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Dysregulation of mRNA Localization and Translation in Genetic Disease

Mini-Symposium

Dysregulation of mRNA Localization and Translation in Genetic Disease

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RNA-binding proteins (RBPs) acting at various steps in the post-transcriptional regulation of gene expression play crucial roles in neuronal development and synaptic plasticity. Genetic mutations affecting several RBPs and associated factors lead to diverse neurological symptoms, as characterized by neurodevelopmental and neuropsychiatric disorders, neuromuscular and neurodegenerative diseases, and can often be multisystemic diseases. We will highlight the physiological roles of a few specific proteins in molecular mechanisms of cytoplasmic mRNA regulation, and how these processes are dysregulated in genetic disease. Recent advances in computational biology and genomewide analysis, integrated with diverse experimental approaches and model systems, have provided new insights into conserved mechanisms and the shared pathobiology of mRNA dysregulation in disease. Progress has been made to understand the pathobiology of disease mechanisms for myotonic dystrophy, spinal muscular atrophy, and fragile X syndrome, with broader implications for other RBP-associated genetic neurological diseases. This gained knowledge of underlying basic mechanisms has paved the way to the development of therapeutic strategies targeting disease mechanisms.

Key words: Fragile X Mental Retardation Protein (FMRP); Fragile X Syndrome (FXS); Muscleblind-like Splicing Regulator (MBNL); Myotonic Dystrophy (DM); RNA Binding Protein Fox-1 Homolog 1 (RBFOX1); Spinal Muscular Atrophy (SMA); Survival of Motor Neuron (SMN)

Dysregulation of mRNP assembly and localization in spinal muscular atrophy (SMA)

The assembly of mRNA-binding proteins (mRBPs) and mRNAs into messenger ribonucleoproteins (mRNPs) determines the fate of the transcripts during all steps of post-transcriptional regulation, including its localization and translation. Recent studies have shown that both hyperassembly or hypoassembly of various RNPs can lead to human neurodegenerative diseases, including spinal muscular atrophy (SMA) and amyotrophic lateral sclerosis (ALS) (Shukla and Parker, 2016). Although there has been a lot of progress to understand basic principles of RNP hyperassembly and formation of persistent stress granules, it is still not clear how the proper assembly of specific transport mRNPs is regulated (Li et al., 2013). The molecular machinery that brings together transcripts with a specific set of proteins that regulate their translocation and local translation remains unknown.

In the case of spliceosomal small nuclear ribonucleoproteins (snRNPs), it has been shown that the faithful assembly of Sm proteins into a hepatameric complex on the uridine-rich snRNAs depends on the activity of a multiprotein assemblysome consisting of SMN and associated gemin proteins (Meister et al., 2001; Pellizzoni et al., 2002). Reduced SMN protein levels cause SMA, which is characterized by axonal dying back of spinal motor neurons leading to muscular atrophy and typically death in early childhood. While widespread splicing defects occur in all SMA models characterized thus far (Gabanella et al., 2007; Zhang et al., 2008, 2013; Lotti et al., 2012), the role of these defects in the disease process may very well represent a secondary nonspecific effect of neurodegeneration, and their significance for SMA pathogenesis remains to be fully elucidated (Bäumer et al., 2009).

