions (Komor et al., 2016; Gaudelli et al., 2017). However, the disability to generate precise edits beyond the allowed mutations might be a huge challenge.

Transcription activator-like effector nucleases is a newly discovered genome editing tool. It relies on modular transcription factors called transcription activator-like effectors, which enables the targeting of any specific DNA sequence (Sun and Zhao, 2013). Previous studies have reported that a dedicated TALEN can induce a dsDNA break into a CAG/CTG tri-nucleotide repeat in heterozygous yeast diploid cells, which shortened the repeat tract with nearly 100% efficacy and very high specificity (Richard et al., 2014). Currently, TALENs has shown great potential in the treatment of DM1. For example, TALENs application corrected the genetic defect of iPSCs, which contribute to the development of autologous stem cell therapy (Xia et al., 2015; Gao et al., 2016). By the way, TALENs seem to be the safest way to shorten trinucleotide repeats to non-pathological lengths, though more research is needed to combat possible off-target effects, immunogenicity to either the genome editing components or delivery particles and unpredictable DNA repair upon cleavage near the unstable repeat.

Non-coding RNAs

NcRNAs are RNA molecules that cannot be translated into proteins but are responsible for important regulatory events in cells (Fabbri et al., 2019). There are several types of ncRNAs, including microRNAs (miRNAs), long ncRNAs (lncRNAs), and circular RNAs (circRNAs). To date, global changes in ncRNA expression patterns in DM1 (Czubak et al., 2019a; López Castel et al., 2019; Voellenkle et al., 2019), as well as their key roles in contributing to DM pathogenesis have been presented (Perbellini et al., 2011; Wheeler et al., 2012; Gudde et al., 2016, 2017; Koutsoulidou et al., 2017; Czubak et al., 2019a,b; López Castel et al., 2019; Koehorst et al., 2020), which make them attractive biomarkers (Gambardella et al., 2010; Perbellini et al., 2011; Rau et al., 2011; Fernandez-Costa et al., 2013; Kalsotra et al., 2014; Perfetti et al., 2014, 2016; Koutsoulidou et al., 2015, 2017; Fritegotto et al., 2017; Koehorst et al., 2020; Pegoraro et al., 2020) and therapeutic targets in DM1 (Rau et al., 2011; Koutalianos et al., 2015; Zhang et al., 2016; Cerro-Herreros et al., 2018, 2020; López Castel et al., 2019; Sabater-Arcis et al., 2020). For example, muscle-specific miRNAs (myomiRNAs) like miR-1, miR-133a, miR-133b, and miR-206 as well as myostatin have been considered as attractive biomarkers of DM1 rehabilitation (Pegoraro et al., 2020). Besides, the therapeutic potential of miRNAs have been detected. Koutalianos et al. (2015) shown that in muscle cells from patients with congenital DM1, upregulation of the miR-206 expression by transfection with a miR-206 mimic into cells overexpressing CEFL1 induced myogenesis by inhibiting the expression of CELF1 and Twist-1. Replenishing of miR-7 with agomiR-7 reversed DM1 myoblast fusion defects and myotube growth, while blocking of miR-7 mediated by oligonucleotide worsen the outcomes (Sabater-Arcis et al., 2020). Silencing the regulatory

dme-miR-277 and dme-miR-304 by miRNA sponge constructs successfully upregulated MBNL expression at the RNA and protein levels in a DM1 drosophila model, which then rescued mis-splicing and reduced muscle atrophy (Cerro-Herreros et al., 2016). This attempt evaluated miRNA sponge constructs as a powerful and attractive strategy to treat DM1 by blocking specific miRNAs. In recent years, RNA interference (RNAi) technology has attracted increased attention in DM1 (Bisset et al., 2015). Bisset et al. (2015) reported that miRNA-based RNAi hairpins delivered by rAAV vectors significantly downregulated mutant transcripts and reduced muscle pathology in HSA^{LR} mice. Besides, the intramuscular injection and electroporation of synthetic short interfering RNAs (siRNAs) significantly reduced toxic RNA transcripts and nuclear foci in HSA^{LR} mice (Sobczak et al., 2013). Antisense technology (antagomiRs) is a newly developed approach to block specific miRNA. Cerro-Herreros et al. (2020) reported that subcutaneous administration of antagomiR-23b in HSA^{LR} mice strongly increased the level of MBNL1 protein and reversed mis-splicing, grip strength, and myotonia in a dose-dependent manner. However, despite the huge potential of miRNA-based interventions, most of these attempts are still in preclinical phases because of their instability and delivery deficits.

