

# Altered Translational Control of Fragile X Mental Retardation Protein on Myelin Proteins in Neuropsychiatric Disorders

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## Abstract

Myelin is a specialized structure of the nervous system that both enhances electrical conductance and insulates neurons from external risk factors. In the central nervous system, polarized oligodendrocytes form myelin by wrapping processes in a spiral pattern around neuronal axons through myelin-related gene regulation. Since these events occur at a distance from the cell body, post-transcriptional control of gene expression has strategic advantage to fine-tune the overall regulation of protein contents *in situ*. Therefore, many research interests have been focused to identify RNA binding proteins and their regulatory mechanism in myelinating compartments. Fragile X mental retardation protein (FMRP) is one such RNA binding protein, regulating its target expression by translational control. Although the majority of works on FMRP have been performed in neurons, it is also found in the developing or mature glial cells including oligodendrocytes, where its function is not well understood. Here, we will review evidences suggesting abnormal translational regulation of myelin proteins with accompanying white matter problem and neurological deficits in fragile X syndrome, which can have wider mechanistic and pathological implication in many other neurological and psychiatric disorders.

**Key Words:** Myelin, Fragile X mental retardation protein, Translational control, Oligodendrocyte

## INTRODUCTION

Fragile X syndrome (FXS) is a monogenic disorder that arises from abnormal expansion of a CGG repeat (> 200 CGG repeats) in the 5'-untranslated region (UTR) of the X-linked FMR1 gene, leading to loss of fragile X mental retardation protein (FMRP) expression (Saldarriaga *et al.*, 2014; Chen and Joseph, 2015). FMRP is an RNA-binding protein, which binds to almost 4% of brain transcripts to regulate mRNA transport, translation, and stability. FMRP is known to inhibit mRNA translation and its absence results in the elevated translation of intracellular signaling components, such as group 1 metabotropic glutamate receptors (mGluR), which results in the defects of ERK1/2 and PI3K-Akt-mTOR intracellular signaling pathways (Richter *et al.*, 2015). These findings suggest that loss of FMRP leads to general deficits in the efficiency and regulation of cellular signaling, dysfunctions that might be common to psychiatric disorders. Indeed, FXS patients often show comorbid psychiatric symptoms, such as cognitive

deficit, communication problem, attention deficit, and aggression (Tranfaglia, 2011, 2012). Likewise, most FXS patients have been diagnosed with mood disorder, attention-deficit hyperactivity disorder (ADHD), autism, anxiety, and depression (Tranfaglia, 2011). In case of fragile X-associated tremor/ataxia syndrome (FXTAS), another genetic variant with CGG repeat in 5'-UTR within FMR1 gene (55-200 CGG repeats), mRNA gain-of-function toxic effects result in a neurodegenerative condition (Hagerman and Hagerman, 2015). Major features of FXTAS are inattention, tremor or ataxia with an increase in incidence and prevalence with age (Brown and Stanfield, 2015; Hagerman and Hagerman, 2015). In addition, white matter intensities are affected in FXTAS patients, with symptoms like Parkinsonism, cognitive decline, memory problems, autonomic dysfunction, and neuropathy (Brown and Stanfield, 2015). Nevertheless, the association between white matter dysfunction and FMRP-related psychiatric or neurologic dysfunction, not to mention its mechanism of action, is unclear yet.