The interaction of SMN with diverse mRBPs and its localization to mobile RNA transport granules in axons *in vitro* and *in vivo* (Dombert et al., 2014; Hao le et al., 2015) has led to the hypothesis that SMN may have a noncanonical role in axonal mRNA metabolism that may explain the vulnerability of motor neurons to reduced SMN protein levels (Briese et al., 2005; Rossoll and Bassell, 2009; Fallini et al., 2012). Work from several laboratories has demonstrated SMN-dependent defects in the localization and local translation of axonal mRNAs and mRBPs. Since the discovery of defective axonal localization of *β-actin*
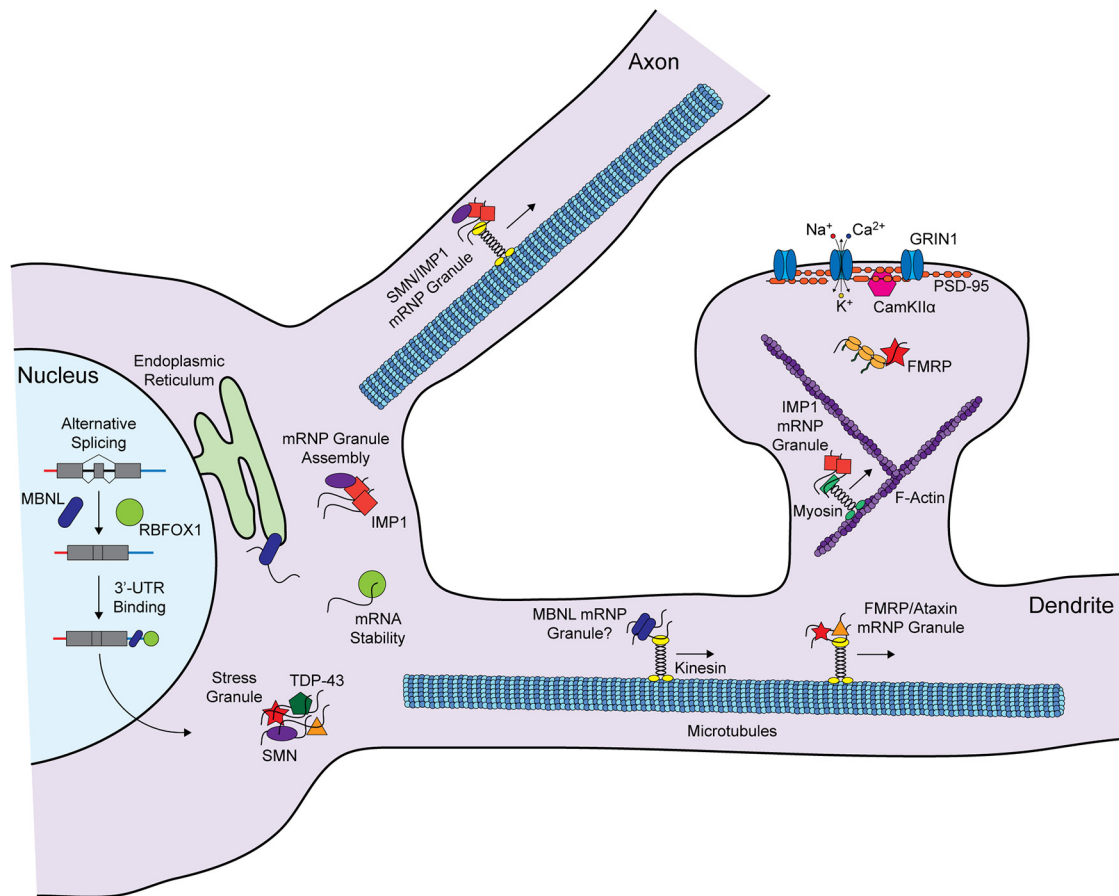
Figure 1. Spatiotemporal regulation of RNA processing and local translation in neurons by RNA-binding proteins. In the nucleus, MBNL and RBFOX proteins regulate splicing and bind 3′-UTR sequences. Both proteins coregulate many transcripts. In the cytoplasm, MBNL binds to the rough endoplasmic reticulum (RER) where it facilitates the synthesis of membrane proteins, and also associates with the cytoskeleton to regulate mRNA localization. The cytoplasmic isoform of RBFOX1 regulates mRNA stability. Several RNA-binding proteins (e.g., FMRP, Ataxin, TDP-43, and Smn) are associated with stress granules. FMRP and Imp1 regulate mRNA granule transport by kinesin and local translation in dendritic spines. Imp1 also regulates mRNA localization in axons, and Smn plays a role in the assembly of Imp1 RNA transport granules. RNA localization and translation in spines may involve myosin motor and anchoring to F-actin. Locally synthesized proteins include glutamate receptor subunits, components of the postsynaptic density, and signaling proteins.

