Local RNA Translation at the Synapse and in Disease

Mini-Symposium

Liqun Liu-Yesucevitz,1 Gary J. Bassell,3,4 Aaron D. Gitler,6 Anne C. Hart,9 Eric Klann,10 Joel D. Richter,11
Stephen T. Warren,5,6,7 and Benjamin Wolozin1,2

Departments of 1Pharmacology and 2Neurology, Boston University School of Medicine, Boston, Massachusetts 02118, Departments of 3Cell Biology, 4Neurology, 5Human Genetics, 6Biochemistry, and 7Pediatrics, Emory University School of Medicine, Atlanta, Georgia 30322, 8Department of Cell and Developmental Biology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104, 9Department of Neuroscience, Brown University, Providence, Rhode Island 02912, 10Center for Neural Science, New York University, New York, New York 10003, and 11Program in Molecular Medicine, University of Massachusetts Medical School, Worcester, Massachusetts 01605

Local regulation of protein synthesis in neurons has emerged as a leading research focus because of its importance in synaptic plasticity and neurological diseases. The complexity of neuronal subcellular domains and their distance from the soma demand local spatial and temporal control of protein synthesis. Synthesis of many synaptic proteins, such as GluR and PSD-95, is under local control. mRNA binding proteins (RBPs), such as FMRP, function as key regulators of local RNA translation, and the mTORC1 pathway acts as a primary signaling cascade for regulation of these proteins. Much of the regulation occurs through structures termed RNA granules, which are based on reversible aggregation of the RBPs, some of which have aggregation prone domains with sequence features similar to yeast prion proteins. Mutations in many of these RBPs are associated with neurological diseases, including FMRP in fragile X syndrome; TDP-43, FUS (fused in sarcoma), angiogenin, and ataxin-2 in amyotrophic lateral sclerosis; ataxin-2 in spinocerebellar ataxia; and SMN (survival of motor neuron protein) in spinal muscular atrophy.

Introduction

Neurons are cells with complex, polarized, highly elaborated processes that extend great distances. The large distance of synapses from the soma creates a fundamental challenge for the neuron: neurons must prevent synthesis of synaptic proteins during mRNA transport, yet quickly allow synthesis upon demand in response to synaptic activity. The solution to the geometry of neurons demands local mechanisms for control of RNA translation to allow synthesis of new proteins in a manner that is spatially and temporally restricted.

mRNA binding proteins (RBPs) have emerged as one of the major mechanisms for local regulation of RNA translation/protein synthesis. Regulation of the localization, stability, and translation of mRNAs is mediated in part by RBPs that bind to mRNAs in untranslated regions (3′-UTR and/or 5′-UTR) or coding regions of mRNA (Martin and Ephrussi, 2009; Richter and Klann, 2009). RBPs regulate mRNA distribution and metabolism by consolidating RNA–protein complexes to form RNA granules in which translation is repressed (Kiebler and Bassell, 2006; Thomas et al., 2011). Upon synaptic demand, mRNA is shuttled from storage granules to the synapse where RNA translation is rapidly initiated. The consolidation to form RNA granules occurs through a mechanism of reversible protein aggregation of RBPs such as TIA-1, TIAR, and G3BP, which contain polyglutamine- and asparagine-rich domains that aggregate readily and share homology (physical and functional) with the yeast prion protein Sup35 (Anderson and Kedersha, 2008). Dendrites contain at least three different types of RNA granules. Ribonucleoprotein particles (RNPs) appear to function in transport and storage of mRNA transcripts. Stress granules (SGs) sequester nonessential capped mRNAs in response to stress, which promotes translation of essential stress response proteins, such as HSP70. Processing bodies (P-bodies) regulate degradation of mRNA (Kiebler and Bassell, 2006; Wang et al., 2010). Working in concert with microRNA (miRNA) and microtubes, these RNA granules regulate the distribution, translation, and degradation of mRNA transcripts throughout the neuron.