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White matter is the brain region underlying the gray matter, composed of neuronal fibers coated with electrical insulation called myelin (Fields, 2008). Myelin is a multilayered, lipid-rich coating of axons, which enhances the conduction velocity of nerve impulses, contributes to compact nervous systems, and reduces metabolic costs of neural activity (Fields, 2008; Haroutunian *et al.*, 2014). Myelination continuously occurs for decades in human brain and is modifiable by experience. In addition, myelin affects information processing by regulating conduction velocity. Recent post mortem studies have revealed structural differences in white matter tracts related to a wide range of neurological and psychiatric illnesses, including ADHD, depression, bipolar disorder, language problem, autism, obsessive-compulsive disorder, posttraumatic stress disorder, cognitive decline, Alzheimer's disease, Tourette's disorder, and schizophrenia (Haroutunian *et al.*, 2014; Mighdoll *et al.*, 2015). An important issue is whether these changes in myelin gene expression or white matter structure are a direct cause of the psychiatric disorders or secondary consequences of abnormal brain function on white matter. However, the altered expression of myelin-associated genes in several neuropsychiatric disorders implies that white matter malfunction may contribute to the neurological and psychiatric illnesses (Mighdoll *et al.*, 2015; Voineskos, 2015). For example, experimental manipulation of oligodendrocytes gene expression regulates glial development and myelination and causes behavioral changes mimicking schizophrenia (Ren *et al.*, 2013). Obviously they are regulated by transcriptional control, but some of these genes are also regulated (targeted) translationally by several mechanisms one of which involves RNA binding proteins such as FMRP. Therefore, the identification, characterization and modulation of the RNA targets of FMRP will provide novel clues about the pathophysiological mechanism of human (psychiatric) disorders affected by white matter dysfunction.

## MYELIN AND ITS FUNCTION

Myelin is a specialized membrane which spirally ensheathes axons by oligodendrocytes and Schwann cells of the central nervous system (CNS) and the peripheral nervous system (PNS), respectively (Fields, 2008; Nave and Werner, 2014). Myelination is one of the most pivotal cell-cell interactions for normal brain development, involving extensive information exchange such as motor, sensory, and higher-order cognitive function between differentiating oligodendrocytes and axons (Nave and Werner, 2014). By wrapping the nervous axons, the membrane sheath facilitates fast conduction of the action potential and maintains the integrity of axons. For example, conduction velocity of myelinated axons is quickened up to 150 m/s, whereas that of non-myelinated axons ranges from 0.5 to 10 m/s (Toritsuka *et al.*, 2015). Thus, myelin is required for proper connectivity during neural development and for electrical activity and maintenance of mature neurons. Myelination in the brain is multi-stage process (Nave and Werner, 2014). First, oligodendrocytes must be differentiated from their pluripotent precursors. This step involves a crosstalk among multiple transcription factors that restricts the developmental potential of the cell. Second, the precursor cells must migrate to the site of myelination, which requires communication between the migrating cells and the axons they are destined to

form. Third, transcriptional and post-transcriptional changes force it to release from the cell cycle and differentiate into a mature oligodendrocyte. Last, processes extended from the mature cells wrap around the target axon and prepare to form the mature myelin structure. Considering the morphological complexities of oligodendrocytes, they necessitate the strategies to control gene expression at regions distal to the cell body. These strategies could influence how the cell decides where to migrate, when to stop dividing and differentiate, and which axons to myelinate (wrap). In addition, myelin formation requires the oligodendrocyte to regulate gene expression in response to changes in its extracellular environment. Because these changes occur at a distance from the cell body, post-transcriptional control of gene expression allows the cell to fine-tune its response (Zearfoss *et al.*, 2008). So fine control of genetic and epigenetic interplay during oligodendrocyte maturation and myelination formation is crucial for proper neural connectivity and higher brain functions.

## DYSREGULATED MYELINATION AND PSYCHIATRIC DISORDERS

Myelin can be disturbed by either damage or genetic problems (Barateiro *et al.*, 2016). For example, several autoimmune diseases (Guillain-Barré syndrome in the PNS and multiple sclerosis in the CNS) (Kamm and Zettl, 2012), inherited disorders affecting structural genes in myelin (Charcot-Marie-Tooth disease, Dejerine-Sottas syndrome and Pelizaeus-Marzbacher disease) (Kleopa *et al.*, 2010; Barrette *et al.*, 2013), metabolic disorders (Canavan, Menke's, Krabbe's and Refsum's disease) (Kumar *et al.*, 2006), infection, trauma, toxins (including alcohol or drugs), hormonal imbalance and asphyxia are the cause of such dysfunction (Kohlhauser *et al.*, 2000). Additionally, astrocyte-related diseases like Alexander disease result in severe hypomyelination, mental retardation and death (Ettle *et al.*, 2016).