mRNA and protein in SMA motor neurons (Rossoll et al., 2003), SMN has been found to regulate the axonal localization of transcripts encoding growth-associated protein 43 (GAP43) and neuritin/cpg15 (Akten et al., 2011; Fallini et al., 2011, 2014, 2016; Hubers et al., 2011; Sanchez et al., 2013) (Fig. 1). This mislocalization is accompanied by reduced local translation in axonal growth cones and can be rescued by overexpression of the SMN-interacting mRBPs HuD and IMP1/ZBP1 (Fallini et al., 2016). Based on these findings, a more general role for SMN in RNP complex assembly that goes beyond its well-characterized function in snRNP assembly and splicing, including a critical role in the assembly of mRNP transport granules, appears likely (Li et al., 2014; Donlin-Asp et al., 2016; So et al., 2016).

An open question remains what is the scope of snRNP and mRNP assembly defects in SMA *in vivo*, and how these defects contribute to the specific motor neuron degeneration observed in SMA. In a disease of general RNP hypoassembly, one can expect widespread downstream effects on various post-transcriptional regulation mechanisms (Donlin-Asp et al., 2016; Shukla and Parker, 2016). It will be interesting to find out whether rescuing mRNP assembly and localization defects can mitigate the SMA disease phenotype. Future work will need to show which defects are most relevant for the SMA pathogenesis and will provide insight into potential therapeutic strategies that target RNP assembly.

Global approaches for studying RNA dysregulation in myotonic dystrophy

The dominantly inherited neuromuscular disease myotonic dystrophy (DM) is caused by an expanded CTG (DM1) or CCTG (DM2) microsatellite repeat in the 3′-UTR of the dystrophia myotonica protein kinase gene, or the first intron of the CCHC-type zinc finger nucleic acid binding protein, respectively (Cooper, 2009; Lee and Cooper, 2009). These repeats are transcribed into RNA and sequester members of the Muscleblind-like (MBNL) family of RNA-binding proteins into nuclear foci (Fig. 1) (Miller et al., 2000; Cooper, 2009). MBNL proteins are deeply evolutionarily conserved and are required for the terminal differentiation of a number of cell types, including neurons, skeletal muscle, and cardiac muscle (Begemann et al., 1997; Artero et al., 1998). They have been most extensively studied in the context of alternative splicing regulation, as they are required for the transition from fetal-to-adult isoform expression throughout development (Pascual et al., 2006). Loss of MBNL function in DM leads to numerous missplicing events (Kanadia et al., 2003a, b), some of which have been linked to specific phenotypes in DM, such as *Chloride Channel 1* (myotonia) (Charlet et al., 2002), *Insulin receptor* (insulin resistance) (Savkur et al., 2001), *Bridging integrator 1* (muscle weakness) (Fugier et al., 2011), *CaV1.1 calcium channel* (muscle weakness) (Tang et al., 2012), *sodium chan-*

nel 5a (cardiac arrhythmia) (Wahbi et al., 2013; Freyermuth et al., 2016), and *cardiac troponin T* (cardiac arrhythmia) (Philips et al., 1998). These changes all essentially reflect shifts in expression of adult-to-fetal isoforms. Recent studies in human DM1 and mouse models reveal missplicing of numerous mRNAs encoding proteins that play important cytoskeletal and synaptic functions (Charizanis et al., 2012; Goodwin et al., 2015). A key open question is whether specific missplicing events are linked to specific CNS symptoms, which include profound hypersomnia and intellectual disability (Thornton, 2014).

