Local Protein Synthesis in Neurons

and the role of microRNA in activity-dependent translational regulation

Amir Kadivar

Abstract

mRNA localization and local protein synthesis have emerged as a universal mechanism with high spatiotemporal resolution involved in many developmental and adaptative processes of multicellular organisms. Similarly, in recent years, miRNA-mediated translational regulation has been understood as an integral component of gene regulatory networks. Here we review the findings that implicate both of these processes in activity-dependent plasticity of neurons as well as the challenges facing the further development of this field of research.

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1 Introduction

Neurons exhibit a variety of structural adaptations in a manner dependent on external stimuli. In growing neurons, axonal development follows growth factor cues released by post-synaptic targets. In mature neurons, pre-synaptic and post-synaptic adaptations in structure and excitability occur in an activity-dependent fashion. The former process is crucial in the neural patterning and wiring of the nervous system and the latter process underlies the plasticity required for memory formation,

learning, and a variety of higher cognitive capacities. Plasticity occurs in two qualitatively distinct timescales. Short term plasticity, for instance early long-term potentiation (E-LTP), appears to be dependent upon local adjustments to electrophysiological properties (e.g. neurotransmitter sensitivity and electrical excitability). Furthermore, early plasticity appears to be independent of nuclear transcription and is typically reversible. Long term plasticity, for instance late long-term potentiation (L-LTP), has been long understood to involve new protein synthesis and involve consolidated morphological changes (although as we will see, the early phase, too involves new protein synthesis). Although the distinction between early and late phase adaptations is not quite sharp, the dynamics appear to reflect fundamental neural properties since they are also seen in behavioral studies of memory.

Given the large size and highly polarized character of neurons, the spatiotemporal regulation of stimulus-dependent adaptations pose questions in terms of gene expression (at the transcription or translation level) and subcellular transport. In the past few decades mRNA localization as well as miRNA translational regulation have emerged as evolutionarily conserved mechanisms with high temporal and spatial resolution involved in assymetric developmental and plastic processes. In this paper, we review the functional role and underlying mechanisms for mRNA localization and local protein synthesis in neurons. Specifically, we will focus on the role miRNA-mediated translational regulation in activity-dependent morphological and electrophysiological adaptations in neurons.

1.1 mRNA Localization: an evolutionarily conserved process

Until recently, mRNA localization seemed to be an isolated process utilized by a few transcripts during critical developmental periods in highly assymetric cells. However, it is currently understood that localization of mRNA to specific subcellular compartments (and subsequent local translation) is a common, evolutionarily conserved process (Fig. 1).

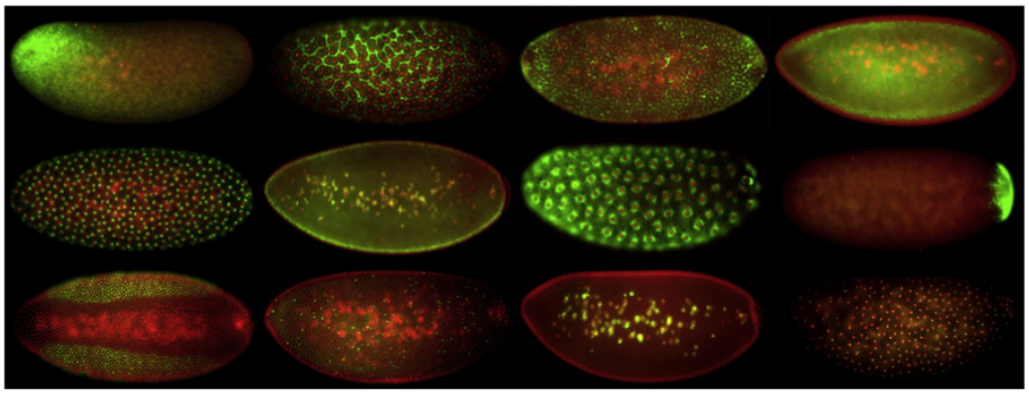

Figure 1: Almost two thirds of mRNA transcripts in *Drosophila* embryos show striking patterns of subcellular localization (Martin and Ephrussi 2009).

