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Review

mRNA trafficking and local translation: the Yin and Yang of regulating mRNA localization in neurons

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Localized translation and the requisite trafficking of the mRNA template play significant roles in the nervous system including the establishment of dendrites and axons, axon path-finding, and synaptic plasticity. We provide a brief review on the regulation of localizing mRNA in mammalian neurons through critical post-translational modifications of the factors involved. These examples highlight the relationship between mRNA trafficking and the translational regulation of trafficked mRNAs and provide insight into how extracellular signals target these events during signal transduction.

Keywords mRNA trafficking; local translation; RNA binding proteins; post-transcriptional regulation

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Introduction

Interest in mRNA localization and trafficking began in earnest with reports of the asymmetric distribution of mRNA within the cytoplasm of different cell types [1–6]. The early characterization of translation machinery in dendrites suggested that mRNA would be localized there as well [7–9]. mRNA is also translated locally in developing and regenerating axons of neurons [10–12]. Now it is evident that mRNA is translated in neurons in a very spatio-temporally controlled fashion that is likely to be integral to the way the brain processes and stores information [13–16]. The interconnection between mRNA trafficking and local translation has been observed for the expression of important neuronal regulatory proteins, providing many contributions to the field of mRNA localization. Yet the fundamental question remains, how do mRNAs get to the dendrites and axons? Proposed models have attempted to explain the mechanism of neuronal trafficking but there is no conclusive data to evaluate the applicability of the models.

Important signal transduction pathways regulate the activation of translation [17]. Stimulation of these signaling pathways within the cytoplasm can be spatially limited in neurons by focal sources of activation, such as individually active synapses or attractant-proximal regions of a growth cone [18–21]. These sites of local translation activation provide a spatial cue within the cytoplasm where a localized domain for translation exists. An mRNA must be trafficked away from the cell body to gain access to these localized translation domains. As a result, active trafficking of mRNA is necessary for mRNAs to reach distal sites for translation. How mRNA is actively sorted to axons and dendrites in an mRNA-specific manner is a central question to mRNA trafficking.

Localization of mRNA in Ribonucleoprotein Particles

Many studies suggest localized mRNA is actively trafficked within the cytoplasm by interaction with cognate RNA binding proteins (RBPs), as well as other factors, in complexes called ribonucleoprotein particles (RNPs, or mRNPs when mRNA is involved) [22]. Several different proteins that bind to trafficked mRNAs can be observed routinely in a non-uniform and punctate distribution within the cytoplasm [23,24]. This suggests that they are found in large complexes consisting of numerous putative mRNP transport factors that have come to be known as RNA granules. Biochemical data supports a view of these granules as large heterogeneous entities containing RNA as well as RBPs. Several different studies that identified components of these complexes support this view, and while several proteins have been identified by multiple independent RNA granule purification strategies, no consensus for what constitutes these RNA granules has yet emerged [25–30]. The number of mRNA granule associated RBPs highlights the numerous unanswered questions about their role in mRNA trafficking, how mRNA is trafficked, how

trafficking is regulated, as well as how many different mechanisms might co-exist.

We consider that for mRNA to traffic and translate locally there must be multiple molecular steps to assemble a localizing mRNP (L-RNP) that is sensitive to signals for initiating translation in distal regions of the cytoplasm (**Fig. 1**). Initially, mRNAs are thought to assemble into transport granules, where the mRNA may be stabilized and translationally silenced [18,31]. These granules can contain signals to interact with cytoskeletal elements that provide spatial guidance for transport or local anchoring [18,22]. Cytoskeleton components that direct or guide mRNAs can be molecular motors or cytoskeletal filaments themselves, but how specific mRNAs connect to the motor complexes remains mysterious. The L-RNP encodes the information to direct mRNA to a site in the cytoplasm where it is remodeled so it can be translated. Remodeling, defined as altering the mRNP composition and/or structure, can occur through loss of bound factors, joining of novel factors, changing interaction among existing components, or combinations of these possibilities. Remodeling is the crucial step that activates translation of the L-RNP and many examples indicate that this occurs through post-translational modification. After translation ensues, the stability of the mRNA may also help in regulating the amount of protein that can be produced. Signals dictating stability are usually encoded within the mRNA sequence too [32]. The final localization of an mRNA, as defined by where it can be found within the cytoplasm at any given time, is influenced by its ability to traffic, as well as the regulation of its translation and stability. An mRNA can thus achieve a particular spatial distribution (also referred to as localization) within the cytoplasm through controlling these events.