Although RNA granules share common protein components, each kind of RNA granule contains a distinct population of proteins and performs separate functions (Fig. 1): (1) RNA transport granules deliver transcripts to dendrites while inhibiting RNA translational activity. RBPs such as FMRP and Pumilio participate in dendritic transcript transport and function as translational repressors (Knowles et al., 1996). (2) Stress granules form transiently to reprogram RNA translation under stressful conditions. The primary consolidation-initiating SG proteins include TIA-1, TIAR, G3BP, and survival of motor neuron protein (SMN), but a number of disease-linked proteins also associate with SGs as they expand; these proteins include FMRP, fused in sarcoma (FUS), TAR DNA binding protein-43 (TDP-43), ataxin-2 (Anderson and Kedersha, 2008). (3) P-bodies are the sites for mRNA degradation, often integrating with miRNA machinery. Dcp1a (decapping enzyme 1a) is a RBP that is classically used to identify P-bodies (Parker and Sheth, 2007). Dendritic...
Translational control by RBPs. RBPs act in the nucleus, where they have been implicated in splicing and transcription. The same RBPs also exhibit important roles outside the nucleus. RBPs function to transport mRNAs to the synapse, during which they silence translation. At the synapse, RBPs function in a complex network regulating local translation. Finally, in response to stress, RBPs sequester 7mG capped mRNA in large aggregates, which allows synthesis of protective uncapped mRNA, such as heat shock proteins. Orange, RBPs that function silence translation. Magenta, RBPs that function in splicing and transport. Green, RBPs that activate RNA translation. Blue/orange striped line, Microtubules.

RNA granules do not function as isolated particles, but instead constantly interact with each other exchanging transcripts and proteins. The dynamics of RNA granules control all stages of mRNA processing including biogenesis, translation, and degradation.

The RBPs that make up RNA granules are emerging as major sources of mutations linked to neurological diseases. For instance, impaired expression of FMRP, due to trinucleotide repeat expansions, is the cause of fragile X mental retardation syndrome, which is the most common cause of inherited mental retardation (Kelleher and Bear, 2008; Darnell et al., 2011). Expanded trinucleotide repeats in several different ataxin genes are the cause of spinocerebellar ataxia (Orr and Zoghbi, 2007). Mutations in SMN are linked to spinal muscular atrophy (SMA), and mutations in TDP-43 and FUS are both causes of amyotrophic lateral sclerosis (ALS) (Lefebvre et al., 1995; Lagier-Tourenne et al., 2010). Each of these proteins falls into the class of RBPs and exert functions across more than one category: specific mRNA transport to dendrites, mechanisms of translational control in dendrites (in response to synaptic stimulation), and the function of the newly synthesized proteins in synaptic efficacy.

Local translational control impacts at the level of individual synapses and synaptic networks. Synapse-stimulating agents elicit protein synthesis (Jiang and Schuman, 2002); conversely, protein synthesis inhibitors disrupt some forms of synaptic plasticity including long-term facilitation, long-term potentiation (LTP), and long-term depression (LTD) (Kang and Schuman, 1996; Martin et al., 1997; Huber et al., 2000). One form of LTP, long-lasting late-phase LTP (L-LTP), requires both gene transcription and RNA translation (Klann and Dever, 2004). Hippocampal LTD mediated by metabotropic glutamate receptors requires rapid translation of preexisting mRNA (Huber et al., 2000).