Although a role for MBNLs in regulating alternative splicing is well established, previous studies have also indicated a role for MBNLs in regulating mRNA localization and local translation. MBNL2 was shown to interact with the 3′-UTR of *Integrin α3* and carry it to the plasma membrane, where it is locally translated (Adereth et al., 2005). MBNL2 has also been suggested to enhance the stability of mRNAs encoding extracellular matrix components (Du et al., 2010), and MBNL1 has been implicated in the regulation of message stability (Wang et al., 2015; Masuda et al., 2012). Using a combination of genomics and biochemical approaches, MBNL1 was shown to be a global regulator of RNA localization and membrane-associated translation. RNAseq of subcellular compartments from mouse myoblasts showed that 3′-UTR CLIP targets of MBNL1 relocalize toward the insoluble and away from the membrane compartments, following depletion of MBNL1 and 2 (E. T. Wang et al., 2012). Many of the dysregulated mRNAs were found to encode secreted proteins, extracellular matrix components, and proteins involved in cell–cell communication and synapse function, with potential implications for neuromuscular junctions in muscle. Ribosome footprinting of myoblasts depleted of MBNL1/2 also indicated decreased translation of those mRNAs whose normal localization to the membrane compartment was relocalized toward the insoluble compartment. MBNL1 and MBNL2 CLIPseq in mouse and human brain corroborate many MBNL binding sites in the 3′-UTRs of numerous mRNAs encoding synapse and cytoskeletal proteins (E. T. Wang et al., 2012).

These observations raise a number of outstanding questions that require further investigation to answer. Whether regulation of RNA localization by MBNLs is achieved through diffusion/anchoring and/or active transport along cytoskeletal filaments is unknown. The specific membrane and insoluble compartments from which MBNL targets are relocalized are also unclear, although the rough endoplasmic reticulum likely comprises a large fraction of the membrane compartment. The role of MBNLs in regulating mRNA localization and translation in fully differentiated tissues, such as muscle and neurons, has also not been fully explored; it is likely that localization patterns are more complex in tissues than in cell culture, and possible that mislocalization of mRNAs in MBNL-depleted tissues has significant physiological consequences. The mRNAs whose splicing patterns are regulated by MBNLs also tend to exhibit 3′-UTR binding and regulation of localization by MBNLs; whether this coordination exists for functional or biophysical reasons has not been addressed. Similar questions could be asked of additional RNA-binding proteins implicated in neurological disease, and further investigation may yield general principles that apply to regulation of RNA localization and local translation across other RBPs and other diseases.

Gene-distal 3′-UTR sequences often regulate mRNA localization

Although several hundred transcripts are preferentially localized to neuronal projections (Taylor et al., 2009; Zivraj et al., 2010;

Gumy et al., 2011; Cajigas et al., 2012; Minis et al., 2013), for the overwhelming majority of these transcripts, the RNA sequences within them that drive their localization are unknown. In cases where the localizing sequence is known, it is often located in the 3′-UTR of the transcript (Andreassi and Riccio, 2009). Still, 3′-UTRs are often >1 kb in length, making identification of localization elements difficult.

If multiple transcript isoforms are expressed from a single gene locus, however, then this problem becomes more manageable, especially if the isoforms display differing localization patterns. By comparing sequence elements present in localization-competent isoforms with those in localization-incompetent isoforms, the search space for relevant features can be considerably narrowed (Taliaferro et al., 2016). Given that many known RNA localization elements lie in 3′-UTRs, this effect is, perhaps not surprisingly, often most apparent in genes that express isoforms that differ in 3′-UTR composition.

For example, during *Drosophila* oocyte development, two isoforms of the cyclin B gene are expressed: one containing a longer 3′-UTR and another containing a shorter 3′-UTR that is a subset of the long one. Transcripts containing the longer 3′-UTR become localized to the posterior pole of the oocyte, whereas those with the shorter 3′-UTR do not, implying the existence of a localization element in the sequence specific to the long 3′-UTR (Dalby and Glover, 1992). Similarly, two *Bdnf* transcript isoforms that differ in polyadenylation site, and thus 3′-UTR length, are expressed in mouse brain cortex. Transcripts that contain the long 3′-UTR are efficiently trafficked to dendrites, whereas those that contain the short UTR remain in the soma (An et al., 2008).

