Mini-Review

RNA Trafficking and Local Protein Synthesis in Dendrites: An Overview

Kelsey C. Martin[1] **and R. Suzanne Zukin**[2]

[1]Department of Psychiatry and Biobehavioral Sciences, Department of Biological Chemistry, David Geffen School of Medicine, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, California 90095-1761, and [2]Department Neuroscience, Rose F. Kennedy Center, Albert Einstein College of Medicine, Bronx, New York 10461

It is now widely accepted that mRNAs localize to dendrites and that translation of these mRNAs is regulated in response to neuronal activity. Recent studies have begun to reveal the underpinnings of these processes and to underscore the importance of local protein synthesis to synaptic remodeling and plasticity.

When Steward and Levy (1982) first reported their observation of polyribosomes at the base of spines, the prevailing view was that all proteins were synthesized in the cell body and then transported to distal compartments of neurons. Steward and Levy's discovery, however, raised the intriguing possibility that mRNAs could be transported to synapses and locally translated in response to synaptic stimulation. This provided an elegant mechanism for spatially restricting gene expression within the neuron, such that individual synapses could independently regulate their morphology and efficacy, in a persistent, protein synthesis-dependent manner, in response to specific stimuli. It is now widely accepted that mRNAs do localize to dendrites and that translation of these mRNAs contributes to synaptic plasticity. As is evident from the collection of Mini-Reviews on dendritic protein synthesis in this issue of *The Journal of Neuroscience*, the field has evolved to focus on a series of key questions, including the following: (1) what mRNAs are present in dendrites? (2) How are these mRNAs transported from the nucleus into the dendrite? (3) How is translation of these mRNAs regulated by neuronal activity? and (4) What is the function of local translation of specific transcripts? In this brief introductory overview, we will consider each of these questions in turn.

Key words: **synaptic plasticity; mRNA trafficking; dendrites; transcriptional regulation; excitatory synapses; dendritic localization**

What mRNAs are present in dendrites?

Using radioactive uridine precursors, Davis et al. (1987) demonstrated that RNAs were transported into dendrites of cultured hippocampal neurons. Subsequent *in situ* hybridization studies revealed the presence of specific mRNAs encoding cytosolic, cytoskeletal, and integral membrane proteins in dendritic layers of the hippocampus and at postsynaptic densities of hippocampal neurons *in vivo* and *in vitro*. These include mRNAs encoding microtubule-associated protein 2 (MAP2), (Garner et al., 1988; Kleiman et al., 1990), the α-subunit of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKIIα) (Miyashiro et al., 1994), brain-derived neurotrophic factor (BDNF), activity-regulated cytoskeleton-associated protein (Arc) (Lyford et al., 1995), tyrosine-related kinase B (TrkB) receptor, IP_3 receptor, the atypical protein kinase Mζ, the NMDA receptor (NMDAR) NR1 subunit and glycine receptor α subunit (for review, see Steward and Schuman, 2003).

More recently, unbiased approaches to amplify mRNAs from purified dendritic and/or synaptic compartments (Miyashiro et al., 1994; Tian et al., 1999; Moccia et al., 2003; Sung et al., 2004) have generated lists of localized mRNAs numbering in the hundreds. These experiments suggest that there is a rich repertoire of mRNAs whose translation can be regulated in a spatially restricted manner in response to stimulation. Wide acceptance of the dendritic localization of such a large number of mRNAs, however, has been delayed by the lack of *in situ* hybridization data demonstrating that the mRNAs are indeed present in dendrites.

The population of dendritically localized mRNAs is likely to be regulated by development and by activity. Thus, many mRNAs localize to dendritic growth cones of developing neurons but are not present in dendrites of mature neurons (Crino and Eberwine, 1996). Other mRNAs appear to become dendritically localized in response to activity. One example is the mRNA encoding Arc, which is transcriptionally induced by activity and then rapidly transported into dendrites (Link et al., 1995; Lyford et al., 1995). Similarly, the dendritic localization of mRNAs encoding BDNF and trkB increases after neuronal activity (Tongiorgi et al., 1997, 2004). These findings suggest that the complement of mRNAs that is present in dendrites is dynamically regulated.

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Correspondence should be addressed to either of the following: Dr. R. Suzanne Zukin, Department of Neuroscience, Rose F. Kennedy Center, Room 602, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY 10461, E-mail: zukin@aecom.yu.edu; or Dr. Kelsey C. Martin, Department of Psychiatry and Biobehavioral Sciences and Department of Biological Chemistry, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, CA 90095-1761, E-mail: kcmartin@mednet.ucla.edu.