For instance, in budding yeast, the mRNA transcripts for the transcriptaional repressor ASH1 localize to the bud tip of a dividing cell ensuring proper mating type switching between mother and

dauther cells. Similarly, oocytes of the fruit fly *Drosophila* and the frog *Xenopus* exhibit anterior and posterior localization of several mRNA transcripts. This localization has been shown to underly the establishment of morphogen gradients required for embryonic spatial patterning and cell fate determination. In mature fibroblasts, β-*actin* mRNA localize to the lamellipodia where local translation drives cytoskeletal-induced motility. Similarly, in oligodendrocytes, the myelin basic protein (MBP) mRNA localizes to distal sites of myelination (Fig. 2; Martin and Ephrussi 2009; Costa-Mattioli et al. 2009; Sutton and Schuman 2006; Holt and Bullock 2009).

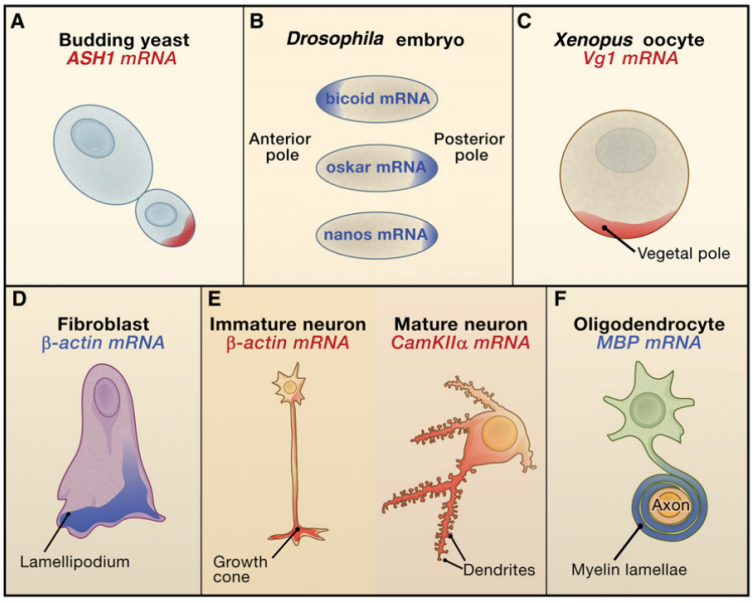

Figure 2: mRNA localization is a conserved evolutionary process in various multicellular organisms (Martin and Ephrussi 2009).

There are several advantages to regulating gene expression by mRNA localization. First, mRNA localization allows for high temporal resolution in the reaction of the gene network in response to internal or external stimuli. Second, localization allows spatial restriction of gene expression which may be crucial for proper function (especially when ectopic expression of certain protein products is toxic). Finally, the default alternative to mRNA localization, which involves targetting protein products to distal sites of interest, is disadvantageous from the point of view of economy: a single mRNA transcript can be transported once and used translated multiple times to produce large amounts of the protein product (Martin and Ephrussi 2009; Costa-Mattioli et al. 2009; Holt and Bullock 2009).

All these advantages are relevant in the nervous system: neurons are highly polarized (in morphology and function) and thus require spatially organized patterns of sustained differential gene expression. Aditionally, this differential pattern of gene expression must respond with high temporal resolution to external stimuli (growth factor cues during development and synaptic signals in mature neurons). Furthermore, the sheer size of neurons (with the distance between dendritic or axonal processes from the soma being orders of magnitude larger than the radius of soma) amplifies the economy advantage of mRNA localization. Finally, in the case of oligodendrocytes, MBP can be toxic or deleterious in

proximal cell compartments and, therefore, exclusively distal translation is a requirement for survival (Martin and Ephrussi 2009; Costa-Mattioli et al. 2009).

