Coordinated Regulation of Synaptic Plasticity by microRNAs

Sourav Banerjee, PhD, Pierre Neveu, PhD,
and Kenneth S. Kosik, MD

Neuroscience Research Institute
University of California, Santa Barbara
Santa Barbara, California

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Introduction

Neurons are interconnected through specialized junctions, known as synapses, that modulate all our brain functions. Structural and functional modification of these synapses (also known as synaptic plasticity) that occurs in response to neuronal activity is a critical regulator of various nervous system functions, including long-term memory formation (Malenka and Nicoll, 1999; Sutton and Schuman, 2006). Thus, a comprehensive understanding of the mechanisms of synaptic plasticity is a prerequisite for visualizing how synaptic changes can modulate the formation of long-term memory. Current understanding of synaptic plasticity centers on remodeling the cytoskeleton, neurotransmitter receptor trafficking, and activity-dependent gene transcription mechanisms. More recently, however, protein synthesis mechanisms at synapses have emerged as critical modulators of synaptic plasticity (Malenka and Nicoll, 1999; Sutton and Schuman, 2006).

In polarized neurons, mRNAs are synthesized in the cell soma and then transported far away, to dendritic spines: a specialized biochemical compartment of the neuronal dendrite. These dendritic spines are equipped with the biochemical machinery necessary for autonomous regulation of various synaptic functions. MicroRNAs (miRNAs) are among several players that have been shown to modulate synaptic protein synthesis. These small noncoding RNAs emerged recently as critical regulators of dendritic protein synthesis.

miRNAs are ~21-nucleotide-long transcripts that can fine-tune gene expression in a variety of systems, including the nervous system. miRNAs reside in RNA-induced silencing complex (RISC) and bind to the 3′ untranslated region (UTR) of mRNAs, resulting in translational suppression (Kosik, 2006; Schratt, 2009). For example, a recent study showed that synaptic activation could release miRNA-mediated translation suppression and subsequent *de novo* protein synthesis from its mRNA target, *LimK1* (Schratt et al., 2006). Although this observation and others implicate miRNA-mediated control of protein synthesis in synaptic plasticity, the mechanistic details of this regulatory control remain largely unknown (Kosik, 2006; Schratt, 2009; Vo et al., 2010).

In a recent study, we showed that activity-dependent rapid, bidirectional modulation of RISC function can regulate synaptic protein synthesis from specific mRNAs that contain miRNA binding sites. We also observed that one of the key RISC factors (MOV10, a DEAD box helicase) is degraded rapidly by the proteasome and subsequently releases RISC-mediated translational inhibition.

In order to gain insight into the spectrum of dendritic mRNAs that are modulated through RISC's degradative control, we designed a Translational Trap method to identify miRNAs that RISC targets. This method relies on the fact that removal of the key RISC protein, MOV10, by RNA interference (RNAi)–mediated knockdown would release translational suppression. This de-repression of protein synthesis would then allow RISC-regulated mRNAs to redistribute from a translationally suppressed pool to an actively translating polyribosomal fraction. Based on this hypothesis, we performed ribosomal fractionation after MOV10 RNAi and analyzed polyribosome-associated mRNAs by quantitative PCR (qPCR) using primers specific for 54 dendritically localized mRNAs (Duncan and Gilman, 1998; Poon et al., 2006; Zhong et al., 2006). Apart from the two previously known RISC-regulated mRNAs, *LimK1* and αCaMKII, our screen identified a dozen synaptically localized mRNAs whose protein synthesis could be modulated through activity-dependent control of RISC. Interestingly, we also observed that one such novel RISC-regulated mRNA, Lysophospholipase 1 (Lypla1), is regulated by dendritically localized miR-138. Furthermore, using a translation reporter, we were able to visualize proteasomal degradation of MOV10 as a critical regulatory step for localized protein synthesis from synaptic mRNAs, such as Lypla1. Significantly, Lypla1 is a depalmitoylating enzyme that has been shown to remove the palmitate group from a cytoskeleton regulator, G_{α} (Duncan and Gilman, 1998); in addition, palmitoylation (a reversible posttranslational modification) has recently been identified as a key regulatory switch for synaptic plasticity (Kang et al., 2008).