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Export of mRNAs to neuronal processes

Early, pioneering studies used nucleic acid stains and green fluorescent protein fused to RNA-binding proteins to visualize mRNA translocation in live neurons (Kohrmann et al., 1999; Kiebler and DesGroseillers, 2000; Huang et al., 2003; Tiruchinapalli et al., 2003). These studies showed that localized mRNAs are transported in the form of large granules containing mRNAs, RNA-binding proteins, ribosomes, and translational factors (RNA-containing granules) in a rapid (average speed, 0.1 μm/s), bidirectional, and microtubule dependent manner (Knowles et al., 1996). As reviewed in the accompanying Mini-Review by Wells (2006), the dendritic localization of mRNAs appears to be mediated by a family of RNA-binding proteins. Disruption of RNA-binding proteins such as zipcode-binding protein (ZBP) 1 and 2, Staufen, or cytoplasmic polyadenylation element-binding protein (CPEB) impairs localization of targeted mRNAs (Zhang et al., 2001). These observations suggested a critical role for mRNA-binding proteins as molecular adapters between *cis*-acting mRNA localization sequences and microtubule-based transport machinery. Of binding proteins known to mediate mRNA trafficking in dendrites, perhaps the best characterized is CPEB. CPEB facilitates mRNA targeting to dendrites (Huang et al., 2003) and triggers "on-site" translation in response to external signals (Shin et al., 2004).

Most of the *cis*-acting sequences that have been identified as being involved in dendritic localization are in the 3′UTR of the mRNA. Recent studies of *oskar* mRNA localization in *Drosophila melanogaster* oocytes have indicated that the nuclear history of the mRNA is important in mediating its ultimate localization and specifically that the complement of RNA-binding proteins that associate with mRNAs during processing in the nucleus have a significant impact on the localization of the mRNA in the cytoplasm (Hachet and Ephrussi, 2004). Proper identification of *cis*-acting sequences that mediate dendritic localization will thus likely require analyses in systems in which reporter mRNAs undergo normal pre-mRNA processing in the nucleus.

Recent studies, described in the companion review by Hirokawa (2006), have begun to characterize the RNA granules that carry mRNAs into dendrites. In a *tour de force*, Hirokawa used affinity chromatography and proteomics to identify >42 proteins that constitute the large RNA-containing granule and showed that a subset of component proteins, such as hnRNP U (heterogeneous nuclear ribonucleoprotein), staufen, PURα, and PSF (pyrimidine tract binding protein-associated splicing factor), are critical to dendritic RNA transport (Kanai et al., 2004). These investigators identified the kinesin superfamily protein KIF5 as a motor involved in the active transport RNA-containing granules into distal dendrites (Kanai et al., 2004). Whereas KIF5 is distributed to both axons and dendrites, RNA-containing granules are transported exclusively to dendrites (Kanai et al., 2004). In that neuronal mRNA transport is bidirectional, it is likely that future studies will uncover a role for dynein in retrograde mRNA transport.

As described above, the transport of mRNAs into dendrites appears to be regulated by neuronal activity. Synaptic stimulation *in vivo* delivers Arc mRNA to segments of dendrites with activated synapses and promotes on-site synthesis of Arc protein (Steward et al., 1998; Steward and Worley, 2001). Depolarization of hippocampal neurons in culture promotes movement of CaMKIIα mRNA granules within dendrites (Rook et al., 2000) and the transport of a β-actin mRNA/ZBP1 complex into dendrites and spines (Tiruchinapalli et al., 2003). Dopamine receptor activation promotes transport of endogenous mRNAs such as glutamate receptor subunit 1 (GluR1) and GluR2 (Smith et al., 2005). These findings are, in principle, consistent with a model in which activated or "tagged" synapses might recruit mRNAs, thereby enabling activity-dependent regulation of local protein synthesis and synaptic efficacy.

Translational regulation of mRNAs at the synapse

The mRNAs that are present in RNA granules are thought to exist in a dormant state. Thus, an important aspect of mRNA localization involves the repression of mRNA translation until a specific stimulus activates translation. Studies of activity-dependent translation in dendrites have indicated a central role for rapamycin-dependent regulation at the level of translation initiation (Klann and Dever, 2004), described in more detail in the companion reviews by Pfeiffer and Huber (2006) and Wells (2006). In addition to this more classical means of translational regulation, Edelman and colleagues (Pinkstaff et al., 2001) have suggested that dendritic mRNAs are preferentially translated via internal ribosomal entry sites. Two recent studies have discovered a role for microRNA (miRNA)-mediated translational regulation in dendrites. In one study, Kunes and colleagues (Ashraf et al., 2006) found that the mRNA encoding CaMKIIα was present in dendrites of *Drosophila* neurons, in which its translation was regulated during olfactory learning. They noted that the 3′UTR contained two putative miRNA-binding sites, indicating that binding of miRNAs might function to repress translation. Importantly, Kunes and colleagues (Ashraf et al., 2006) found that components of the miRNA processing machinery were also present at synapses and further found that one of these proteins, encoding the RNA helicase armitage, was degraded at the synapse during learning. Together, these findings suggest that persistent generation of miRNAs is required to repress translation and that neuronal activity leads to degradation of components of the RNA interference machinery such that miRNAs are no longer generated, thereby lifting translational repression. In another study, Greenberg and colleagues (Schratt et al., 2004, 2006) used bioinformatics approaches to look for potential miRNA binding sites in a group of mRNAs that they had previously shown to be translated in cultured neurons in response to BDNF. They found that the miRNA mir134 bound to sites in the 3′UTR of one of the mRNAs, encoding LimKinase 1 (LimK1), and that modulation of mir134 concentrations altered LimK1 concentrations, which in turn altered spine structure. These findings are also consistent with miRNAs functioning to regulate translation at the synapse and indicate that such regulated translation is required for normal spine development. In the past year, studies in non-neuronal cells have revealed that components of the RNA interference pathway and targets of miRNAs localize to "RNA processing bodies," or "P-bodies" (Liu et al., 2005). Studies of the relationship between P-bodies and RNA granules in neurons may elucidate many aspects of translational regulation.