Three factors that control translation in neurons have received considerable attention: miRNAs, FMRP, and cytoplasmic polyadenylation element-binding protein (CPEB). miRNAs represent a major field of study unto themselves and have been reviewed previously (Schart, 2009). FMRP is discussed immediately below. CPEB is a sequence-specific RBP that represses translation until stimulated, then responds to signaling events by elongating poly(A) tails of mRNA, which leads to translational activation (Richter and Klann, 2009). To accomplish these tasks, CPEB associates with a number of factors that constitute the cytoplasmic polyadenylation complex; this complex effects polyadenylation-induced translation of specific mRNAs in dendrites in response to synaptic stimulation (Wu et al., 1998). The importance of the cytoplasmic polyadenylation complex in synaptic function is highlighted by the changes in synaptic plasticity that occur in response to depletion of polyadenylation complex factors (Richter and Klann, 2009). The physical biology of CPEB highlights structural behavior potentially similar to other disease-linked RBPs. CPEB exhibits prion-like properties in yeast, and in Aplysia neurons aggregates to form amyloid-like multimers that appear to potentiate synaptic efficacy (Si et al., 2010). Thus, the CPEB-containing cytoplasmic polyadenylation complex is a coherent posttranscriptional molecular mechanism that underlies essential brain function.
**FMRP and fragile X syndrome**

FMRP is a translational repressor that is essential for proper synaptic function. Mutations within the X-linked _FMR1_ gene, coding for FMRP, cause fragile X syndrome (FXS), which is the most prevalent genetic cause of intellectual disability and autism in humans (Garber et al., 2008). The most frequent mutation is an expansion within a CGG repeat located in the 5′-untranslated region of the first exon, where the normal repeat length of 30 increases dramatically. Subjects with repeat expansions of 55–200 are considered to have a premutation, while repeat expansions exceeding 200 cause disease and are classified as full mutations (Penagarikano et al., 2007; Garber et al., 2008). The premutation alleles are unstable and can expand upon meiotic transmission to create a full mutation. Repeat lengths exceeding 200 triplets silence transcription of the _FMR1_ gene causing FXS (Penagarikano et al., 2007).

FMRP is a selective RBP that is highly expressed in the brain, including in dendritic spines (Ashley et al., 1993). FMRP is found associated with ribosomes or in large RNP in the cytoplasm or dendritic fields where it is thought to regulate local RNA translation; however, small amounts of FMRP are also present in the nucleus (Ashley et al., 1993). The RGG-box domain of FMRP mediates binding to mRNA through RNA secondary structures, such as the G-quadruplex (Melko and Bardoni, 2010). Phosphorylation of serine 500 (499 in the mouse) regulates the action of FMRP (Ceman et al., 2003). Phosphorylated FMRP suppresses translation, but dephosphorylation by protein phosphatase-2A occurs in an activity-dependent manner to enable immediate translation of bound mRNAs (Narayan et al., 2008). In the absence of FMRP, target mRNAs normally bound to FMRP are over-translated in the dendritic spine, which leads to excess internalization of the AMPA receptor and enhanced LTD following activation of group 1 metabotropic glutamate receptors (Bassell and Warren, 2008). Conversely, mGluR5 antagonists appear to correct fragile X phenotypes in animal models, providing the basis for clinical trials in patients.

Recent studies indicate how FMRP selectively and reversibly represses translation of its target mRNAs at synapses. FMRP associates with the RNA-induced silencing complex (RISC) and microRNAs (Jin et al., 2004). FMRP appears to regulate translation by acting on the mi-RISC complex containing miR-125a to modulate translation of postsynaptic density protein 95 (PSD-95) (Muddashetty et al., 2011). When FMRP is phosphorylated, FMRP recruits argonaute 2 (Ago2) complexes containing miR-125a and represses synthesis of proteins, such as PSD-95. In response to mGluR signaling, FMRP dephosphorylation leads to the release of RISC from PSD-95 mRNA, which stimulates translation (Muddashetty et al., 2011). miR-125a levels and its association with RISC is reduced at synapses of _Fmr1_ KO mice, leading to excess translation of PSD-95 mRNA and impaired spine morphology (Muddashetty et al., 2011). Dysregulation of microRNAs may thus be a defining molecular signature of synaptic dysfunction in fragile X syndrome and other neuropsychiatric disorders.