Our observations, together with those of another study regarding miRNA-mediated control of long-term olfactory memory (Ashraf et al., 2006), set the stage for further study whose goal is to obtain a comprehensive view of regulatory control over synaptic plasticity. Next we discuss the methodologies used to identify synaptic mRNAs that are regulated by RISC and translated locally within the synaptodendritic compartment.

Translational Trap: A Novel Approach to Identifying Biological Targets of miRNAs

To gain insight into miRNA-mediated regulatory control of synaptic plasticity, it is important to know

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the entire set of synaptic mRNAs that miRNAs target. miRNAs bind to the 3′UTR region of their target mRNAs through imperfect base pairing. This imperfect base-pairing rule provides a significant challenge to identifying biological targets using *in silico* sequence analysis. However, nucleotides 2–8 in the miRNA (also known as the "seed region") have been shown to hybridize to an mRNA target through perfectly complementary base pairing. This seed-pairing rule is critical for appropriate target recognition (John et al., 2004; Lewis et al., 2005).

Based on this rule and other hybridization properties (e.g., free energy of duplex formation, accessibility of target site, and neighboring sequence around the miRNA binding site), several target prediction algorithms have been generated. All these target prediction tools provide a list of large numbers of putative mRNA targets for a single miRNA, and there is little overlap among target sets of specific miRNAs. Although the majority of miRNA-mediated neuronal gene expression control occurs at the translational level, miRNA–target interaction also has been shown to regulate gene expression through mRNA degradation (Kosik, 2006). However, target prediction algorithms do not account for the mode of regulatory control. In addition to these challenges, *in silico* target prediction tools do not assess the effect of cellular factors on miRNA–target interaction.

To overcome the limitations of target prediction tools and to identify biological targets of miRNAs, we designed a novel method we named "Translational Trap" (Banerjee et al., 2009). It has been shown that the core components of RISC play a critical functional role. One such novel core factor is MOV10, a DEAD box helicase and ortholog of the *Drosophila* homolog Armitage that has been implicated in miRNA-guided translational control (Cook et al., 2004; Chendrimada et al., 2007). Interestingly, we also observed that MOV10 is rapidly degraded by the proteasome in response to neuronal activity. Based on these observations, we reasoned that the removal of MOV10 could relieve RISC-mediated translational suppression, after which RISC-associated mRNAs would then be redistributed from the translationally suppressed pool to an actively translating fraction (Fig. 1).

The Translational Trap method takes advantage of short hairpin (sh) RNA–mediated RNAi against MOV10. We used a lentiviral delivery system for efficient RNAi knockdown because the efficacy of transfection methods in primary neuronal culture is very low. In order to visualize lentivirus-infected neurons, we cloned shRNA constructs in a lentiviral vector (pLVTHM) that also express EF1α promoter–driven enhanced green fluorescent protein (eGFP). Recombinant lentivirus was made by cotransfecting transfer vector (pLVTHM containing shRNAs against MOV10), packaging plasmid (psPAX2)–expressing viral packaging proteins, and envelope plasmid (pMD 2.G)–expressing viral coat proteins into HEK293T cells. The transfection was performed using the calcium phosphate method. Following transfection, we collected recombinant lentivirus from culture supernatant and viral titer analyzed by fluorescent-activated cell sorter (FACS) analysis. Primary neuronal culture at day *in vitro* (DIV) 7 was then infected with the recombinant lentivirus expressing shRNA against MOV10 at a multiplicity of infection (MOI) of 4. Following virus transduction,