1.2 mRNA Localization: mechanisms

Targetting mRNA transport to specific subcellular compartments has multiple functional requirements. First, there must be a molecular mechanism that tags localized transcripts for proper localization. Second, translation and degradation must be inhibited throughout transport. Third, translational machinery must also be available at the site of localization.

The cellular "address" is is encoded by *cis*-acting elements, known as *mRNA localization elements*, which predominantly reside in the 3' UTR of the mature transcript. Almost all these localization elements appear in high repeat numbers and have a stem loop secondary structure which appears to be essential for proper targetting. The crucial significance of this addressing scheme is that 3' UTRs are free to evolve various targeting schemes without interfering with the protein product sequence. Additionally, the redundancy in the localization elements allows for combinatorial combination of multiple regulatory processes. The latter two requirements are satisfied through the use of RNA transport granules in localization. The most important components of the *trans*-acting components of RNA granules are Zipcode Binding Proteins (ZBP) and Staufen (both of which bind 3' UTR stem loop structures), Exon Junction Complex (ECJ) proteins (which bind to mRNAs during splicing in the nucleus), and ribosomal RNA. Finally, transport and anchorage of localized granules to sites of interest rely on the actin and microtubule cytoskeletal infrastructure (Bramham and Wells 2007; Costa-Mattioli et al. 2009; Martin and Ephrussi 2009; Holt and Bullock 2009).

2 Local Protein Synthesis in Neurons

The first concrete evidence that local protein synthesis is critically required for synaptic plasticity came from microlesion studies of neurotrophin-induced plasticity in rat hippocampal slices. Dendritic trees and axonal terminals of post-synaptic and pre-synaptic cells that were separated from their cell body were able to show the characteristics of short-term plasticity, as measured by increased EPSP amplitude (Kang and Schuman 1996). Similarly, but at a different level, it was later shown that intense synaptic activity leads to rapid local translation of activity-regulated cytoskeletal (Arc) protein as well as nuclear upregulation of transcription followed by targeted delivery of Arc mRNA to active dendritic sites (Steward and Worley 2001).

Another interesting find involves isomorphs of the brain-derived neurotrophic factor (BDNF). Alternative splicing of the corresponding gene leads to two main variants of BNDF with identical protein coding regions but with significantly different 3' UTR lengths. In accordance with general mechanisms of mRNA localization, long 3' UTR variants were targetted for dendrites whereas short 3' UTR variants remained close to the soma as observed by real-time PCR (RT-PCR) of rat CA1 and cortical

neurons. Furthermore, using fusion fluorescent transcripts containing long and short UTR variants it was shown that the long 3' UTR is sufficient for dendritic targetting *in vivo*. Most importantly, mutant mice with constitutively short 3' UTR in the *Bdnf* gene showed dysmorphogenesis in dendritic spines (An et al. 2008).

These findings pose a further question: aside from temporal organization of protein synthesis to allow for a rapid response and a long term re-supply of local translation machinery, why are some proteins exclusively translated in the soma while others are also translated in dendrites? Two factors appear relevant in this regard. First, different components of plasticity-related complexes, like the postsynaptic density (psd) or the NMDA receptor complex (NRC), have different half-lives. This means although their transcription should be triggered by the same external stimulus, their translation must be coordinated according to their turnover rates. Second, certain protein-protein interactions in these complexes require cotranslational assembly (Steward and Worley 2001; Bramham and Wells 2007) which, again, would require local protein synthesis in axonal or dendritic sites.

2.1 Neuronal mRNA Localization: mechanisms

The characterization of the molecular components of RNA granules responsible for transporting mRNA to distal sites have shown two important characteristics. First, the distribution of RNA binding proteins (RBP) in granules are not uniform. Second, RNA granules are not translationally competent and instead, act as local storage compartments for mRNAs under translational arrest. Furthermore, norhtern blot and RT-PCR experiments show that the mRNA content of dendrites shift from granules to polysomes following depolarization (Fig. 3; Krichevsky and Kosik 2001).