Induced Pluripotent Stem Cell Technique

Nowadays, different differentiated cell models, such as neurons or muscle cells, have been used to investigate pathological mechanisms and to evaluate therapeutic strategies of DM1 before clinical validation (Larsen et al., 2011). However, these cell models are strongly limited due to the low *DMPK* transcript levels in affected cells and genetic background variation. Thus, there is a great need to generate alternative myogenic models that can be reliably used for *in vitro* disease modeling and/or drug screening purposes. It's well-known that iPSCs are self-renewal and can differentiate into any cell type, including neurons and muscles cells. Since genome editing methodology could correct the genetic defect of iPSCs as mentioned before, the various phenotypes observed in DM1 can be subsequently reversed by correcting the lengths of CUG repeats in iPSCs and iPSC-derived cells, thereby offering a great translational platform for therapeutic development. Combining human iPSC lines and genome editing technology to create isogenic cell lines can also eliminate background genetic variation that might affect the expected results. In addition, reprogramming of somatic cells to iPSCs has been reported a valuable tool for disease modeling and drug discovery. Mondragon-Gonzalez and Perlingeiro (2018) established two DM1 iPSC lines from patient-derived fibroblasts, which then be differentiated into myotubes. The iPSC-derived myotubes highly recapitulate the molecular features of DM1 while ASO treatment successfully abolished RNA foci and rescued BIN1 mis-splicing. These results indeed confirmed DM1 iPSCs a kind of valuable alternative myogenic model to study DM1 pathogenesis and screen candidate drugs.

Assisted Delivery Systems

The inefficacy of conventional drug delivery and low bioavailability of drugs led to the rapid progress of assisted delivery systems in recent years. Currently, a number of delivery strategies have shown great potential in enhancing the efficacy of therapeutic molecules while minimizing their off-target effects, which can be broadly divided into four types: polymeric, peptide, lipid, and viral delivery systems, wherein AAV-based gene therapy has emerged to be a potent and promising therapeutic tool for DM1. Compared with other strategies, AAV vectors permanently change genetic defects and avoid repeated administrations. Given the multisystemic symptoms of DM1, they can also achieve systemic delivery (Gregorevic et al., 2004; Arruda et al., 2005). Kanadia et al. (2006) reported that upregulation of MBNL1 by AAV-mediated transfection to skeletal muscle effectively reversed mis-splicing and myotonia in HSA^{LR} mice. Besides, systemic AAV-delivered RNAi significantly improved disease phenotype in HSA^{LR} mice (Bisset et al., 2015). Currently, a possible AAV-delivered ASO, AT466 is being established to reduce the toxic RNA levels in cells derived from DM1 patients by RNA degradation, exon skipping or both (Audentes).[1] Recent efforts on viral delivery to the CNS have also taken an exciting leap forward (Miller et al., 2012). The delivery of AAV9 *via* intravenous administration could traverse the BBB in both neonate and adult animals (van der Bent et al., 2018), which provides a promising tool to treat CNS disorders.

The hydrophilic nature as well as large size and high charge of peptides and proteins prevents their penetration across biological membranes. In order to achieve delivery of therapeutic peptide and protein into cells as well as across epithelial barriers and the BBB, a family of delivery vectors called CPPs has been developed, which shown the potential to traverse cellular membranes and promote the uptake of therapeutic peptides with lower toxicity. To date, CPPs have been applied for intracellular, transepithelial, and transendothelial delivery of various therapeutic cargos. Regarding DM1, one study using the CPP mimic as a scaffold to assemble the multivalent ligand construct significantly increased their binding affinity, which then contributed to phenotypic improvement in a DM1 drosophila model (Bai et al., 2016). Compared to unconjugated PMO, systemic administration of Pip6a-conjugated morpholino PMO remarkably enhanced ASO delivery into DM1 mice muscles. Besides, several CPPs have also been identified to mediate cargo delivery across the BBB and exerted protection in the brain (Kilic et al., 2003, 2004; Dietz et al., 2006). And the combination of CPPs and intranasal administration may further enhance CNS delivery (Kamei and Takeda-Morishita, 2015; McGowan et al., 2016; Khafagy et al., 2020; Akita et al., 2021). However, the BBB-specific CPPs remain not to be found and the mechanisms driving the transportation of CPPs are still unknown.

In order to overcome the instability, limited distribution, rapid degradation and toxicity of therapeutic molecules, nanomedicine has been rapidly developed as an effective drug delivery system in recent years, which greatly improved the efficiency and tissue compatibility of gene therapy, increased safety, and ensured systemic distribution (Koebis et al., 2013; Hermans et al., 2015; Lee et al., 2017; Amini et al., 2019), relying on their adjustable physicochemical properties to prevent toxicity and to carry

[1] www.audentestx.com/innovative-therapies

specific biological molecules to target sites (Andreana et al., 2021). In HSA^{LR} mice, using bubble liposomes as delivery tools significantly improved the delivery efficiency of PMO into muscles, which then increased the expression of chloride channel 1 (Clcn1) protein in skeletal muscle and ameliorated the myotonia (Koebis et al., 2013). Besides, given the inefficiency of macromolecules to cross the BBB, the small nanocarriers-mediated transport, including active transport (e.g., receptor-mediated endocytosis) and facilitated diffusion, also provided a promising pathway for smooth BBB passage of large cargos and targeting various cells with intracellular localization specificity (Hernando et al., 2018; Di Filippo et al., 2021; Nehra et al., 2021; Song et al., 2021). Toward future directions, the combinative applications of these delivery vectors and administration routes would attracted more and more attentions since they provide numerous chances for the discovery of both safe and effective delivery strategies to avoid the side effects of any signal technique.