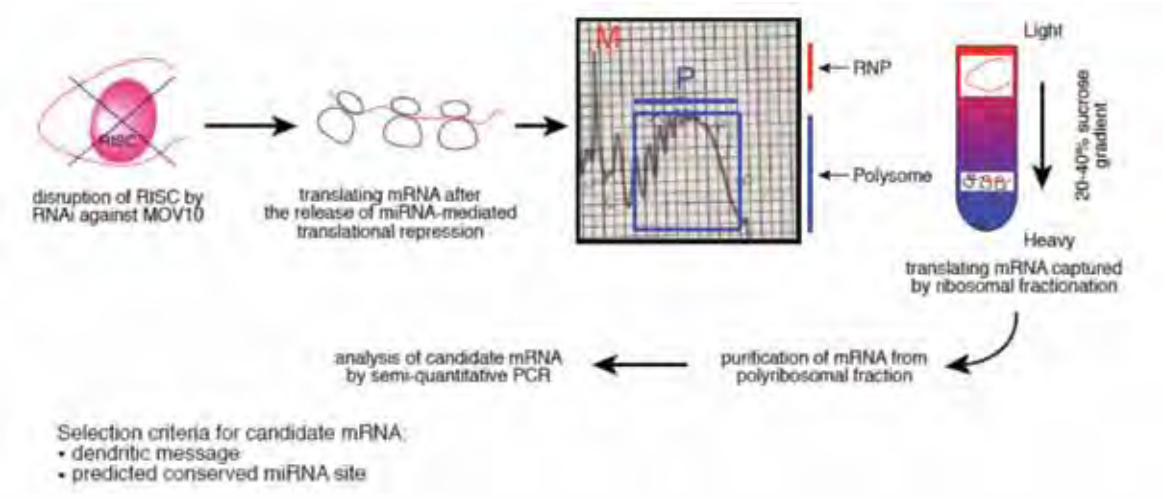


Figure 1. Schematic diagram of Translational Trap method.

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RNAi-mediated knockdown of MOV10 was tested at various time points. After obtaining more than 70% knockdown of MOV10 level at DIV18-19, neurons were used for polyribosomal fractionation.

We isolated polyribosomal pool from transduced neuronal culture using sucrose gradient fractionation, as described previously (Stefani et al., 2004), with minor modifications. We next arrested translation of mRNAs in primary neuronal cultures by washing them with ice-cold phosphate buffer saline (PBS) containing the protein synthesis inhibitor cycloheximide (15 μg/ml). Neurons were then homogenized and the cytoplasmic extract obtained by differential centrifugation. The cytoplasmic extract was then loaded onto 20–50% w/w linear density gradient of sucrose. The gradient was centrifuged at 40,000 × *g* for 2 h at 4°C in a SW41 rotor (Beckman Instruments, Fullerton, CA). Following centrifugation, the gradient was fractionated with continuous monitoring absorbance at 254 nM using a UA-6 ultraviolet (UV) detector (Teredyne ISCO, Lincoln, NE). Polyribosomal fractions were pooled, denatured by 1% SDS, and total RNA obtained via the precipitation method. The crude RNA fraction was further purified by using an Absolute RNA reverse transcriptase PCR (RT-PCR) Miniprep kit (Stratagene, La Jolla, CA).

To visualize mRNA distribution in polyribosmal fractions, 4 μg of total RNA was reverse-transcribed into double-stranded cDNA using a First Strand SuperScript II kit (Invitrogen, Carlsbad, CA) and analyzed by qPCR (quantitative polymerase chain reaction) using primer specific for 54 dendritic mRNAs. These mRNAs were chosen based on their localization (Poon et al., 2006; Zhong et al., 2006) and predicted conserved miRNA binding sites. qPCR was performed using SYBR Green–containing PCR amplification (Applied Biosystems, Carlsbad, CA). The 7500 Fast System Sequence Detection Software (Applied Biosystems) was used to analyze real-time PCR data, and the threshold cycle chosen in the linear amplification range of all samples. The qPCR data were normalized using glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and 18S ribosomal RNA (rRNA) as internal standard. After normalization, the differential distribution of candidate mRNAs was assessed using the comparative C_T method (Schmittgen and Livak, 2008).