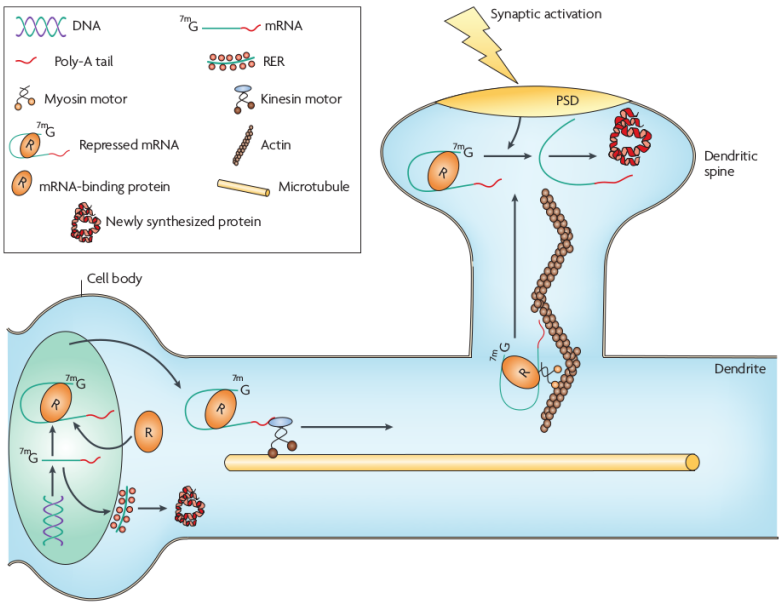

Figure 3: Shcematic representation of translation inhibition during transport and activity-dependent initiation of translation in dendrites (Bramham and Wells 2007).

Two important examples of granule-associated RBPs are the fragile X mental retardation protein (FMRP) and cytoplasmic polyadenylation element binding protein (CPEB). As we shall see, the mechanism of FMRP-mediated translational inhibition involves microRNA recognition of target transcripts. But the translation inhibition mechanism of CPEB, originally elucidated in *Xenopus* oocytes, involves the interaction between dephosphorylated CPEB bound to the 3' UTR and eIF4E bound to the 5' UTR forming a deactivated closed loop. Phosphorylation of CPEB then can release the closed loop and allow translation initiation (Bramham and Wells 2007; Krichevsky and Kosik 2001).

Both the older notion of targeted transport of plasticity-related proteins from the soma and the later findings that Arc mRNA produced in the nucleus are transported to active dendritic sites poses a question of targeted transport. Although the mechanisms for such targeted delivery are not clearly understood, an analogy with other cell organelles seems relevant. Mitochondria and other organelles show bidirectional movement on cytoskeletal filaments. The same basic pattern together with a mechanism of docking and anchoring RNA transport granules at sites of dendritic activity (or alternatively degradation in sites of inactivity) can explain differential targeting of active dendritic sites (Steward and Worley 2001; Bramham and Wells 2007).

2.2 Translational Regulation: general mechanisms

Translation of nuclear or localized mRNA can be regulated through several general mechanisms. Since translation *initiation* is the rate-limiting step, phosphorylation and dephosphorylation of initiation factors (eIF) are typically the strongest force of translational regulation. For instance, $eIF2\alpha$ phosphorylation has been shown to be critical for persistent synaptic plasticity and memory. Genetic manipulations of eIF2α phosphorylation using knockouts of GCN2 (the main eIF2α kinase), constitutively dephosphorylated eIF2α mutants, and pharmocological inhibition of eIF2α phosphatase, have all shown that eIF2α phosphorylation is critical for synapticity-related protein syntehsis. Similar results have been obtained for the mTOR signalling pathway, which itself is at the downstream of the ERK pathway. The ERK pathway also affects (de)phosphorylation of another initiation factor eIF4E which has been shown to phosphorylate during LTP as well as mGluR-dependent LTD. In mGluR-LTD, another proven site of translational regulation is the phosphorylation of the translation *elongation* factor eEF2 which is required for the increased expression of the Arc protein Arg3.1 as well as the microtubule-associated protein (MAP)-1B (Fig. 4; Steward and Worley 2001; Krichevsky and Kosik 2001; Costa-Mattioli et al. 2009).