Numerous psychiatric disorders, including schizophrenia, depression, bipolar disorder, obsessive-compulsive disorder and posttraumatic stress disorder, and neurodevelopmental disorders such as autism and ADHD have recently been associated with white matter defects evidenced by brain imaging and histological analysis of post mortem tissues (Onnink *et al.*, 2015). Brain imaging methods show volumetric and microstructural white matter changes as well as differences in functional connectivity, biochemical changes in white matter or alterations in white matter tracts or myelin genes between normal and patient (Rowley *et al.*, 2015). For instance, an analysis of 6000 genes in prefrontal cortex of schizophrenia brains, 89 genes were abnormally regulated, of these 35 were genes involved in myelination (Hakak *et al.*, 2001). This includes genes encoding myelin-associated glycoprotein (MAG), myelin and lymphocyte protein (MAL), MBP, myelin proteolipid protein (PLP), myelin oligodendrocyte glycoprotein (MOG) and 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNP), peripheral myelin protein 22 (PMP22); growth factors and receptors ErbB3, NRG1 and BDNF; transcription factors Sox10, Olig 1 and Olig 2; and other genes associated with oligodendrocyte development and myelination, including QKI and Claudin11. In addition, genetic abnormalities resulting in demyelination have been implicated in psychiatric disorders (Voineskos, 2015). Polymorphisms of several genes includ-

ing MAG, CNP, MOG, NRG1 and Olig 2 are susceptible to numerous psychiatric disorders. Taken together, dysregulation of myelination and manifestation of psychiatric disorders are closely related and affected by common genetic factors, implying understanding the mechanism of their expression may provide hints for the development of better diagnostic and therapeutic options.

## FMRP AND FXS

Fragile X mental retardation protein (FMRP) is a genetic product of FMR1 gene. FMRP, most commonly found in the brain, is essential for normal cognitive development and female reproductive function (Lozano *et al.*, 2014). Mutations of this gene can lead to fragile X syndrome (FXS), FXTAS, mental retardation, premature ovarian failure, autism, Parkinson's disease, developmental delays and other cognitive deficits. FMRP harbors two k-homology (KH) domains and one arginine-glycine repeated (RGG box) domain and binds to RNA. As an RNA binding protein, FMRP regulates bound mRNA stability, translation, and transport to modulate physiological functions within brain (Chen and Joseph, 2015). As discussed above, 90% of FXS patients show comorbid conditions including ADHD, autism, depression, and aggression. 85% is connected with intellectual disability, 41% of patients shows a mood disorders among them, 70% and 12% presents anxiety and depression, respectively (Scharf *et al.*, 2015). FXTAS patients also show a spectrum of symptoms such as tremor, motor dysfunction and cognitive deficit (Lozano *et al.*, 2014). As shown in recent clinical study, FXTAS had slower nerve conduction velocities, prolonged F-wave latencies, and slower compound muscle action potential amplitudes compared with controls and unaffected permutation males (Soontarapornchai *et al.*, 2008). Collectively, there was a significant relationship between the number of CGG repeat and reduction of nerve conduction velocity. The significant relationship also applies between elevated messenger RNA levels of FMR1 and reduction of the muscle action potential velocity in the permutation group, suggesting that the FMR1 gene is a causal factor.