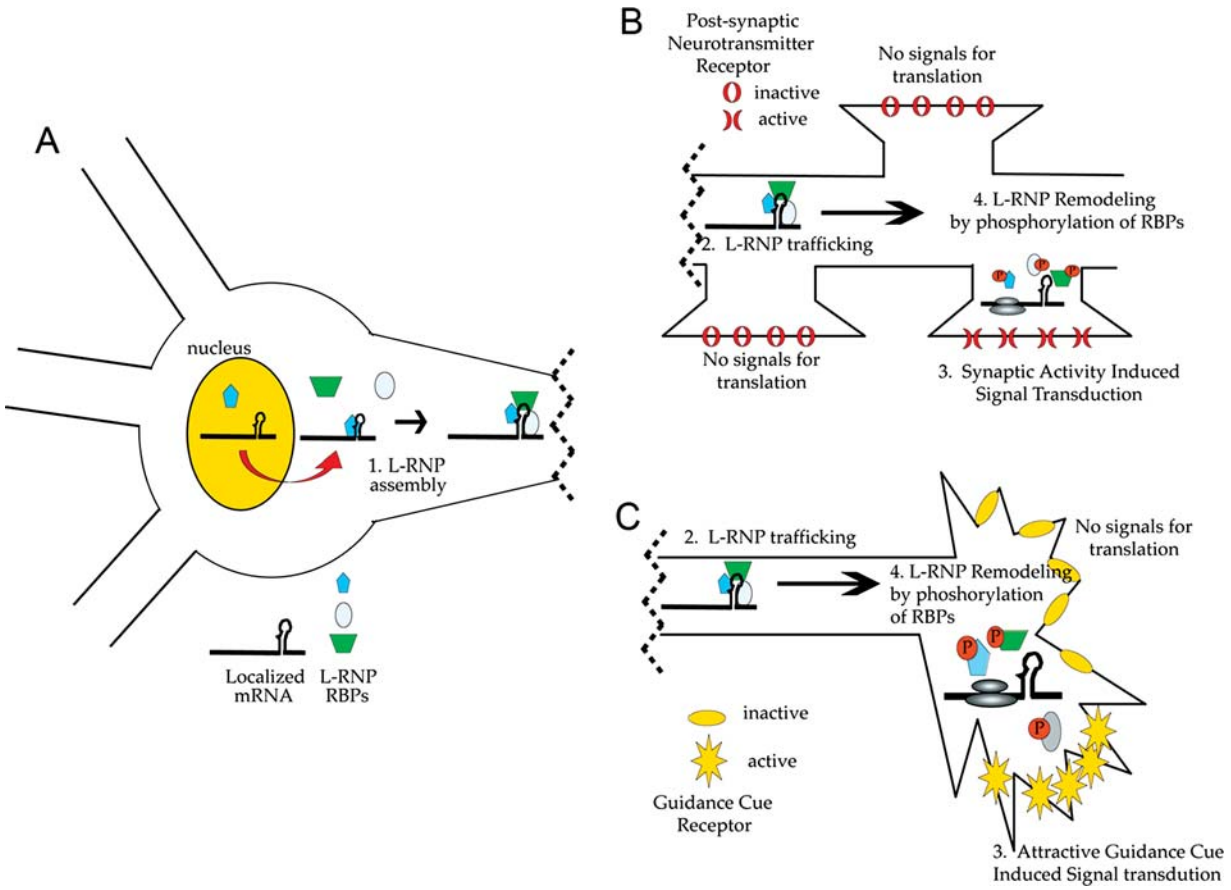

Figure 1 mRNA trafficking to localized translation domains (A) L-RNP formation occurs in the cell soma, where nuclear RBPs (blue pentagon) bind mRNAs to be localized and export with them to the cytoplasm. After export, cytoplasmic RBPs or other L-RNP factors join the mRNA to form a translationally repressed L-RNP (step 1). The L-RNP interacts with the cytoskeleton (not pictured) to traffic the L-RNP (step 2) to either dendrites (B) or axons (C). The factors and connections to the cytoskeleton remain poorly understood, although microtubule motor dependent cargo trafficking plays a role in this process. Trafficking L-RNPs are formed so that they initiate translation on encountering a translation inducing signaling environment (step 3). (B) In dendrites L-RNPs remodel when they encounter the cytoplasm near activated synapses (step 4). The kinases activated by synaptic activity modify factors on the L-RNP (P groups attached to RBPs) to induce remodeling of the L-RNP so that the RNA is now available for translation. The lack of signaling in inactive synapses can explain why only active synapses activate translation. (C) In axon growth cones L-RNPs remodel when guidance cues asymmetrically signal to growth cones, activating the kinases that phosphorylate RBPs in the L-RNP. The text describes examples of RBPs contained within L-RNPs that are modified by signal transduction kinases.

RBPs and Post-translational Modifications

The common thread to studies of mRNA trafficking is RBPs. They regulate processing steps of mRNA and are the most numerous type of protein that co-purify in RNA granules. The molecular steps described above imply L-RNP formation by RBP binding, and L-RNP remodeling by RBP modification in distinct spatio-temporal distributions. How do RBPs accommodate all the steps involved in trafficking mRNA in the cytoplasm? The steps above imply an assembly and remodeling/disassembly process, suggesting that regulation of binding may be involved in L-RNP function, as early as during transcription [33].