Other Potential Strategies

Artificial site-specific RNA endonucleases (ASREs) are newly discovered molecules specifically targeting mutant RNA accumulated in the nucleus. The results of Zhang et al. (2014) shown that ASRE treatment significantly decreased nuclear foci formation and reversed the mis-splicing of DM1-related genes with few side effects on wild-type alleles. U7 small nuclear ribonucleoproteins (snRNPs) are a specific type of snRNPs that do not participate in splicing mediation but is a key factor in the unique 3′ end processing of replication-dependent histone (RDH) pre-mRNAs. The modified U7 snRNP (U7 Sm OPT) has been used as a promising tool for gene therapy in splicing defects-associated diseases by targeting splicing to induce efficient skipping or inclusion of selected exons. It has multiple advantages, such as small size, good stability, ability to accumulate in the nucleus without toxicity and immunoreactivity, and low risk of transgene dysregulation. In addition, using U7 Sm OPT as a tool in gene therapy also ensures lifelong treatment. Gadgil and Raczyńska et al. (2021) demonstrated that incorporating ASO into the U7 Sm OPT successfully avoided repeated administration. Injection of U7 Sm OPT containing ASO with 15 CAG repeats in skeletal muscle cells isolated from DM1 patients resulted in long-time improvement in splicing and differentiation defects in a dose-dependent manner, without affecting the wild-type *DMPK* transcripts (Le Hir et al., 2013). The critical properties of U7 snRNP might deploy it as a new tool in gene therapy in the future. In a DM1 drosophila model, researchers screened a D-amino acid hexapeptide (ABP1) which can induce the CUG hairpin into a single-stranded conformation and bind the CUG RNA without displacing MBNL1. Compared to ASOs, this method avoids affecting endogenous transcripts. In fly eyes and muscles, overexpression of natural, L-amino acid ABP1 analogs reduced RNA toxicity. And in HSA^{LR} mice, ABP1 reversed muscle histopathology and partially rescued mis-splicing of MBNL1 targets (García-López et al., 2011). Notably, combination approaches such as different small molecules or gene therapies targeting different processes have also attracted increasing attention. This may produce greater benefits in disease modulation than simply additional effects. Importantly, this combination treatment might also reduce off-target effects.

Therapeutic Strategies Targeting Central Nervous System

The current advances in therapeutic strategies should also be applicable in principle to CNS since the pathogenesis of CNS deficits is similar to that of other organs, such as RNA toxicity and splicing defects. However, the existence of BBB hinders the delivery and distribution of drugs in the brain. Therefore, the ideal therapeutic agents need to be able to cross the BBB readily. Some improvements have been made, such as intracellular delivery of the therapeutic molecules to promote uptake, administering molecules intracerebroventricularly or intrathecally (Baughan et al., 2009; Geary et al., 2015), or regulating the molecule size and charge to achieve an efficient delivery to the brain. Recent advances also found that intranasal delivery efficiently bypasses the BBB and highly increases the CNS concentrations of drugs and is non-invasive. Besides, the combination of U7 methodology with highly efficient AAV-mediated delivery, receptor-mediated endocytosis of ASOs, and nanoparticles-, exosomes- or CPP-based delivery of large cargos also favor the BBB passage and the higher distributions of drugs in the CNS (Foust and Kaspar, 2009; Krupa et al., 2014; McGowan et al., 2015, 2016; Bai et al., 2016; Kristensen et al., 2016). In conclusion, all of these therapeutic agents, administration routes, and assisted delivery systems create numerous chances for the discovery of effective therapies for CNS disorders.