**Mammalian target of rapamycin complex 1 signaling: synaptic plasticity, memory, and developmental disorders**

The mammalian target of rapamycin complex 1 (mTORC1) provides a potentially important mechanism for reversing the synaptic dysfunction associated with loss of FMRP action. A mouse model of FXS exhibits increased mTORC1 signaling (Ehniger et al., 2008; Kelleher and Bear, 2008; Hoefffer and Klann, 2010; Sharma et al., 2010). Mouse models of tuberous sclerosis complex (TSC) and knock-out of phosphatase and tensin homolog (PTEN) also exhibit behavior consistent with autism spectrum disorders (ASDs). Both PTEN and TSC1/2 are upstream negative regulators of mTORC1, and multiple phenotypes in PTEN and TSC mutant mice are ameliorated by rapamycin (Butler et al., 2005; Kwon et al., 2006; Ehniger et al., 2008; Zhou et al., 2009). Finally, mice with a deletion for FKBP12, the intracellular receptor of rapamycin, display perseverative and repetitive behaviors that are also tightly correlated with excessive mTORC1 signaling (Hoefffer et al., 2008). Thus, upregulation of mTORC1 signaling and cap-dependent translation may be a common molecular anomaly that contributes to aberrant behaviors in mouse models of ASD. mTORC1 and its downstream effectors represent potential therapeutic targets for the treatment of these developmental disorders.

The mechanisms by which mTORC1 regulates synaptic and cognitive function is an area of avid investigation. mTORC1 regulates cap-dependent translation initiation during both mGluR-LTD, L-LTP, and memory consolidation (Tang et al., 2002; Cammalleri et al., 2003; Hou and Klann, 2004; Banko et al., 2005, 2006, 2007; Gelin et al., 2007; Tsokas et al., 2007; Hoefffer et al., 2008, 2011). However, the mechanisms of translation control downstream of mTORC1 mediating synaptic plasticity and memory are incompletely understood. The development of novel tools such as small molecule inhibitors of elf4E–elf4G interactions, elf4A, and p70 S6 kinase 1, and mice with inducible deletions of mTORC1 effector molecules hold great promise for elucidating the mechanisms underlying signaling in synaptic plasticity and memory by mTORC1 (Ran et al., 2009; Pearce et al., 2010; Hoefffer et al., 2011).

**RNA binding proteins and motoneuron disease**

Motoneuron diseases are frequent phenotypes associated with mutations in RBPs. Examples include mutations in SMN causing SMA (Lefebvre et al., 1995), TDP43, FUS, and angiogenin defects in ALS (Greenway et al., 2006; Ladiger-Tourenne et al., 2010), mutations in SETX for ALS4 (Chen et al., 2004), long expanded polyglutamine repeat domains in ataxin-2 causing spinocerebellar ataxia-2 (Imbert et al., 1996; Elden et al., 2010; Corrado et al., 2011; Lee et al., 2011; Van Damme et al., 2011), and mutations in IGHMBP2 causing infantile spinal muscular atrophy with respiratory distress Type 1 (Grothmann et al., 2001). Many of the RBPs exhibit dual roles that include nuclear functions, such as splicing, and cytoplasmic functions, such as mRNA transport and silencing. Dysregulation of axonal or dendritic transport is a common phenotype associated with mutations in genes causing motorneuron disorders (Sau et al., 2011).