## MYELINATION DEFECT IN FXS: ABNORMAL MYELIN-RELATED GENE EXPRESSION IN FXS

Recently, several groups reported that FMRP is expressed in MBP-positive oligodendrocytes of rodents and human (Giampetruzzi *et al.*, 2013; Pacey *et al.*, 2013) as well as oligodendrocyte lineage cells in differentiation stage-specific manner (Wang *et al.*, 2004), raising the possibility that FMRP regulates some aspects of myelination processes. Lack of FMRP in FXS could lead to premature myelination or myelin abnormalities. Several groups reported that FMRP binds myelin basic protein (MBP) mRNA, one of major myelination proteins, both *in vivo* and *in vitro* and inhibits MBP mRNA translation *in vitro* (Li *et al.*, 2001; Wang *et al.*, 2004; Darnell *et al.*, 2011; Giampetruzzi *et al.*, 2013). In addition, FMRP expression decrease during oligodendrocyte maturation either *in vivo* or in culture (Giampetruzzi *et al.*, 2013), suggesting that FMRP represses translation of MBP mRNA in immature oligodendrocytes and later allows translation of MBP mRNA in mature oligodendrocytes concomitant with the decreased FMRP expression (Wang *et*

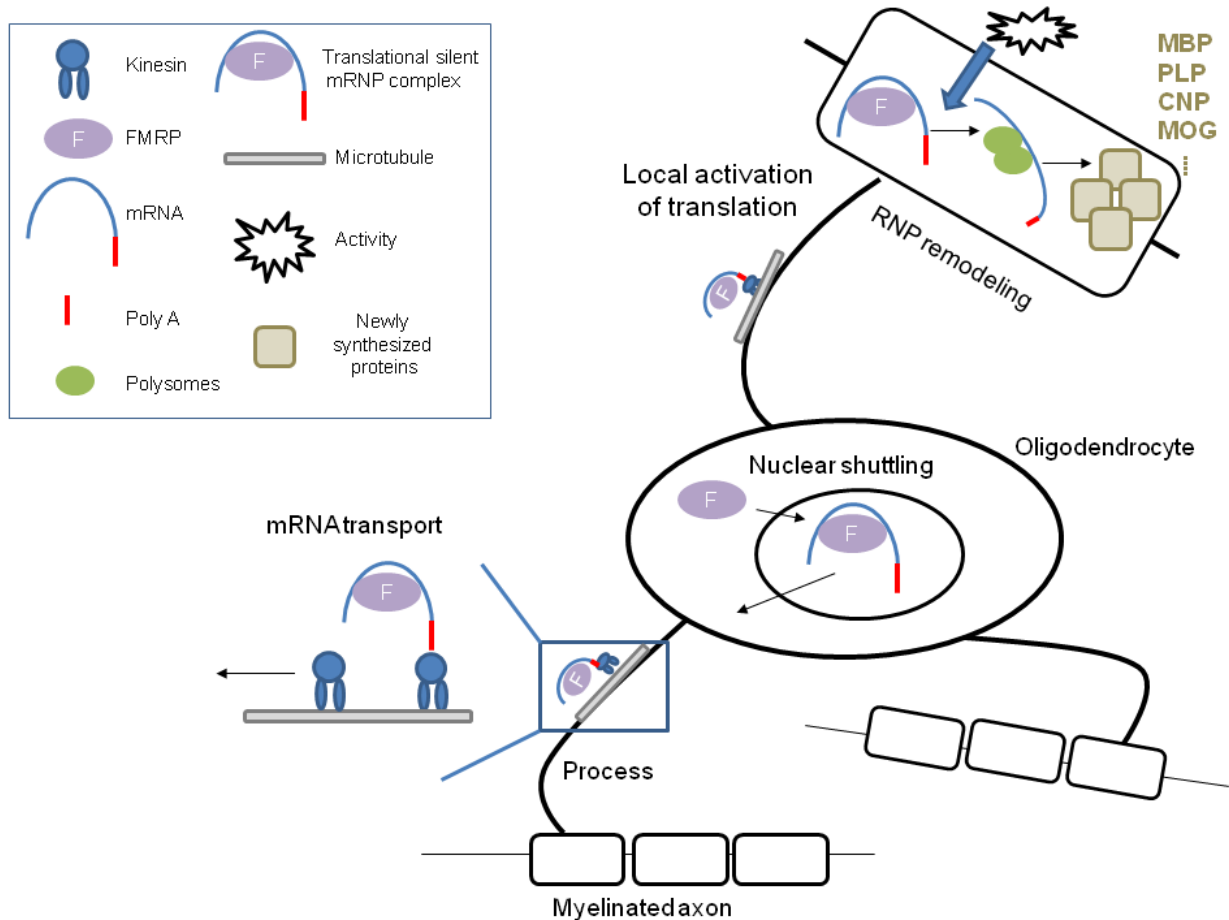
*al.*, 2004). Pacey *et al.* (2013) showed that Fmr1 knockout mice display abnormalities in the myelination of cerebellar axons as early as the first postnatal week, corresponding to the equivalent time in human brain development when FXS symptoms become apparent. At postnatal day (PND) 7, diffusion tensor magnetic resonance imaging showed an 80-85% reduction of MBP expression, fewer and thinner myelination in Fmr1 knockout mouse cerebellum compared with wild-type mice (Giampetruzzi *et al.*, 2013; Pacey *et al.*, 2013). This altered expression was recovered to the normal levels at PND 30, suggesting that impaired maturation or function of oligodendrocyte precursor cells induces delayed myelination in the Fmr1 knockout mouse brain (Pacey *et al.*, 2013). Taken together, white matter abnormalities in early brain development represent an underlying neurological deficit in FXS and other neuropsychiatric disorders.