Recently, the linkage of gene-distal polyadenylation and RNA localization to neuronal processes was shown to extend beyond these isolated examples as a more general phenomenon affecting hundreds of genes (Taliaferro et al., 2016). The analysis of splice isoform abundances in soma and neurite cell fractions revealed a strong preference for gene-distal UTR sequences in neurites. A similar profile of *in vivo* ribosome-associated transcripts in mouse neurons also demonstrated many examples of alternative 3′-UTR isoform use associated with differential isoform localization in axons (Shigeoka et al., 2016). Thus, the composition of a transcript's 3′-UTR and its RNA localization fate seem to be tightly linked.

The mechanisms and consequences of 3′-UTR regulation and localization are becoming better understood. The regulation of 3′-UTR composition through alternative cleavage and polyadenylation (APA) has been well correlated to broader cellular states. In general, gene-proximal polyadenylation sites are preferentially used following oncogenic transformation and cellular reprogramming (Sandberg et al., 2008; Mayr and Bartel, 2009). Conversely, gene-distal polyadenylation sites are more often used as cells progress along developmental pathways (Ji et al., 2009; Miura et al., 2013), with neurons in particular expressing long 3′-UTRs that have generally unknown function (Miura et al., 2013). The localization competency of many genes may therefore be a function of the developmental or oncogenic state of the cell.

Similarly, perturbations to factors that regulate alternative cleavage and polyadenylation or 3′-UTR-mediated transcript stability may disrupt the post-transcriptional regulation of transcripts containing particular 3′-UTRs, indirectly resulting in the mislocalization of many transcripts, thus contributing to disease phenotypes. Muscleblind-like proteins, as described above, are known RNA localization factors in their own right (Adereth et al., 2005; E. T. Wang et al., 2012; Taliaferro et al., 2016), and regula-

tors of transcript stability through 3′-UTR binding (Wang et al., 2015). RNA-binding proteins from the CELF family also bind 3′-UTRs and regulate transcript levels (Wang et al., 2015). Functional impairments for both of these factors are associated with neurological diseases (Gallo and Spickett, 2010; Goodwin et al., 2015).

Regulation of synaptic and autism-related genes by Rbfox1 in the cytoplasm of neurons

Post-transcriptional mechanisms, including mRNA localization, stability, and regulated translation provide a means of building and controlling neural circuits with exquisite temporal and spatial specificity (D. O. Wang et al., 2010; Jung et al., 2014). RBPs play critical roles during these processes by regulating RNA metabolism to modify gene expression in neurons (Zhou et al., 2014). This idea gains further support from human genetic studies that show that mutations in the genes of several RBPs are associated with neurological diseases (Liu-Yesucevitz et al., 2011; Gao and Taylor, 2014).

The RBP, RBFOX1, is the vertebrate homolog of the *Caenorhabditis elegans Feminizing Gene 1 on X* gene product (also known as A2BP1). Each of RBFOX1's paralogs, RBFOX2 (RBM9) and RBFOX3 (NeuN), has distinct but overlapping expression patterns (Kuroyanagi, 2009). Chromosomal translocations and copy number variations in *Rbfox1* have been associated with intellectual disability, epilepsy, and autism (Martin et al., 2007; Sebat et al., 2007). Furthermore, transcriptome analysis of autistic and normal brain tissue identified RBFOX1 as a master regulator of autism-related genes (Voineagu et al., 2011). The CNS-specific conditional *Rbfox1* knock-out mice exhibit spontaneous seizures, indicating that RBFOX1 regulates neuronal excitability (Gehman et al., 2011). All three RBFOX paralogs bind the RNA motif (U)GCAUG and have a well-characterized function in regulating alternative splicing in the nucleus of cells. *Rbfox1* itself is alternatively spliced into nuclear and cytoplasmic isoforms, and the function of the cytoplasmic RBFOX1 has only recently been investigated (Hamada et al., 2015; Carreira-Rosario et al., 2016; Lee et al., 2016). In neurons, RBFOX1 binds to the 3′-UTR of its target mRNAs in the cytoplasm and promotes the stability of these transcripts. These cytoplasmic targets are enriched for synaptic and autism-related genes, supporting the hypothesis that RBFOX1 promotes mRNA stability of autism-related genes in the brain (Ray et al., 2013). One potential mechanism for this regulation is to antagonize microRNA-binding and the repression activity of microRNA machinery. Future work is needed to know whether Rbfox proteins may play a role in mRNA localization.