SMA provides an excellent vantage point for reviewing potential mechanisms by which mutations in RBPs can cause disease. Motoneurons appear to be particularly sensitive to diminished SMN function because they exhibit selective degeneration upon mutation of SMA despite its ubiquitous expression (Lefebvre et al., 1995). SMA is usually caused by decreases in protein levels of SMN, and SMN protein levels correlate directly with the disease severity in most cases (Gennarelli et al., 1995; Lefebvre et al., 1997; Grothmann et al., 2001). Decreases in SMN function were originally considered to primarily cause splicing defects, but increased knowledge highlights other potential targets of SMN action. SMN plays an essential role in assembly of the Gemin complex, which is required for spliceosome assembly and SMN is also required in the formation of stress granules (Liu et al., 1997; Pellizzoni et al., 1998; Hua and Zhou, 2004). SMN is also found in neuronal processes within RNP complexes that include β-actin.
mRNA, which is locally translated during growth cone guidance (Sharma et al., 2005; Leung et al., 2006; Al-Ramahi et al., 2007). SMN is also part of a RNP complex with FMRP, highlighting a putative role in local translational regulation (Piazzon et al., 2008). The hypothesis that SMA defects arise solely because of splicing defects seems too simple in view of the diverse RNP granules that contain/require SMN function.

Studies identifying genetic modifiers of SMA point to potentially important connections between translational control and endocytosis. Plastin3 (PLS3) presents as a modifier of SMA in genetic screens and asymptomatic carriers of SMA mutations exhibit increased levels of PLS3 protein (Oprea et al., 2008). Increasing PLS3 levels in embryonic zebrafish greatly enhances motorneuron outgrowth following knockdown of SMN (Oprea et al., 2008). PLS3 also rescues SMN loss-of-function neuromuscular defects in Drosophila and Caenorhabditis elegans (Dimitriadi et al., 2010). PLS3 encodes a conserved and broadly expressed calcium-binding, actin-bundling protein that binds SMN (Satterfield et al., 2002). PLS3 exhibits functional connections with proteins regulating synaptic vesicle endocytosis and translational control, including Endophilin A (EndoA) and Ataxin-2 (Atx2) (Harris et al., 2000; Schuske et al., 2003). Atx2 also interacts with EndoA and TDP-43 (Nonis et al., 2008; Elden et al., 2010). Overexpressing EndoA or Ataxin-2 is toxic in yeast in the absence of Sac6p, the yeast PLS3 ortholog (Ralsker et al., 2005). These data suggest that PLS3, EndoA, and Atx2 proteins interact to regulate endocytosis and mRNA translation.

Investigations of the localization of protein/miRNA complexes provide additional evidence linking translational control with endocytosis. miRNA silencing of mRNA translation requires association with the GW182 and Argonaute (Ago) protein family in the RISC complex (miRNA-induced silencing complex) (Eulalio et al., 2009b). Perturbation of Dicer function in the RISC complex causes motorneuron disease in mice and prevents translational repression by miRNA (Haramati et al., 2010). GW182 binds directly to Ago proteins and loss of GW182 prevents miRNA-mediated gene silencing across species without impacting Ago or miRNA levels (Eulalio et al., 2009a). This process links to endocytosis because Ago2 and GW182 colocalize on the surface of endosomes, which then fuse with multivesicular bodies, for trafficking to lysosomes or recycling to the cell surface (Gibbings et al., 2009; Lee et al., 2009). Endosomal vesicles contain ligand/growth factor receptor complexes whose signaling output continues during trafficking to the multivesicular bodies. The juxtaposition of signaling receptors and GW182/Ago2 RISC complexes in endosomes, combined with the presence of complexes containing PLS3, EndoA, and Atx2, raises the possibility that receptors might regulate mRNA translation in endosomes and multivesicular bodies.