Our Translational Trap method revealed that miRNAs can potentially regulate 13 candidate mRNAs out of 54 dendritic messages. Interestingly, we also observed that some dendritic mRNAs, such as β-actin, as well as translation initiation factor Eif3s10, are not differentially redistributed after RNAi occurs against MOV10. Among several significantly redistributed candidates, Lypla1 and αCaMKII were studied further. Results from qPCR analysis were further verified by Western blot analysis of endogenous protein level after MOV10 RNAi took place.

Go Fishing: Identifying miRNA That Binds to RISC-Regulated mRNA

After identifying RISC-regulated mRNAs, our next challenge was to identify specific miRNAs that can hybridize to these mRNAs. To visualize such specific miRNA–target interaction, we relied on *in silico* target prediction tools. We first obtained a list of putative miRNAs that multiple algorithms predict will target a specific mRNA. For example, three major target prediction algorithms (TargetScan, PicTar, and miRanda) identified miR-138 as a potential miRNA that can bind to Lypla1. To assess the direct miRNA-target interaction, we performed a reporter assay after a loss-of-function experiment using lock nucleic acid (LNA) inhibitor (Orom et al., 2006) for a specific miRNA. The major advantage of LNA miRNA inhibitor is that it can efficiently and irreversibly bind to complementary miRNA and thus prevent it from functioning.

In order to perform the reporter assay, we fused the full-length 3′UTR of Lypla1 mRNA with Luciferase reporter. We then cotransfected this reporter construct with LNA inhibitor of miR-138 into primary hippocampal neurons at DIV7. We also cotransfected LNA scramble control in order to analyze the specificity of the reporter assay. We analyzed the effect of miR-138 on reporter expression by measuring Luciferase activity at 48 h after transfection. We observed that inhibition of miR-138 function leads to a significant increase in reporter activity, suggesting a direct interaction between miR-138 and Lypla1 mRNA. We further verified the results from the reporter assay by assessing endogenous protein level after similar inhibition of miR-138 function.

In order to assess miR-138–Lypla1 3′UTR interaction–mediated control of *de novo* protein synthesis at synapses, we first tested the localization of both miR-138 and Lypla1 mRNA using double-label *in situ* hybridization. We hybridized primary hippocampal neurons using an LNA antisense probe (Exiqon, Woburn, MA). We labeled miR-138 and Lypla1 with biotin and digoxigenin (DIG), respectively, using a DIG Oligonucleotide Tailing Kit, 2nd Generation (Roche Applied Science, Indianapolis, IN). We

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also used a scramble probe to assess the specificity of hybridization. *In situ* hybridization was performed with biotin or DIG-labeled antisense probes.

Following hybridization, neurons were washed extensively and incubated with cy3-labeled anti-DIG as well as fluorescein isothiocyanate (FITC)–labeled anti-biotin (Jackson ImmunoResearch, West Grove, PA). To visualize synaptic localization, neurons were immunostained with antibody specific to Synapsin I, a synaptic marker, followed by incubation with cy5-conjugated secondary antibody. After immunostaining, confocal microscopy was used to visualize synaptic localization of both miR-138 and Lypla1 mRNA (Fig. 2*A*). Similarly, our *in situ* hybridization procedure, combined with immunostaining, showed that MOV10, a critical component of RISC, colocalizes with Lypla1 mRNA (Fig. 2*B*). These observations suggest that Lypla1 is an ideal candidate for studying the activity-dependent control of RISC-mediated localized protein synthesis that occurs at the synapse.

RISCy Control of Synaptic Protein Synthesis: An Online Approach

After we observed that neuronal activity can lead to rapid synaptic degradation of endogenous MOV10 through NMDA receptor activation, we designed an imaging-based method for quantitatively assessing *de novo* degradation of MOV10 in living hippocampal neurons. For this purpose, we fused a photoactivable green fluorescent protein (PA-GFP) with MOV10 (Patterson and Lippincott-Schwartz, 2002) and expressed the fusion protein in hippocampal neurons using lentivirus transduction. Similar to endogenous MOV10, when imaged, ectopically expressed MOV10-PA-GFP appeared as a punctate pattern. The unique photoactivation property of PA-GFP provides an advantage when scoring localized protein degradation, as any new synthesis of MOV10 will not affect our analysis.

