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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 RNP s 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 translation 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 heptameric 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 (Gabanelia 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...
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 neu-ritin/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 (Coo-per, 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). 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).

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Although several hundred transcripts are preferentially localized to neuronal projections (Taylor et al., 2009; Zivraj et al., 2010; Guny 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 (Li 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-
tutors 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). Func-
tional 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 spa-
tial specificity (D. O. Wang et al., 2010; Jung et al., 2014). RBPs
play critical roles during these processes by regulating RNA met-
tabolism to modify gene expression in neurons (Zhou et al.,
2014). This idea gains further support from human genetic stud-
ies 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 Caeno-
rhabditis 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 ex-
pression patterns (Kuroyanagi, 2009). Chromosomal transloca-
tions 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 sponta-
neous seizures, indicating that RBFOX1 regulates neuronal excit-
ability (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 iso-
forms, 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 en-
riched 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. Fu-
ture 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 exam-
ple, the cytoplasmic targets of RBFOX1 are enriched in genes
involved in calcium signaling pathway. In neurons, the splicing of
Camk2d and Camk2g 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 receptordaf-2 in a single neuron, and
misregulation of this splicing leads to behavioral changes (Tom
ioika 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 regulatorpumilio, to regulate
germ cell differentiation (Carreira-Rosario et al., 2016), indicat-
ing 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-
sequence–interacting RNA-binding proteins as well as other regu-
ulatory 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 loca-
tions (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 den-
trictically localized mRNAs (Krichevsky and Kosik, 2001; H.
Wang and Tiedge, 2004; Zeitelhofer et al., 2008). Prion-like do-
 mains with low amino acid complexity (LC domain) found pre-
dominantly on RNA-binding proteins are considered to mediate
the assembly and disassembly of mRNP granules (Malinovsky
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; To-
lino et al., 2012). Consistently, mutations in the LC domains of
these proteins are predominantly linked to heritable forms of
these disorders (Ramawami 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;
Mollie et al., 2015; Protter and Parker, 2016).

In neurons, mRNA localization and local translation ensure
spatiotemporal regulation of synaptic plasticity required for for-
mation of stable memories. Notable among memory-associated
RNA regulatory proteins are Staufen/Pumilio pathway compo-
nents, as well as Atx2 and FMRP, which are linked to nucleo-
tide 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 un-
derlying 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
habitation 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 bi-chemically, 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; Cusco 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.

References