**RNA binding proteins and ALS**

ALS is a rapidly progressing neurodegenerative disease primarily affecting motorneurons (Cleveland and Rothstein, 2001). ALS occurs with an incidence of ~1 in 10,000, appears in midlife, and exhibits an average life expectancy of ~3 years after onset. Two related RBPs, TDP-43 and FUS/TLS, play key roles in the disease (Chen-Plotkin et al., 2010). In addition, mutations in the RNase/RBP, angiogenin, cause ALS (Greenway et al., 2006). More than 40 mutations in TDP-43 have been identified in patients with familial or sporadic ALS, and nearly all mutations cluster in the C-terminal glycine-rich region (Kabashi et al., 2008; Sreedharan et al., 2008; Pesiridis et al., 2009). Almost all patients with sporadic ALS, as well as patients with familial ALS due to TDP-43 mutations, show abnormal accumulations of TDP-43 in the cytoplasm of spinal cord motorneurons (Neumann et al., 2006; Mackenzie et al., 2007). TDP-43 also accumulates in neurons in cases of frontotemporal lobar degeneration with ubiquitin-positive inclusions (FTLD-U), but in these cases TDP-43 inclusions can be cytoplasmic or nuclear. Patients with ALS caused by FUS mutations show cytoplasmic accumulation of FUS in spinal cord motorneurons. Patients with familial ALS caused develop cytoplasmic inclusions containing FUS or TDP-43, but not both (Kwiatkowski et al., 2009; Vance et al., 2009). FUS and TDP-43 both exhibit a correlation between the tendency to accrue cytoplasmic aggregates in cell models and the clinical disease severity (Dormann et al., 2010). The presence of TDP-43 pathology in ALS and FTLD-U provides a molecular link between the two diseases (Neumann et al., 2006).

Accruing evidence points to a central role for altered RNA-processing pathways in the pathogenesis of ALS (Lagier-Tourenne et al., 2010). TDP-43 and FUS are predominantly nuclear in dividing cells and associate with SGs during stress. Angiogenin can be nuclear or cytoplasmic, and is also secreted (Greenway et al., 2006; Emara et al., 2010). Mutations in FUS largely interfere with a noncanonical nuclear localization signal, leading to abnormal cytoplasmic localization. In neurons, TDP-43 is also present in RNA granules in dendrites and functions as synaptic activity-responsive factor; localization of TDP-43 at dendritic spine is highly regulated by neuronal activity (Wang et al., 2008). Synthetic stimulation by addition of KCl increases the size and numbers of mRNPs containing TDP-43 in dendrites (Wang et al., 2008). TDP-43 and FUS readily form stress granules that are largely cytoplasmic, but can be nuclear depending on the conditions. Angiogenin cleaves tRNA to promote SG formation (Emara et al., 2010). Disease-linked mutations in TDP-43 and FUS increase the tendency of TDP-43 to form SGs in response to stress (Colombrita et al., 2009; Bosco et al., 2010; Dormann et al., 2010; Liu-Yesucevitz et al., 2010; Dewey et al., 2011; McDonald et al., 2011; Sun et al., 2011). Mutations in TDP-43 also increase the tendency of TDP-43 to bind other proteins associated with SGs, such as TIA-1 or FUS (Ling et al., 2010; Liu-Yesucevitz et al., 2010). SG formation appears to be directly linked with the pathology of the disease because in cases of ALS and FTLD-U TDP-43 inclusions colocalize with SGs in human brain (Liu-Yesucevitz et al., 2010). Protein aggregation is thought to play a central role in the pathophysiology of many degenerative diseases, and the role of protein aggregation in SG formation raises the possibility that SG biology contributes to other neurodegenerative diseases. For instance, aggregates of huntingtin protein and prion protein both colocalize with SG proteins (Waeber et al., 2001; Goggin et al., 2008).

Whether the pathological process of RBP aggregation also contributes to neurodegeneration remains to be determined. Cytoplasmic sequestration reduces levels of nuclear FUS and TDP-43. Neurodegeneration could arise from increased levels of cytoplasmic TDP-43 and FUS, loss of nuclear TDP-43 and FUS, or increased formation of RNA granules, such as SGs. Animal models generated by overexpressing TDP-43 (mouse, Drosophila, and C. elegans) show age-dependent motor dysfunction and some evidence of neurodegeneration (Ash et al., 2010; Li et al., 2010; Liachko et al., 2010; Wils et al., 2010; Xu et al., 2010). However, these models do not develop large amounts of cytoplasmic TDP-43 inclusions. This could indicate that inclusion formation is not central to the disease process, or it could indicate that overexpressing TDP-43 causes toxicity by upregulating its normal biological function, independent of the pathological pro-
cesses associated with ALS. For instance, recent studies identify large numbers of neuronal transcripts linked to synaptic functions whose splicing is affected by TDP-43 levels (Polymenidou et al., 2011). TDP-43 also binds numerous proteins linked to translational control (Freibaum et al., 2010). Overexpressing TDP-43 in animal models could affect splicing of synaptic proteins either through effects caused by TDP-43 dosage or effects caused by TDP-43 mutations.