Several hundreds of transcripts have now been identified as targets of RBFOX proteins by different mechanisms. For example, the cytoplasmic targets of RBFOX1 are enriched in genes involved in calcium signaling pathway. In neurons, the splicing of *Camk2d* and *Camk2 g* is regulated by RBFOX1 in the nucleus, and the mRNA concentration of *Camk2a*, *Camk2b*, *Camk4*, and *Ppp3r1* is affected by RBFOX1 in the cytoplasm (Lee et al., 2016), making it challenging to understand the contributions of individual RBFOX1 targets to any neural circuit phenotype. In *C. elegans* nervous system, RBFOX, CELF, and PTB family proteins regulate the splicing of insulin receptor *daf-2* in a single neuron, and misregulation of this splicing leads to behavioral changes (Tomioka et al., 2016), underscoring the need for cell-type-specific approaches in charactering the physiological function of RBPs in neurons.

A growing literature has revealed the multifunctionality of RBPs (Heraud-Farlow and Kiebler, 2014; Vanharanta et al., 2014), and this is the case for RBFOX family proteins as well. *Drosophila* cytoplasmic RBFOX1 represses translation of one of its target mRNAs, the translational regulator *pumilio,* to regulate germ cell differentiation (Carreira-Rosario et al., 2016), indicating that RBFOX1 may either enhance or repress gene expression in the cytoplasm of cells. Recent studies showed that RBFOX2 and RBFOX3 can regulate the biogenesis of microRNAs, and RBFOX2 can bind nascent RNAs to regulate polycomb complex 2 targeting (Kim et al., 2014; Chen et al., 2016; Wei et al., 2016). These data suggest that RBPs might have diverse functions in neurons and an increased understanding of RNA regulation will lead to novel therapies for a range of brain disorders.

Role of FMRP and Ataxin-2 in RNA granules, synapse function, and behavior

Individual mRNPs formed by interaction of mRNAs with *cis*-element-interacting RNA-binding proteins as well as other regulatory factors assemble into larger and heterogeneous RNA granules through trans-mRNP interactions. In such RNA granule assemblies, sequestered and translationally repressed mRNAs are transported on cytoskeletal filaments to specific intracellular locations (Kiebler and Bassell, 2006; Zeitelhofer et al., 2008). In neurons, activity-induced disassembly of RNP granules plays an important physiological role to enable local translation of dendritically localized mRNAs (Krichevsky and Kosik, 2001; H. Wang and Tiedge, 2004; Zeitelhofer et al., 2008). Prion-like domains with low amino acid complexity (LC domain) found predominantly on RNA-binding proteins are considered to mediate the assembly and disassembly of mRNP granules (Malinovska et al., 2013). Aberrant translation arising from abnormal mRNP assembly is causally related to developmental and degenerative disorders of the nervous system (Liu-Yesucevitz et al., 2011; Tolino et al., 2012). Consistently, mutations in the LC domains of these proteins are predominantly linked to heritable forms of these disorders (Ramaswami et al., 2013; Toretsky and Wright, 2014). Genetic mutations affecting LC domains of RBPs affect stress granule dynamics and biophysical properties, which have been linked to neurodegenerative diseases (Kim et al., 2013; Molliex et al., 2015; Protter and Parker, 2016).