Therefore, the phosphorylation cascades regulating translation rates are equally relevant for nuclear, dendritic, and axonal translation. However, as discussed above, RNA transport granules are transcriptionally impotent due to the specific translation inhibition by RBPs during transport. Therefore, it is possible that the rate-limiting step in local translation is the removal of these RNPs (Steward and Worley 2001; Bramham and Wells 2007; Krichevsky and Kosik 2001; Costa-Mattioli et al. 2009).

An important class of translational regulatory mechanisms has emerged in the past decade and in-

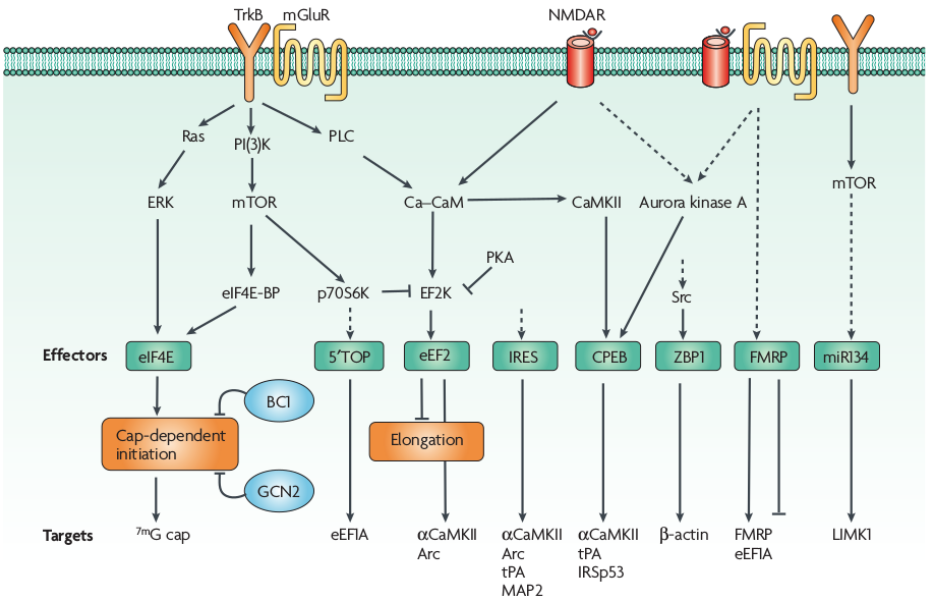

Figure 4: Schematic summary of some of the known activity-dependent translational regulatory networks in dendrites (Bramham and Wells 2007).

volves the complementary pairing of small non-coding RNA sequences known as microRNA (miRNA) to corresponding sequences in the 3' UTR of regulated transcripts. In the following section, we will exclusively focus on miRNA-mediated regulation of local translation in neurons.

3 miRNA-mediated Regulation of Protein Synthesis

The miRNA pathway, together with the closely related RNA interference (RNAi) pathway, is one of the major classes of known RNA silencing mechanisms. Both pathways rely on the complementary binding of short RNA sequences (miRNA or siRNA, respectively) to complementary regions in a target mRNA which leads to translation inhibition or mRNA degradation. The basic structure of the miRNA pathway is as follows. miRNA are short (20-23 nt) non-coding sequences of RNA. The primary transcribed sequence (pri-miRNA) is cleaved by the nuclear ribonuclease III (RNase III) enzyme Drosha yielding a 70-100 nucleotide hairpin precursor (pre-miRNA). The precursor miRNA is transported to the cytoplasm and a second cleavage event involving another RNAase III enzyme named Dicer yields the mature single stranded miRNA (Fig. 5; Kosik 2006; Krol, Loedige, and Filipowicz 2010).