We proceeded to photoactivate MOV10-PA-GFP–expressing neurons using a 365 nm UV lamp and stimulated synaptic activity in these neurons (DIV21-24) with the membrane depolarizing agent KCl (60 mM for 5 min). We used confocal microscopy to capture images at specific time intervals (Fig. 3*A*). We then analyzed time-lapse images to compute MOV10 puncta intensity over time using a custom-written algorithm in MATLAB (MathWorks, Natick, MA). Similar to endogenous MOV10 degradation, we observed that the RISC protein MOV10 is degraded rapidly at synaptodendritic compartments in response to neuronal activity (Fig. 3*B*). Interestingly, we also observed that the rapid degradation of MOV10-PA-GFP was prevented when neurons were pretreated with the proteasome inhibitor lactacystin. These

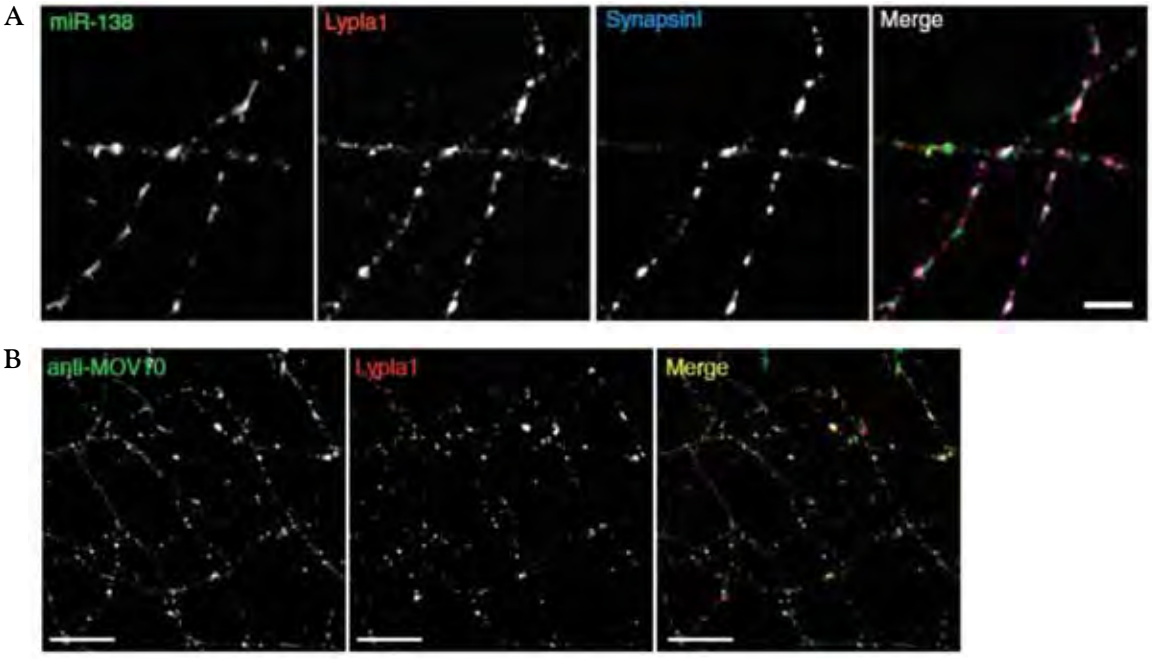
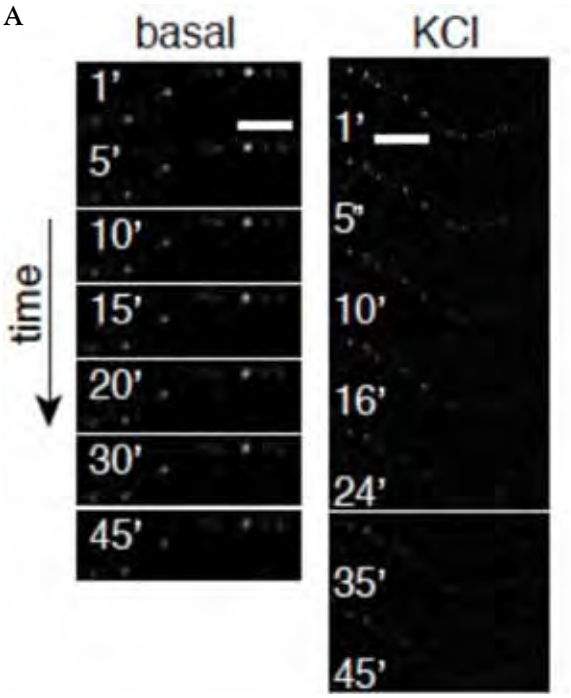