There are many reports of RBPs that are phosphorylated and these modifications can result in a change in affinity for RNA or for interacting proteins. Phosphorylation has the potential to play central roles in coordinating mRNA trafficking and localized translation. We suggest that changing RNA binding or co-factor binding activity by phosphorylation of RBPs is central to regulating these events. If so, then many questions arise: What factors are the targets for phosphorylation? What steps in the trafficking and local translation pathway are these modifications required for? What signaling mechanisms are required for these modifications and when do they occur? Here, we examine several RBPs that have roles in mRNA trafficking and local translation whose function is regulated by their phosphorylation state.

Heterogeneous Nuclear Ribonucleoprotein A2/B1 (hnRNP A2)

In both neurons and oligodendrocytes hnRNP A2 is involved in the localization of several mRNAs [34]. hnRNP A2-dependent mRNA localization is observed in mRNAs that contain elements referred to as hnRNP A2 response elements (A2REs [35]). The mechanism by which hnRNP A2 mediates trafficking has not been explicitly elucidated. But, a microtubule-associated protein, called tumor-overexpressed gene (TOG) interacts with hnRNP A2 and co-precipitates with hnRNP A2 in cytoskeleton fractions of cell extracts. Importantly, hnRNP A2 regulates the expression of myelin basic protein (MBP) through A2RE-dependent mRNA trafficking as well as translational repression during transport [36]. Translational inhibition of A2REs is mediated by an interaction of hnRNP A2 with hnRNP E1, another RBP that functions as a translational repressor of mRNAs in other cell types [36]. Interestingly, hnRNP E1 together with hnRNP K prevent translation initiation of the 15-lipoxygenase mRNA in erythroid cells by prevention association of the 60S ribosomal subunit with the 48S pre-initiation complex, although it is possible another mechanism of repression operates in the nervous system [37]. hnRNP A2 thus represents an L-RNP protein that plays critical roles in both RNA trafficking and translational repression.