The mature miRNA is incorporated in an RNA-induced silencing complex (RISC) which uses the mature miRNA as a template to target specific mRNA transcripts by complentary matching to a short portion (known as the *seed region*) typically in their 3' UTR. miRNAs are weakly specific in their mRNA targetting with increasing degrees of complementarity increasing the strength of miRNA binding. Together with their relatively short length, this allows miRNAs to target different mRNAs with different rates (Kosik 2006; Schratt 2009; Krol, Loedige, and Filipowicz 2010).

The miRNA pathway has been implicated in many developmental processes of the nervous system including the embryonic neural patterning, establishment and maintenance of cell identity, and axonal pathwinding. In what follows, we will exclusively focus on miRNAs that localize to synaptic sights and regulate activity-dependent translation in mature neurons (Kosik 2006; Schratt 2009).

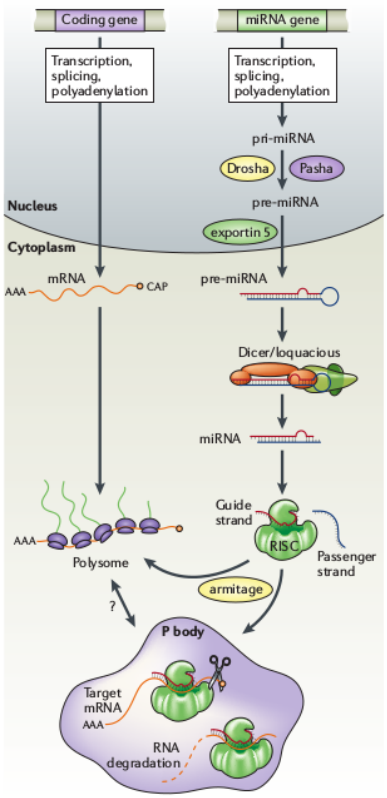

Figure 5: Schematic representation of the miRNA pathway (Kosik 2006).

3.1 miRNA Regulation of Translation

Depending on the degree of complementarity between the miRNA template and the target mRNA, the transcript is either translationally suppressed or degraded. If degradation occurs, RISC is freed to suppress multiple mRNA transcripts using a single miRNA copy. This means that miRNA regulators are typically not on-off switches but fine-tuning agents (Kosik 2006; Schratt 2009). Notably, the flexibility of miRNA to suppress translation without degrading the suppressed mRNA makes them especially suitable for localized control of dendritic translation. Another hint is the observation that proteins involved in miRNA regulation and production (e.g. Dicer, Argonaute, FMRP) are found in RNA Transport granules that target translationally stalled mRNAs to dendrites (Schratt 2009).

One of the first indications of the involvement of the miRNA pathway in mature neurons was demonstrated by the elevated expression of many miRNAs that copurify with polyribosomes in rat cortical neurons. The temporal pattern of expression of different miRNAs follows distinct developmental

stage. Since then, some of the miRNA components of neural development have been identified (Kim et al. 2004; Kosik 2006). In mature neurons, expression level assays of a large number of miRNAs found in hippocampal CA1 cells indicate differential expression of many (~ 90) miRNAs in reponse to NMDA-mediated contextual conditioning in a early/late-phase fasion (at 1-3 hours and 24 hours after conditioning). Furthermore, artificially inducing the same neural conditions by NMDA or bicuculline (GABA antagonist) shows a similar temporal pattern of differential expression potentially implying that a coordinated regulation of miRNA expression occurs with the early and late phases of synaptic plasticity (Kye et al. 2011). NMDA receptors (NMDA-R) are known to regulate activity-dependent morphological changes in dendrites and multiple miRNA species involved in NMDA-R signalling have been identified.

For a miRNA to have a functional role in synaptic plasticity two different questions must be answered. First, how is the expression or activity of the miRNA affected by synaptic activity? Second, how is miRNA activity related to plasticity-related protein synthesis. Strikingly, it has been reported that depolarization induces the release of miRNA and MAP1B enriched exosomes by post-synaptic cells Goldie et al. 2014. It is unclear whether this release is a mechanism to dispose of miRNA which directly inhibit growth-related activity or an unknown channel for intercellular communication between post-synaptic and pre-synaptic cells.