Figure 2. *In situ* hybridization showing localization of miR-138 and Lypla1 mRNA. ***A***, Double *in situ* hybridization to visualize synaptic localization of miR-138 and Lypla1 mRNA. Scale bar, 10 μm. ***B***, Lypla1 mRNA is associated with the RISC component MOV10. Scale bar, 20 μm.

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observations indicate that rapid synaptic degradation of MOV10 occurs through proteasomal control. We also analyzed the diffusion properties of MOV10-PA-GFP and observed that the ectopically expressed protein was not freely diffusing but rather bound to a restricted space. This observation further confirmed that the decrease in puncta intensity occurred as a result of degradation of ectopically expressed protein rather than its free diffusion elsewhere.



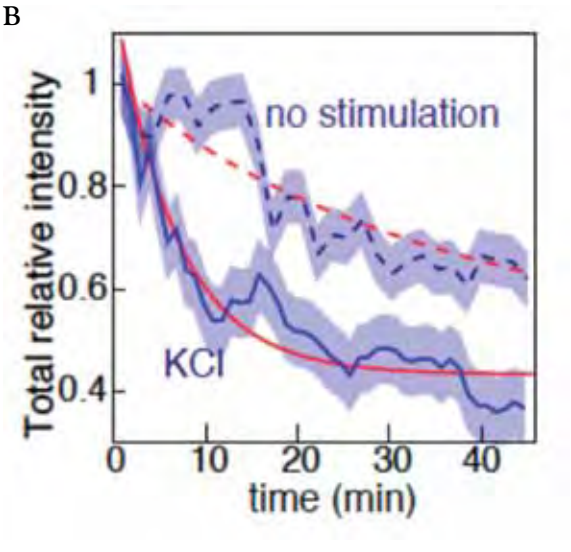


Figure 3. Activity-dependent degradation of MOV10-PA-GFP. ***A***, Time-lapse image of MOV10-PA-GFP–expressing neurons with or without synaptic activation. Scale bar, 10 μm. ***B***, Quantitative profile of MOV10-PA-GFP level with or without stimulation.

To address how activity-dependent control of RISC can regulate dendritic protein synthesis, we took an imaging approach to scoring localized protein synthesis using the photoconvertible reporter Kaede (Ando et al., 2002). The green form of Kaede can be converted to the red form by 365 nm UV light. This photoconversion is efficient, rapid, and irreversible. Kaede's unique photoconversion property offers a tremendous advantage for marking the existing protein and scoring newly synthesized protein following synaptic activation. Thus, we fused Lypla1 3′UTR with Kaede reporter and expressed it in cultured hippocampal neurons using lentivirus transduction. Kaede reporter appears as a punctate pattern because Kaede is a tetrameric protein that can form aggregates even at low concentration; aggregate formation can be enhanced further because of its expression in restricted space, such as a dendritic spine.