hnRNP A2 is a target of Fyn, a Src family tyrosine kinase expressed in the nervous system. Hypomyelination is observed in Fyn-deficient mice; therefore, modification of hnRNP A2 by Fyn has been studied in oligodendrocyte lineage cells since this may play a functional role in myelination by controlling spatio-temporal expression of MBP [38]. Activation of Fyn stimulates translation of an A2RE-containing translation reporter construct and leads to phosphorylation of hnRNP A2 on an unidentified site. This increase in translation is co-incident with a shift of hnRNP A2 from RNA-containing to RNA-free cellular fractions [38]. These results indicate phosphorylation of hnRNP A2 by Fyn releases MBP mRNA from its translationally silenced state, perhaps by concomitant release of hnRNP A2 and potentially other A2-interacting factors from MBP L-RNP granules. Both Fyn and hnRNP A2 are expressed in neurons, where A2RE-dependent mRNA trafficking mechanisms also function. However, whether Fyn modification of hnRNP A2 will have the same effect in neurons has not yet been explicitly demonstrated. Whether loss of RNA binding, A2 co-factor binding, or both is the result of Fyn phosphorylation are important questions that need to be answered to understand its effects on MBP mRNA trafficking and translation.

Zipcode Binding Protein 1 (ZBP1, IMP1, VICKZ1)

ZBP1 was first identified in chick embryonic fibroblasts as interacting with the ‘zipcode’ trafficking sequence in the 3’ untranslated region (UTR) of the β-actin mRNA [39]. ZBP1 is a highly conserved RBP harboring six RNA-binding domains. A crystal structure of two of these domains interacting with a conserved RNA motif in the β-actin zipcode has been solved [40]. β-actin mRNA localizes to the growth cone of neurons and its distribution within the growth cone is responsive to both attractive and repulsive cues [41]. ZBP1 and β-actin mRNA localize to the growth cone of chick neurons in response to neurotrophins, and this effect on localization involves interaction of ZBP1 with the β-actin 3’ UTR [42]. β-actin mRNA also localizes to dendritic spines in hippocampal neurons where it has a role in dendritic spine morphology and arborizatioin [43,44]. Interestingly, ZBP1 can be phosphorylated by Src tyrosine kinase at a conserved tyrosine residue (amino acid 396 in chicken ZBP1) that does not lie within the conserved β-actin zipcode-binding domain, although data suggest this modification disrupts RNA binding [40,45].

It was recently shown that brain-derived neurotrophic factor (BDNF) signaling activates Src during growth cone turning in rodent cortical neurons, leading to phosphorylation of ZBP1Y396 in growth cones. The trafficking of β-actin mRNA to growth cones was not impeded by a non-phosphorylatable Y396F mutant protein; however, a BDNF stimulated increase in translation of β-actin was inhibited by expression of this mutant [46]. This suggests that remodeling of the L-RNP for translation in the growth cone requires phosphorylation of ZBP1 at this site. Cell-free translation data suggest that ZBP1 inhibits translation of β-actin mRNA by preventing 60S subunits from joining the 48S pre-initiation complex [45]. Based on all these data it is hypothesized that the mechanism by which Src-mediated phosphorylation of Y396 frees β-actin mRNA for local translation in the growth cone is through release of ZBP1, thereby allowing 60S ribosomal subunits to enter the initiation complex. Despite this elegant example of regulated localized translation, the mechanism of mRNA trafficking seems to remain unaffected, since the localization of β-actin mRNA was not changed by this mutation. With the crystal structure of ZBP1's zipcode binding domain, it may be possible in the near future to dissect the role of ZBP1 in L-RNP formation from translation to help shed more light directly on the molecular events involved in trafficking prior to translation activation.

Cytoplasmic Polyadenylation Element Binding Protein 1 (CPEB1 or CPEB)

The conserved CPEB1 was initially identified as a protein that mediates translational activation of cytoplasmic polyadenylation element (CPE) containing mRNAs in *Xenopus* oocytes whose polyA tails have been removed [47]. In neurons, CPEB1 binds to the CPEs in substrate RNAs and can recruit the translational repressor protein neuroguidin, which plays an analogous role in repressing translation that the maskin protein plays in *Xenopus* oocytes [48]. Translational repression by a CPE is overcome by phosphorylation of CPEB, which results in recruitment of the polyadenylation machinery to the CPE containing mRNA [49]. This results in elongation of the polyA tail, which in turn recruits translation factors to recognize these mRNAs and begin translation.