Several molecules applied for CNS treatment have shown positive effects in preclinical trials, which may provide new thoughts for DM1 CNS treatment. For example, in mice overexpressing *APP*, intracerebroventricular injections of PS-modified ASOs significantly reduced the expression of APP protein and improved learning and memory deficits (Kumar et al., 2000). In the Alzheimer's disease (AD) mouse model, a designed 2′-O-Me-PS-modified ASO sustainly increased exon 19 splicing of apolipoprotein E receptor 2 (ApoER2) as well as restored synaptic function and learning and memory (Hinrich et al., 2016). Besides, an 2′MOE-modified ASO called IONIS MAPTRx (ISIS 814907) has been evaluated in a phase I/II study in patients with mild AD (NCT03186989), as it highly reduced the expression of tau protein through targeting MAPT mRNA. Hu et al. (2021) using a 20-mer RNase H-active gapmer ASO combined with a 3-month exercise training program in old HSA^{LR} mice reversed all measures of fatigue, though they did not detect the index of fatigue due to CNS dysfunctions. These findings may provide new thoughts for DM1 CNS treatment. Murlidharan et al. (2016) discovered a lab-derived AAV chimeric (AAV2g9), which has favorable CNS properties derived from both parental counterparts, AAV2 and AAV9. Administration of CRISPR/Cas9 with this synthetic AAV vector into the CSF minimized systemic leakage and reduced the sequestration and gene transfer in off-target organs.

The modification of stem cells also offers a new chance for CNS treatment. Previous studies have shown that NSC derived from ES cells or iPSCs could present critical features

of DM1 (Marteyn et al., 2011; Denis et al., 2013; Xia and Ashizawa, 2015; Xia et al., 2015). In DM1 NSCs, insertion of poly A signals upstream of *DMPK* CTG repeats by TALEN-mediated homologous recombination significantly eliminated mutant transcripts and nuclear RNA foci, corrected mis-splicing, and ultimately reversed phenotypes (Xia et al., 2015; Gao et al., 2016). Despite the broad prospects of strategies in CNS treatment, there are still many challenges, such as lower efficiency and distribution to CNS and safety regarding immune response and gene therapy specificity. In addition, no studies have discussed the targeted brain cell types of different strategies and the corresponding alterations of brain cells after treatment. The resolution of these issues may provide a deeper understanding of the therapeutic mechanisms of drugs.

LIMITATIONS AND FUTURE DIRECTIONS

Though great progresses have been made, there are still many limitations in current studies that hinder the understanding of the complex nature of CNS defects and the development of new treatments. Firstly, despite the current knowledge of the molecular basis underlying CNS defects, it is still unclear how these molecular alterations could be translated into specific pathological changes and clinical symptoms, nor do we know how these deficits progress over time. In the future, more longitudinal studies with large sample size are needed to fully understand the DM1 neuropathology and its progression. Secondly, although several cell and animal models have been developed to reproduce the DM1 gene mutation and pathogenesis similar to the human phenotype, such as MBNL-loss or CELF-overexpressing phenotypes, or *in vitro* and *ex vivo* alternatives which can assist animal experimentation, none of them completely recreate the multisystemic phenotypes of DM1, which block the in-depth assessment of DM1 defects and effective evaluations of feasible interventions. Thirdly, more applicable patient questionnaires and clinical neurocognitive evaluation protocols should be investigated to better identify the disease component and serve as potential markers to evaluate the effectiveness of therapeutic strategies. Fourthly, at the pharmacotherapeutic level, more efforts are needed to improve drug delivery efficiency, biodistribution and availability, and reduce toxicity. Meanwhile, the design of drugs for CNS treatment must be able to readily cross the BBB.

CONCLUSION

In this review, we primarily focus on CNS involvement in DM1, outlining the primary pathological alterations and pathogenesis underlying CNS. Then, we highlight promising therapeutic strategies for DM1. Excepting for some available drugs targeting for specific neurological impairments, the promising results of some biological molecules (i.e., ASO, small molecules, CRISPR/Cas9, ncRNA.) *via* targeting mutant DNA, RNA, or downstream proteins in preclinical models or even clinical trials have also provided relevant candidates for DM1 treatment. Particularly, a variety of re-purposed small molecules drugs have been evaluated in DM1, which present with low manufacturing cost, greater safety and stability *in vivo* treatment. Meanwhile, the development of screening and rational design technologies also promote the production of newly potent small molecules, which increases the availability of small molecule therapy in DM1 in the near future. In principle, these interventions should be applicable to the CNS, since strategies such as eliminating toxic RNAs, reducing the formation of nuclear foci, or restoring the levels of splicing-related factors are also effective in brain cells, however, additional researches are still needed to improve the understanding of DM1 progression and to transfer available therapeutic strategies and knowledge into actionable clinical applications.

AUTHOR CONTRIBUTIONS

JL wrote the first draft of the manuscript. X-LY and Z-NG prepared the figures. SH and YY reviewed and edited the manuscript. All authors contributed to critical revision of the manuscript and approved the final manuscript for submission.

FUNDING

This work was supported by the National Natural Science Foundation of China (81971105) to Z-NG, the Program for JLU Science and Technology Innovative Research Team (2017TD-12), and the Jilin Provincial Key Laboratory (20190901005JC) to YY.

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