Following photoconversion, we stimulated hippocampal neurons (DIV21-24) using membrane depolarization (60 mM KCl for 5 min) or glutamate treatment (20 μM for 5 min). After stimulation, we captured time-lapse images in the green channel to score any new protein synthesis, and in the red channel, to monitor changes in dendritic spine volume (Tanaka et al., 2008). The quantitative assessment of new protein synthesis was performed by a custom-written algorithm in MATLAB (MathWorks). Our imaging analysis showed that Lypla1 3′UTR–driven localized translation of Kaede occurs in response to synaptic activity (Fig. 4*A*). This activity-dependent translation was inhibited when neurons were pretreated with the proteasome inhibitor lactacystin, and the protein-synthesis inhibitor anisomycin. However, *de novo* protein synthesis was not prevented by pretreatment with the transcription inhibitor actinomycin D. Taken together, these observations clearly suggest that Lypla1 3′UTR–driven localized control of dendritic protein synthesis is also regulated by proteasomal control, but not through transcriptional mechanisms (Fig. 4*B*).

Because Lypla1 3′UTR duplexed with miR-138 modulates localized translation through proteasomal control, we performed similar imaging analysis to visualize the role that the key RISC component, MOV10, plays in regulating dendritic protein synthesis. To further apply this approach, we first reduced the endogenous level of MOV10 by RNAi and then stimulated these neurons with glutamate. We observed that reducing the level of endogenous MOV10 completely blocked Lypla1 3′UTR–driven new protein synthesis of translation reporter

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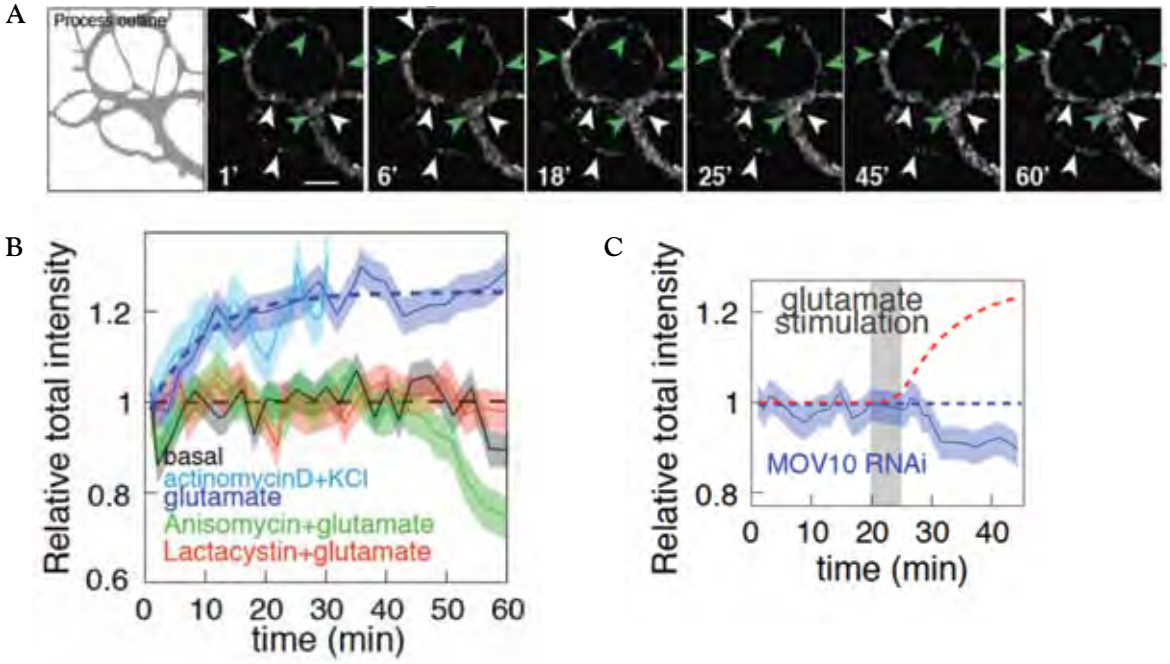


Figure 4. RISC-mediated degradative control of synaptic protein synthesis. ***A***, Lypla1 3′UTR–driven, activity-dependent localized control of protein synthesis. Scale bar, 10 μm. ***B***, Quantitative profile of newly synthesized translation reporter with or without glutamate stimulation. *De novo* protein synthesis of translation reporter is inhibited by the proteasome inhibitor lactacystin and the translation inhibitor anisomycin but not by the transcription inhibitor actinomycin D. ***C***, Lypla1 3′UTR–driven localized protein synthesis is completely blocked by RNAi-mediated knockdown of MOV10.