Here we discuss two miRNAs, namely miR-134 and miR-132, that interact with translational control of local protein synthesis as part of NMDA-induced dendritic growth. Both have been shown to be transcriptionally regulated by CREB in an activity-dependent fashion. We will focus on their connection with activity-dependent dendritic growth.

3.2 Modulation of miRNA Translational Repression by Synaptic Activity

One can imagine four possible answers to the first question posed above: how could synaptic activity affect the expression or activity of any miRNA? Synaptic activity might *(i)* increase the rate of miRNA transcription (e.g. through known signalling pathways such as CREB), *(ii)* increase the rate of miRNA transport to the site of dendritic activity, *(iii)* increase the rate miRNA activity (e.g. through the transport of pre-miRNA and increased activation of Dicer), or *(iv)* remodel the miRNA-RISC complex such that it no longer inhibits translation (recall that miRNAs can induce translation repression without mRNA degradation). The first and last possibilities have been confirmed (Schratt 2009) for certain miRNA (Fig. 6).

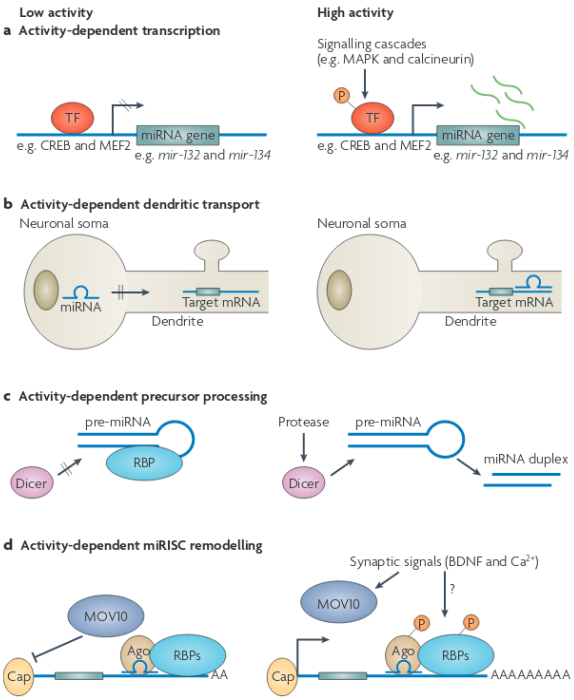

Figure 6: Schematic depiction of the various forms of activity-dependence in miRNA translational regulation (Schratt 2009).

3.3 Two miRNAs Regulating Dendritic Growth: miR-134, miR-132

3.3.1 miR-134

miR-134 shows punctate patterns of concentration in dendritic trees and regulates dendritic spine morphology in hippocampal neurons. Artificial overexpression of miR-134 and its suppression by introduction of an antisense oligonucleotide shows that miR-134 inhibits spine growth (note that dendritic spine size is a good measure of the post-synaptic strength of excitatory synapses). Finding the exact point of contact between miR-134 and the spine growth machinery requires scanning growth-related neuronal genes for miR-134 binding sites in the 3' UTR of their mature mRNA. Among the possible options, fusion fluorescent reporter experiments and electrophoretic mobility shift assays indicate that the target is the mRNA for LIM kinase 1 (*Limk1*) which collocalizes with miR-134 in dendrites and shows significant expression increase when miR-134 is supressed by an antisense oligonucleotide. Limk1 is a kinase that promotes actin polymerization and spine growth. Local translation of *Limk1* is upregulated by BDNF treatment and transfecting hippocampal neurons with fusion *Limk1* mRNA with a 3' UTR luciferase reporter attentuates (but does not abolish) the increase in Limk1 protein synthesis caused by BDNF (Schratt et al. 2006; Schratt 2009).