In neurons CPEB1 can be found near the post-synaptic density, and the mRNA for the α-subunit of the Calmodulin-dependent protein Kinase II (α-CaMKII) is a CPE-containing mRNA that undergoes N-methyl-D-aspartate (NMDA) receptor dependent cytoplasmic polyadenylation, even in purified synaptoneurosome preparations [50,51]. NMDA receptor stimulation has been linked to the phosphorylation of CPEB1 by activation of the Aurora A kinase that can phosphorylate CPEB1 at a conserved site (Ser 174 in *Xenopus* and Thr171 in mouse) [52]. The result of this modification is the CPEB-mediated recruitment of the cytoplasmic polyadenylation machinery to CPE-containing mRNAs in neurons. Elongation of the polyA tail on α-CaMKII mRNA will then translationally activate this and other mRNAs that contain CPE elements [52]. Interestingly, CamKII itself can also phosphorylate this conserved site within CPEB1, and the phosphorylation state is sensitive to activity levels of protein phosphatase 1 (PP1). This dynamic control of CPEB1 phosphorylation by the activity of glutamate receptors could therefore serve as an important cue for localizing synaptic activity-dependent translation at synapses [53–55]. Several studies link these biochemical changes in CPEB1 to synaptic plasticity in brain function, suggesting this mechanism helps interpret synaptic activity to determine, which synapses require local protein synthesis for plasticity during learning and memory [53,56,57].

In addition to its characterized role in translational activation, evidence suggests that CPEB1 may regulate mRNA trafficking in neurons as well [58]. Reporter RNAs containing CPEs are trafficked to dendrites of rat hippocampal neurons [58,59]. α-CaMKII, MAP2, and BDNF are mRNAs that contain an endogenous CPE and their localization can be sensitive to CPEB1 levels [58–60]. A CPE element is involved in accumulation of syntaxin mRNA at the axon hillock of *Aplysia* sensory neurons during long-term facilitation following serotonin stimulation [61]. However, the role of this conserved phosphorylation site in trafficking of the mRNA to these sites has not been specifically addressed, and in *Aplysia*, this site is not conserved [62,63]. Fluorescently tagged CPEB1 deletion variants lacking the phosphorylation site did not show a different distribution than wild-type CPEB1 in *Xenopus* retinal neurons [64]. This raises the question of whether this phosphorylation site might be strictly involved in remodeling the RNP in response to local translation activation cues. If so, then an important question to be answered is how do the CPE-containing mRNA traffic to the post-synaptic sites?

Polypyrimidine-tract-binding Protein (PTB, hnRNP I)

PTB plays many different functions in post-transcriptional regulation including splicing, stability, and localization. In the nervous system PTB plays a role in repressing the splicing of several important neural mRNAs including the D2 dopamine receptor, GABA (A) receptor gamma 2 subunit, clathrin light chain B, NMDA NR1 subunit, and c-Src [65–68]. There are several lines of evidence for a role for PTB in mRNA localization as well. The *Xenopus* ortholog to PTB is important for localizing Vg1 mRNA in oocytes [69]. Knockdown of PTB inhibits neurite outgrowth in