In neurons, mRNA localization and local translation ensure spatiotemporal regulation of synaptic plasticity required for formation of stable memories. Notable among memory-associated RNA regulatory proteins are Staufen/Pumilio pathway components, as well as Atx2 and FMRP, which are linked to trinucleotide expansion disorders (Dubnau et al., 2003; Orr and Zoghbi, 2007; Bolduc et al., 2008; McCann et al., 2011; Sudhakaran et al., 2014). CGG repeats in the 5′UTR of the *FMR1* gene and CAG expansion in the reading frame of the *Atx2* gene lead to genetic disorders; fragile X syndrome (FXS), and spinocerebellar ataxia type 2 (SCA2) and ALS, respectively (Verkerk et al., 1991; O'Donnell and Warren, 2002; Al-Ramahi et al., 2007; Elden et al., 2010). Recent studies demonstrate that the affected proteins are required for mRNP assembly and/or translational regulation underlying memory formation, in a manner that exhibits shared and distinct mechanisms. The KH domain in FMRP and the Lsm domain in Atx2, respectively, mediates their interaction with RNA (Neuwald and Koonin, 1998; Lewis et al., 2000). FMRP and Atx2 are both required in the same subset of central olfactory neurons for formation of long-term but not short-term olfactory habituation in *Drosophila*. Whereas loss-of-function mutations in the genes have no dominant effects, *dfmr1* and *atx2* mutations

show strong transdominant genetic interactions. Several lines of evidence indicate that FMRP and Atx2 proteins interact biochemically, and jointly bind and regulate the expression of dendritic *CaMKIIα* mRNA that is required for long-term memory (Sudhakaran et al., 2014). Excess protein synthesis is thought to underlie *Fmr1* loss-of-function phenotypes, including defective long-term memory formation (Bolduc et al., 2008). Although both dFMR1 and Atx2 possess prion-like LC domains and are mRNA granule components, *in vivo*, FMRP is dispensable and Atx2 is crucial for assembly of the majority of RNA granules visible in neurons that encode habituation associated memory (Sudhakaran et al., 2014). One potential explanation for this observation is that dFMR1 is only required for assembly of a subset of mRNP granules. Alternatively, the Q/N domain of FMRP, which does not exhibit typical prion-like behavior in yeast assays, may facilitate protein–protein interactions involved in its function as a translational repressor (Banerjee et al., 2010).

Although the loss-of-function effects of *dfmr1* and *atx2* mutations are similar, FXS-related pathologies are generally not associated with inclusion bodies, whereas ALS or SCA2 patients show formation of inclusion bodies in affected neurons (Orr, 2012). This is consistent with the observation that fragile X is an X-linked disorder (caused by loss of FMRP function) and SCA2 is autosomal dominant, caused by a polyglutamine expansion that confers enhanced aggregation efficiency to Atx2.

The work in *Drosophila* argues that LC-domain containing RNA regulatory proteins may be generally involved in the activity-dependent translational regulation of memory-associated mRNAs, such as CaMKII. Consistent with this, Q/N domains of FMRP are required for the formation of long-term memory (Banerjee et al., 2010). A prediction of this model is that similar domains of Atx2 will also be required for long-term memory and that loss of function mutations in human Atx2 or its closely related paralog Atx2L could cause symptoms that overlap with FXS.