## TRANSLATIONAL CONTROL OF mRNAs IN OLIGODENDROCYTES

Polarization and functional compartmentalization of cells necessitate the specific transport and localization of mRNAs. Local and specific translation of a subset of these mRNAs can allow rapid responses to stimulation. Since oligodendrocyte processes trap onto the several axons at the same time, an appropriate regulation of rapid protein induction only at the site of activation is crucial for performing and maintaining proper myelin function. Local regulation of protein synthesis represents one mechanism used to control the different requirements for myelin sheath at each axo-glia interaction (Laursen *et al.*, 2011). Supporting to this hypothesis, polyribosomes as well as a number of myelin-related mRNAs are observed in distal oligodendrocyte processes, sometimes in proximity to the forming myelin sheaths (Barbarese *et al.*, 1995). Colman confirmed the distribution of newly synthesized myelin proteins from rats after an intracranial injection of <sup>35</sup>S-methionine (Colman *et al.*, 1982). MBP, one of myelin-forming proteins, was rapidly induced in the myelin sheath, and was not detected in rough microsome, suggesting direct synthesis in the process. Similar results were obtained in the *in vitro* translational experiments (Colman *et al.*, 1982). Both *in vivo* labeling and *in vitro* translation experiments support that MBP-synthesizing polysomes are rapidly activated in the oligodendrocyte processes.

Translational regulation of myelin-related mRNAs is also shown by inhibition of elongation inhibitor (Geva *et al.*, 2010) or treatment of protein synthesis inhibitor (Cullen and Webster, 1989). The anomalous development of white matter in eukaryotic translation initiation factor 2B knockout mice underscores the importance of tight translational control in normal myelin formation and maintenance (Geva *et al.*, 2010). Cycloheximide, a protein translation inhibitor, reduced the number of polyribosomes or cell processes of oligodendrocyte by reducing myelin proteins synthesis (Cullen and Webster, 1989).

The translatability of the local mRNAs may be influenced by its 3' UTR which bound to RBPs. In neurons, the cytoplasmic polyadenylation element (CPE) within the 3'UTR is recognized by an activated CPE-binding protein (CPEB) thus triggering poly A elongation and enhancing its translation (Huang and Richter, 2007). Similar mechanism of mRNA activation could occur for pre-existing messengers in oligodendrocyte, which



**Fig. 1.** Schematic representation of local mRNA transport and translation in oligodendrocyte processes. Under physiological condition, FMRP (violet) and target mRNA (circles) mRNP components moves into distal process in association with motor proteins such as kinesin (blue circle), which usually kept relatively dormant until the activation. When exposed to an appropriate signal, the mRNP complex dissociates RBP such as FMRP, which initiates translation of mRNA locally, resulting in the increased protein synthesis specifically in places of activation.