PC-12 cells, and PTB-mediated mRNA localization appears to also be involved in neurite outgrowth through regulating β-actin mRNA localization [65]. PTB associates with β-actin mRNA in cytoplasmic extract, and a PTB binding motif is conserved in the β-actin zipcode [65]. In this case the localization of PTB at neurite terminals appears to be dependent on phosphorylation of PTB at Ser16 by cyclic-AMP- dependent protein kinase (PKA) [70]. This site is within the nuclear localization sequence and not within its RNA binding domains and should not therefore affect RNA binding directly [70]. The phosphorylation of Ser16 increases cytoplasmic levels of PTB, which has significant L-RNP regulatory potential, since acute changes in the nucleocytoplasmic distribution may provide many remodeling possibilities. It is simple to hypothesize how nuclear localization of PTB sequesters it from the cytoplasmic pool of trafficking RNAs in the inverse way that nuclear export sequences sequester transcription factors from the transcription machinery in the nucleus. A sudden release of the nuclear pool of PTB by activation of the PKA pathway has the potential to rapidly remodel β-actin mRNA and other cytoplasmic substrates it was previously sequestered from, such as internal ribosomal entry sites [71,72]. There are many possibilities for such remodeling of cytoplasmic RNPs, such as competition with other RBPs, or acting as a cofactor for other proteins previously unable to associate with an mRNA. Interestingly, expression of PTB in the nervous system appears to be limited to neural progenitor cells, glia, and other non-neuronal cells, while a paralog called neuronal/brain PTB (nPTB, brPTB, or Ptbp2) is expressed in neurons [73]. The amino terminus of the mouse Ptbp2, including the ser16 residue, is mostly identical to that of mouse PTB (sequences compared from www.ensembl.org). Since PTB is not expressed in mature neurons demonstration of a similar properties for localization involving nPTB will be required to know if this mechanism could be applicable during synaptic plasticity in neurons. However, this mechanism can certainly function during neurogenesis where PTB remains expressed.

Conclusion and Perspectives

Understanding the mechanism of how mRNA traffics in the cytoplasm of metazoans has been complicated by using the assay of mRNA localization, which may be influenced by the translatability of an mRNA. There might be convergence of trafficking and translation through individual RBPs although no direct example of this has been demonstrated. There is also no clear molecular definition of a 'minimal L-RNP complex' in mammals as has been characterized in yeast [74]. Given the complex composition of RNA granules it is reasonable to think one may not even be found. Determining the mechanism of transport will require the ability to study the correlation between movement of mRNAs in real time directly with the sequences within the mRNA in living cells and/or in cell free assays. Live imaging systems for the study of mRNA movements have been developed in recent years and are still in early phases of application, although advances are being made [75,76]. Minimizing the sizes of RNA sequence that correlate with specific movements will provide a narrow handle for biochemical experiments that can help elucidate how these sequences work to mediate trafficking.

The studies reviewed here pose some very interesting mechanistic questions for the process of localized translation. Cell-free translation assays suggest both hnRNP A2 and ZBP1 are involved in preventing 60S joining as a mechanism of inhibiting translation of a trafficked mRNA. But, it is not clear as to whether one can infer that this means trafficking mRNAs engage the 40S subunit prior to and during trafficking, and await remodeling before a 60S subunit can join. However, if this was the case, many more questions would follow: Are the large subunits present at sites of local translation? How would large ribosomal subunits get transported if they are not engaged in translation on a localizing mRNA? Explicit support for this mechanism in living cells would be challenging but would be a very exciting extension of the *in vitro* studies.

We have reviewed examples where post-translational modifications have had demonstrated effects on mRNA trafficking or local translation in the mammalian nervous system. We expect that post-translational modification of other identified L-RNP RBPs by signal transduction pathways will be critical to mechanisms of localized translation. Proteins such as Staufen1 and Staufen2, Translin and Trax, Nova, the ELAV families of proteins as well as numerous other RBPs have been linked to local translation or trafficking, directly or indirectly, in neurons as well as other cell types [77–82]. Three other paralogous CPEB proteins (CPEB2, CPEB3, and CPEB4) are also conserved, and expressed in the nervous system [83–85]. The available evidence suggests that these proteins are probably not functionally equivalent to CPEB1 despite their similarity and they may mediate translational repression by a different mechanism [86]. Understanding the roles that modification of any of these factors plays in regulating the translation and trafficking of any mRNA remains an under-explored territory, but lies at the intersection of these intertwined processes.

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