3.3.2 miR-132

p250GAP is a known GTPase-activating protein (GAP) for Rho family proteins. p250GAP interacts with GluRϵ 2 (NR2B) subunit of NMDA-R *in vivo* such that NMDA-R activity leads to its dephosphorylation (Nakazawa et al. 2003). Furthermore, p250GAP interacts with scaffold protein PSD-95 (Wayman et al. 2008). Through this connections, p250GAP is involved in a pathway that increases dendritic growth following NMDA-R activity. Mutants of p250GAP with changes only in a few positions of the 3' UTR show attenuated dendritic growth in response to NMDA-R activity. The key is a microRNA, miR-132, which is highly expressed in response to NDMA-R activity which suppresses p250GAP translation by recognizing a seed region in its mRNA (Wayman et al. 2008).

In contrast to miR-134, which is only involved in activity-dependent dendritic growth, miR-132 appears to be involved in both basal and activity-dependent dendritic growth (Schratt 2009) since miR-132-dependent regulation of p250GAP is necessary for basal dendritic spine formation (Impey et al. 2010; Edbauer et al. 2010). Furthermore, the mechanism of miR-132 action is through activating Rac proteins which in turn connects the pathway to the miR-132/Limk1 pathway (Wayman et al. 2008; Impey et al. 2010; Schratt 2009).

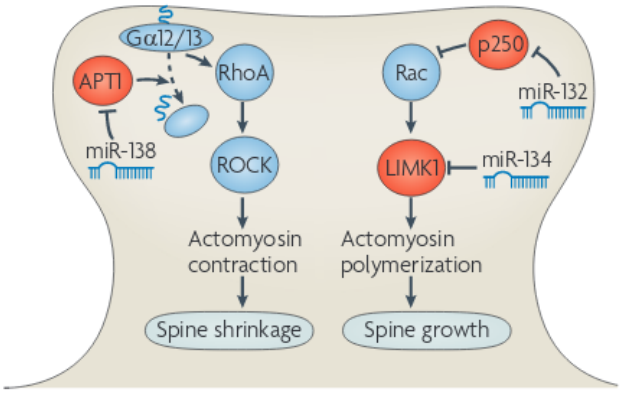

Figure 7: Schematic depiction of the miRNA pathways modulating dendritic growth (Schratt 2009)

4 Future Directions

Research into the mechanisms of translational regulation of localized mRNA in neurons and, specifically, its miRNA-dependent regulatory elements is in its early stages. Nevertheless, it presents promising opportunities for a deeper understanding of the molecular underpinnings of plasticity and its implications in higher cognitive research as well as disease.

In this section we will summarize some of the most important challenges and unanswered questions. First, it remains unclear what differentiates those mRNAs that are only found near the soma and those

that also localize in synaptic (dendritic or axonal) sites. Undoubtedly, the choice of mRNA localization is related to temporal dynamics of plasticity or requirements of protein complex synthesis like cotranslational assembly or different turnover rates of constituent proteins. Second, a similar question can be raised about the corresponding regulatory miRNA. Which miRNA are only expressed in the soma and which ones are transported to synaptic sites? Furthermore, the processes of miRNA transport remain mostly unclear although there are hints for simultaneous transport of miRNA and target mRNA. Third, what are the mechanisms that bring miRNA expression and activity in downstream control of synaptic activity? We have discussed examples of transcriptionally regulated miRNAs and there is evidence for activity-dependent miRNA-RISC remodelling relieving translational repression. However, the existence of miRNA processing proteins in RNA transport granules as well as activity-dependent increase of Dicer activity hints at the possibility of regulation through increased local miRNA maturation. Fourth, dynamics and stoichiometry of the interactions between miRNA and target mRNAs are not properly understood.

On a broader level, miRNA-mediated translational regulation poses many technical challenges. First, as discussed above miRNA do not require exact complementarity with their target mRNA and, in fact, provide fine-tuned regulation based on the degree of binding rigidity. This, together with the fact that miRNA recognition requires only a relatively small seed region in the target mRNA, implies that miRNAs can interact with many different mRNA and regulate each in a graded manner. These complications necessitate systems biology approaches for analysis of regulatory networks and bioinformatics approaches for prediction and scanning of potential plasticity-related regulatory miRNA.

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