(Fig. 4C). This observation set the stage for analyzing whether MOV10 degradation and Lypla1 3′UTR–driven localized synthesis occurs in a coordinated manner.

To visualize the direct link between these two biochemical processes, we cotransduced hippocampal neuron with lentivirus-expressing cyan fluorescent protein (CFP)–fused MOV10 (MOV10-CFP) and Lypla1 3′UTR–fused Kaede (Fig. 5*A*). After photoconversion, we analyzed MOV10 degradation by following CFP intensity as well as new protein synthesis by measuring the level of green-form Kaede in the same punctum. Quantitative analysis of time-lapse images revealed that 35% of puncta showed a strong correlation between localized protein degradation and synthesis (Fig. 5*B*). Our observation was also supported by double-label *in situ* hybridization data showing that a similar percentage of puncta contains both endogenous Lypla1 mRNA and miR-138. Furthermore, an increase in MOV10 degradation directly correlated with the

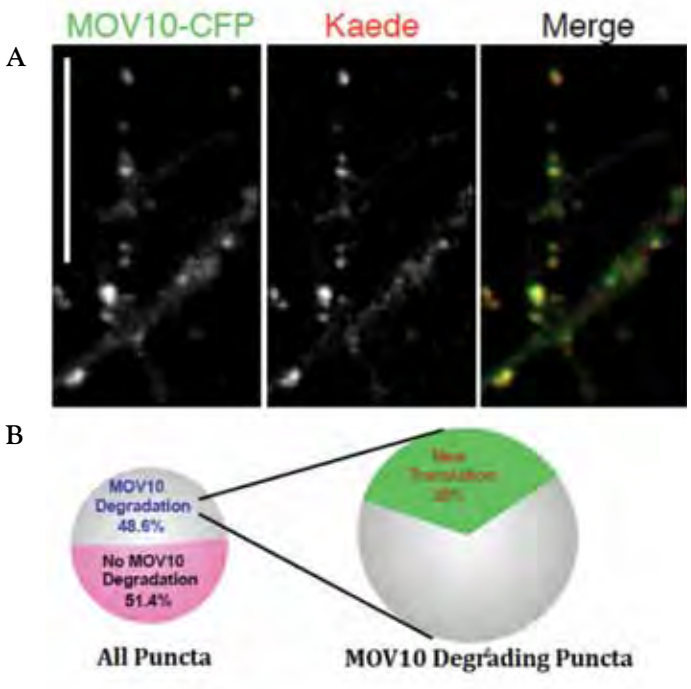


Figure 5. Degradative control of RISC is directly linked with localized protein synthesis from a specific class of mRNAs. ***A***, Localization of ectopically expressed MOV10 and Lypla1 3′UTR–fused Kaede. Scale bar, 20 μm. ***B***, MOV10 degradation and Lypla1 3′UTR–driven localized protein synthesis occur at the same location.

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enhancement of *de novo* protein synthesis. As further support, a related recent study showed that miR-138–mediated control of Lypla1 (also known as APT1) expression can modulate synaptic development (Siegel et al., 2009). These observations suggest that activity-dependent control of synaptic modification can be regulated by this novel type of posttranslational modification.

Conclusion

A comprehensive understanding of miRNA-mediated posttranscriptional control of synaptic function has just begun. Towards this end, our recent analysis established a novel cell-biological and biochemical approach to understanding miRNA-mediated regulation of synaptic plasticity. However, a holistic view of miRNA-mediated control of long-term memory formation through this type of novel plasticity mechanism remains relatively unexplored. Future experiments will need to incorporate new methodologies for visualizing miRNA-mediated control over synaptic protein synthesis in a living animal during memory acquisition. Insight into these novel memory mechanisms could eventually lead to the discovery of new therapeutic strategies for a variety of neurodegenerative diseases, such as Alzheimer's disease, as well as neurological conditions such as autism and mental retardation.

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