Identification of key roles for TDP-43 and FUS in ALS suggests new concepts for the mechanisms of motorneuron diseases, as well as autism spectrum disorders. Both TDP-43 and FUS are aggregation-prone proteins that harbor prion-like domains and can be mutated in ALS, raising the intriguing possibility that they might sit at the tip of an iceberg for RBPs in ALS. Could additional RBPs, with properties similar to those of TDP-43 and FUS (e.g., aggregation-prone) also contribute to the disease? Mutations that modify the tendency of other proteins to aggregate appear sufficient to induce ALS. Large polyglutamine expansions of ataxin-2 (>35) cause spinocerebellar ataxia-2 (Imbert et al., 1996; Sanpei et al., 1996). However, patients with moderate polyglutamine expansions in ataxin-2 (27–33 repeats) are at increased risk of ALS (Elden et al., 2010; Chen et al., 2011; Corrado et al., 2011; Lee et al., 2011; Ross et al., 2011; Van Damme et al., 2011). The role of ataxin-2 as a RBP that participates in RNA granule biology raises the possibility that factors that increase formation of RNA granules might increase the risk of disease. Individuals subjected to the stress of repetitive head trauma, such as professional athletes who played American football or soccer/European football, exhibit increased risk of ALS (Abel, 2007; Chen et al., 2007; Chio et al., 2009; McKee et al., 2010). A repeated cycle of aggregation and disaggregation, over the course of a lifetime might be prone to misregulation, leading to a failure to restore TDP-43 to the nucleus, resulting in its cytoplasmic accumulation and subsequent disease pathology. Perhaps polyglutamine expansions in ataxin-2 contribute to ALS risk by hampering the ability of stress granules to dissolve properly and/or by reducing the efficiency by which TDP-43 returns to the nucleus, with the cumulative effect being a greater propensity for TDP-43 to aberrantly accumulate in the cytoplasm (Elden et al., 2010). This concept suggests that pathogenesis of ALS and other motorneuron disorders might be deeply rooted in core cell-biological pathways that are inherently prone to protein aggregation.

Conclusion

The family of RBPs includes >500 proteins. Many of these proteins have multiple functions and multiple sites of activity, ranging from the nucleus to the synapse. The predilection for mutations in RBPs to cause brain disorders suggests that the functional abnormalities are impacting on a feature selective to neurons. Mutations in RBPs associated with neurodegenerative diseases exhibit several characteristics in common: a strong tendency to aggregate and form RNA granules, and a role in mRNA transport. In the nucleus, both TDP-43 and SMN function in splicing. In contrast, FMRP exhibits a primary role in regulating synaptic efficacy, and loss of FMRP leads to mental retardation rather than neurodegeneration. The biology of RBPs also presents novel strategies for therapeutic intervention. Studies of FMRP delineate a critical role in translational repression that is tightly regulated by mTOR and able to be modulated by the mTORC1 inhibitor rapamycin. Increased aggregation of RBPs contributes to the pathology of ALS and FTLD-U. Aggregation of RBPs is reversible, which raises the possibility that pharmacological interventions moderating RBP aggregation might decrease the progression of motorneuron pathology and also delay symptomatic progression.

References


Liu-Yesucevitz et al.

Local RNA Translation J. Neurosci., November 9, 2011 • 31(45):16086 –16093