might be dictated by the prior transport and availability of the appropriate mRNAs in situ. Subcellularly localizing mRNAs are packaged into ribonucleoprotein (RNP) complexes that engage with motor proteins for directed transport along cytoskeletal tracks and ensure their translational silencing. These RNP complexes are mainly composed of cis-regulatory elements that are present on the mRNA and specific trans-acting factors recognizing the cis-elements. Among these trans-acting factors, conserved RNA-binding proteins control both targeting of the mRNA and translational repression. Translation of most local mRNAs including MBP is an event temporally separated from transcription and transport. In respect of energy cost, direct translation of distally localized mRNAs would be easier and economical way of regulation.

Interestingly, many of the myelin genes are targets for specific RNA binding proteins (RBP) (Zearfoss *et al.*, 2008). Numerous RNA binding proteins are expressed in oligodendrocyte lineage (from precursor cell to mature one), and control multiple aspects of gene expression, including regulation of mRNA stability and degradation, transport, alternative splicing, and translation (Campagnoni *et al.*, 1991). Dysregulation of such RBPs in psychiatric disorders will affect downstream RNA metabolism, which further modulates oligodendrocyte

development and myelination process (Larocque and Richard, 2005).

One such target is FMRP and the remaining questions are what the molecular targets and the mechanism of the regulation are (Fig. 1).

**OLIGODENDROCYTE MOLECULAR TARGETS MODULATED BY FMRP**

**Oligodendrocyte-related genes**

FMRP negatively regulates the translation of two myelin-related transcripts: MBP and PLP (Giampetruzzi *et al.*, 2013). Binding assays using *in vitro* translated FMRP and biotin-labeled MBP and PLP mRNAs demonstrate an interaction between FMRP and these transcripts (Darnell *et al.*, 2011). One of well-defined FMRP targets in neurons is microtubule associated protein 1B (MAP1b) (Lu *et al.*, 2004; Darnell *et al.*, 2011). The MAP1b knockout mouse has been reported to have myelin defects in the PNS, demonstrating its requirement for myelination (Gonzalez-Billault *et al.*, 2002). Further study is necessary to determine whether an interaction between FMRP and the MAP1b mRNA occurs in oligodendro-



**Table 1.** Myelination-related genes regulated by FMRP expression

Class	Molecules	Myelin-function	References
Transcription regulators	Tcf7l2/Tcf4	Myelination decrease/increase	Fancy <i>et al.</i> , 2009
	Sox4, Sox5, Sox6, Sox8, Sox9, Sox10, Sox11, Sox17	Myelination decrease/increase Oligodendrocyte pool	Stolt <i>et al.</i> , 2006, Stolt and Wegner, 2010
	Nuclear hormone receptor	Myelination increase	Pombo <i>et al.</i> , 1999
	Nkx2.2	Myelination decrease/increase	Qi <i>et al.</i> , 2001
	Nkx6.1, NKx6.2	Myelination increase Oligodendrocyte maturation	Wei <i>et al.</i> , 2005

cyte and mediates myelination. Although the function of FMRP in oligodendrocytes has not fully investigated yet, it is notable that both MBP and MAP1b are also targets of QKI, one of RBPs. Interestingly, and the expression of MBP and MAP1b is regulated by QKI, suggesting the role of RBPs in the regulation of myelin function (Wu *et al.*, 2001; Larocque *et al.*, 2002). It is therefore possible that the two RNA binding proteins, i.e. FMRP and QKI could coordinate expression of target proteins for appropriate control of myelin function. FMRP silences translation of the RNAs in precursors, while QKI would stabilize the RNAs and lead to increased expression of target mRNAs during myelination. As FMRP is a KH and RGG box RNA binding protein, many studies have been conducted to find its targets (Darnell *et al.*, 2011; Chen and Joseph, 2015). FMRP RGG box binds an RNA motif known as a G-quartet, identified by SELEX (Chen *et al.*, 2003). Most recently, SELEX experiments carried out using the FMRP KH domain demonstrate that the KH domain recognizes a complicated tertiary RNA structure called a kissing complex (Chen *et al.*, 2003). Below, we will further discuss previously reported FMRP targets, which might be related to oligodendrocyte progression and myelination (Table 1).