The PI3K/mammalian target of rapamycin (mTOR) pathway is important for local protein synthesis and regulated by FMRP: implications for FXS and other autism spectrum disorders

A prerequisite for synaptic translation of localized mRNAs is that components of the protein synthesis machinery are present and active in dendrites. The PI3K/mTOR pathway is an essential regulator of mRNA translation in neurons and localized to dendrites and synapses (Banko et al., 2006; Ohno et al., 2014). A few studies show that activation of the PI3K/mTOR pathway is important for stimulus-dependent local mRNA translation in dendrites. A PI3K inhibitor prevents metabotropic glutamate receptor 1/5 (mGlu1/5)-mediated protein synthesis in synaptic fractions (Gross et al., 2010), and mTOR inhibition by rapamycin or siRNA-mediated silencing blocks BDNF-induced synaptic protein synthesis in isolated dendrites and axons (Takei et al., 2004). Apart from the effect on general dendritic protein synthesis, mTOR also regulates the local translation of specific mRNAs, such as *CaMKIIα* and *Kv1.1* (Sosanya et al., 2013, 2015).

Recent studies suggest that the expression of the PI3K complex is controlled through activity-dependent protein synthesis and degradation (Gross et al., 2010; Briz et al., 2013). Large-scale screens for mRNAs associated with FMRP, the protein lost in FXS, have identified several PI3K/mTOR pathway components (Brown et al., 2001; Darnell et al., 2011; Ascano et al., 2012). Two of these, the PI3K catalytic subunit *p110β* and the regulatory subunit *PI3K enhancer* (*PIKE*), have been confirmed independently to bind to FMRP leading to upregulated p110β and PIKE

protein levels in cells from patients with FXS and/or in FXS mouse models (Gross et al., 2010; Sharma et al., 2010; Gross and Bassell, 2012; Kumari et al., 2014). FXS is characterized by increased and stimulus-insensitive synaptic protein synthesis, which may underlie defects in synaptic plasticity and neuronal function (Darnell and Klann, 2013). The fact that FMRP directly controls central regulators of general and dendritic mRNA translation makes them attractive candidates for therapeutic intervention to correct dysregulated local protein synthesis, which may restore synaptic plasticity in FXS. In line with this hypothesis, genetic reduction of p110β or PIKE restored stimulus-induced synaptic protein synthesis in *Fmr1* knock-out mice and reversed deficits on the cellular, behavioral, and cognitive level in both mouse and fly models of FXS (Gross et al., 2015a, b; Monyak et al., 2016). As a next step, it will be important to assess whether selective inhibitors of p110β, which are available from cancer research, likewise rescue phenotypes in animal and human cell models. Inhibitors of PI3K/mTOR signaling components could have a broader applicability in neurodevelopmental disorders, as defects in expression or activity of the PI3K/mTOR complex leading to dysregulated protein synthesis have been associated with different forms of autism spectrum disorders (Kelleher and Bear, 2008; Cuscó et al., 2009; Gross, 2016).

FMRP is transported into dendrites and synapses (Antar et al., 2004) and regulates the local translation of its targets at synapses (Ifrim et al., 2015; Liu and Cline, 2016). An open question is whether the components of the PI3K/mTOR pathway, which are regulated by FMRP, are translated locally. There is evidence for local translation of *p110β* as the mRNA is localized into dendrites *in vivo* and associates with actively translating polysomes in synaptic fractions (Gross et al., 2010), but so far, it is unknown whether mRNAs for PIKE or any of the other potential FMRP targets within the PI3K/mTOR pathway are present in dendrites and may be locally translated. It will be interesting to investigate whether the local synthesis of the PI3K/mTOR complex, an important regulator of protein synthesis (Kye et al., 2014), adds another layer of complexity to the regulation of synaptic mRNA translation.

In conclusion, here we have highlighted recent progress in our understanding of some proteins that are linked to local regulation of mRNA and neurogenetic diseases. The field of RNA-based neurological disease has grown rapidly (Gao and Taylor, 2014). We present a model that integrates the proposed roles of several RBPs and associated factors in splicing, RNA granule assembly (both stress granules and RNA transport granules), cytoskeletal-based transport, association with RER for synthesis and localization of membrane proteins, and local regulation of mRNA translation in axonal and/or dendritic compartments.

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