### Transcription factors

Numerous transcription factors are involved in the functional regulation of myelination-mediating glia (Emery, 2010). The list includes Nkx6.2 (Gtx), POU domain protein Tst-1/Oct-6, Brn-1/2, MyTI (Myelin transcription factor I), new Cys2/His2 zinc finger proteins rKR1/2, Krox-24 (Egr-1, Zif286), and Sox family. These transcription factors work together in sequential manner to induce and complete fine-tuning of myelination structures. Among these known factors, sox family transcription factors, Nkx6.2, and Brn-1/2 are reported as FMRP targets (Kunde *et al.*, 2011).

Sox family transcription factors are well-established regulators of cell fate decisions during development. Sox family maintains precursor or stem cell properties (undifferentiated state) and prevents differentiation promoting proteins from acting normally. By interaction of cognate mRNAs with FMRP, Sox family expression is repressed, which may inhibit neural differentiation (Telias *et al.*, 2015). In addition, when FMRP expression is abolished as shown in FXS, altered neurogenesis and increased neuronal differentiation is observed (Luo *et al.*, 2010). It should be determined whether FMRP-mediated regulation of Sox transcription factor expression affects oligodendrocyte pool size as well. Recent studies have also suggested that Nkx6.2/Gtx homeodomain transcription factors are involved in the regulation of oligodendrocyte maturation and myelination, which occur predominantly in postnatal stages

**Table 2.** Micro RNAs targets of FMRP

miRNA	Myelin-function	References
miR 124	Myelination decrease by Sox9 inhibition	Morris <i>et al.</i> , 2015
miR 138	Myelination decrease by Notch inhibition	Lau <i>et al.</i> , 2008
miR 144	Myelination increase by Enp6 inhibition	Svaren, 2014
miR 219	Myelination decrease by Sox2/Hes5 inhibition	Zhao <i>et al.</i> , 2010
miR 338	Myelination decrease by Sox2/Hes5 inhibition	Zhao <i>et al.</i> , 2010

(Cai *et al.*, 2010). Nkx6.2 is initially expressed in differentiating oligodendrocyte precursor cells but quickly downregulated as oligodendrocyte precursor cells undergo terminal differentiation (Cai *et al.*, 2010). Intriguingly, Nkx6.2 expression is upregulated in mature myelinating oligodendrocytes at later stages. Although data demonstrating direct interaction of FMRP with Nkx6.2 mRNA is unavailable yet, Nkx6.2 and FMRP is coincidentally expressed in the oligodendrocyte developmental tract and microarray data revealed the interaction between them, which warrants further investigation to uncover the link.

Brain-2 (Brn-2), a Class III POU transcription factor, plays function largely overlapping with that of Oct-6 in driving the transition from promyelinating to myelinating cells (Friedrich *et al.*, 2005). Miyashiro *et al.* showed the possible interaction of FMRP and Brn-2, which was later reproduced by other groups using photoactivatable-ribonucleoside-enhanced crosslinking and immunoprecipitation (PAR-CLIP) assay (Miyashiro *et al.*, 2003; Darnell *et al.*, 2011). Largely devoted to the study of neuronal development (Patel *et al.*, 2014; Contractor *et al.*, 2015), investigating the role of FMRP on the regulation of oligodendrocyte development will pave the new way to understand the complex process.

### micro RNAs

Recently, micro RNAs (miRNA) have emerged as important regulators of gene expression in oligodendrocyte (Svaren, 2014). FMRP can regulate miRNA pathway through interaction with miRNA biogenesis components or through direct association with miRNAs (Jin *et al.*, 2004). The interaction between miRNA and FMRP would mediate miRNA-dependent repression of translation through the RNA interference pathway, by interacting with the components of the RNA-induced silencing

complex (RISC) (Jin *et al.*, 2004). Several defined miRNAs described below have been reported as potential FMRP targets (Yi *et al.*, 2010) (Table 2).

Micro RNA-219 (miR-219) relatively specific to oligodendrocytes within the CNS, is induced along with oligodendrocyte differentiation (Zhao *et al.*, 2010). Target mRNAs of miR-219 are Sox6, Hes5, PDGFR alpha, ZFP238, FoxJ3, Evolv7, and ENPP6 (Zhao *et al.*, 2010; Svaren, 2014), which enhance the oligodendrocyte differentiation by inhibiting pro-proliferation transcription factors. Indeed, knockdown of miRNA-219 blocks oligodendrocyte differentiation *in vivo* as well as *in vitro* (Zhao *et al.*, 2010). Additionally, its expression is downregulated in the CNS following deletion of dicer in oligodendrocytes (Dugas *et al.*, 2010), suggesting its crucial role for differentiation. Recent research has identified miR-219 as a key molecule in the behavioral manifestations associated with pathophysiology of schizophrenia (Kocerha *et al.*, 2009), which is related to the abnormal FMRP-dependent Sox expression. Another potential FMRP target is miRNA-338 (Yi *et al.*, 2010), which is relatively specific to oligodendrocytes and induced with oligodendrocyte differentiation. Its target includes Sox6 and Hes5, which explains why knockdown of miRNA-338 blocks oligodendrocyte differentiation (Zhao *et al.*, 2010). Micro RNA-138 is transiently induced at early stage of oligodendrocyte differentiation. In FMRP knockout studies, the role of miR-138 in synaptic development and dendritic arborization is revealed (Bicker *et al.*, 2014). *In vivo* experiments in the mouse subventricular zone (SVZ) have demonstrated that miR-138 down-regulates Sox9 and thereby inhibits precursor division and stimulates differentiation. Overall, miR-138 appears to play a major role in oligodendrocyte differentiation by down-regulating genes essential for precursor proliferation, while stimulating oligodendrocyte-specific genes and cytoskeletal rearrangements. Similar to miRNA-219, micro RNA-144 is down-regulated following the deletion of dicer in oligodendrocytes. Its target mRNA includes Enp6 (Svaren, 2014). Previously, miR-144 is reported to be involved in neurite outgrowth, neurogenesis, signaling of PTEN, ERK, and Wnt/beta-catenin pathways (Zhou *et al.*, 2009; Tawk *et al.*, 2011). Interestingly, Edbauer *et al.* (2010) showed that miR-124 and miR-144, as well as several other miRNAs, are associated with FMRP in mouse brain. FMRP controls pre-miR-144 processing into mature miR-144. Since miR-144 stimulates oligodendrocyte differentiation, its association with FMRP will suggest its role in FXS pathology including abnormal myelination.

## CONCLUSIONS

In FXS patients or knockout mice studies, many behavioral and neuroanatomical problems show comorbidity symptoms observed in psychiatric disorders. The most prevalent symptoms are cognitive decline, mood problem, mental retardation, and lipid metabolism abnormality, which have some association with the reduction in oligodendrocyte pool or delayed myelin formation. The common pathophysiological mechanism is abnormal regulation of gene expression either transcriptionally or post-transcriptionally, which further impairs myelin forming process such as altered oligodendrocyte population or dysregulated myelin component and structure, leading to a malfunction problem. In fact, FMRP knockout rodents still showed behavioral and synaptic problems even after their re-

covery from white matter abnormality in later period, demonstrating fine tuning and cooperative in-time transcriptional and post-transcriptional regulation are important for appropriate oligodendrocyte development and myelin function. Collectively, integration of findings in recent studies at multiple levels of research have allowed a deeper understanding of myelination defects and neuropsychiatric behaviors, identifying the functional role of FMRP in this process, which provide additional targets for therapeutic intervention.

## CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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