As outlined in the accompanying Mini-Review by Schuman et al. (2006), synaptic stimulation may serve to globally upregulate translation or to recruit translation of specific mRNAs. Given that such a large number of mRNAs appear to be present in dendrites, one might presume that distinct stimuli activate the translation of distinct mRNAs. In one example, however, stimuli that produce synaptic weakening (application of the mGluR agonist 3,4-dihydroxyphenylglycol) and stimuli that produce synaptic strengthening (2 × 100 Hz tetanic stimuli) of hippocampal synapse were both found to increase translation of elongation factor 1α (EF1α) in hippocampal dendrites (Huang et al., 2005; Tsokas et al., 2005). In one fascinating study, Schuman and col-

leagues (Sutton et al., 2004) found that local translation in dendrites was negatively regulated by spontaneous release. These results suggest that one function of spontaneous release may be to sustain translational repression of localized mRNAs.

What is the function of dendritic mRNA localization and regulated translation?

Studies of fragile X mental retardation (FXMR), reviewed in the accompanying article by Greenough and colleagues (Grossman et al., 2006), highlight the importance of local translation for neuronal structure and function. The fragile X mental retardation protein (FMRP), mutated in patients with FXMR, is an mRNA-binding protein thought to function as a translational repressor. Loss of FMRP leads to abnormal spine structure, a hallmark of FXMR.

Elucidating the function of specific, locally translated mRNAs is technically challenging and requires new methodologies to differentiate between newly translated and preexisting protein and to resolve events occurring at individual synapses or subsets of synapses. Mayford and colleagues (Miller et al., 2002) undertook a creative approach to investigate the function of dendritically translated CaMKIIα in which they expressed a CaMKIIα transgene lacking the 3′UTR (which contains the *cis*-acting dendritic targeting sequences) in CaMKIIα null mice. Using this strategy, they succeeded in generating a mouse that expressed CaMKIIα but lacked dendritically localized CaMKIIα mRNA, allowing them to specifically assay the function of dendritically translated enzyme. These mutant mice showed deficits in the late phase of long-term plasticity at hippocampal synapses and in long-term memory. Furthermore, the postsynaptic density (PSD) in the mutant mice showed a selective loss of CaMKIIα (and enrichment of CaMKIIα), which occurred although CaMKIIα protein was present throughout the neuron, including in the dendrite. This finding suggests that locally synthesized CaMKIIα is especially well incorporated into PSDs and indicates that the function of locally translated proteins may differ in subtle ways from that of somatically synthesized proteins.

Recent studies have shown that AMPA receptors are synthesized in dendrites in response to stimulation. Ju et al. (2004) found that chronic activity blockade increased the synthesis of a GluR1 reporter mRNA in dendrites and that acute activation of metabotropic glutamate receptors (mGluRs) or acute depolarization with KCl increased the synthesis of both GluR1 and GluR2. Using quantitative fluorescence *in situ* hybridization, Grooms et al. (2006) recently demonstrated that a substantial fraction of synaptic sites in hippocampal neurons contain GluR2 mRNA fluorescence clusters, consistent with strategic positioning and availability for "on-site" protein synthesis. Brief NMDAR activation, a signaling paradigm that drives endocytosis of AMPA receptors (AMPARs) (but not NMDARs) in hippocampal neurons in culture and induces long-term depression (chemical LTD) in hippocampal slices selectively depleted AMPAR mRNAs in dendrites. In contrast, group I mGluR activation elevated dendritic levels of AMPAR mRNAs by transport of mRNA from soma to dendrites. Bidirectional regulation of dendritic AMPAR mRNAs is a novel mechanism for long-lasting modifications of glutamate receptor composition and number and provides a potentially powerful means to effect long-lasting changes in synaptic efficacy.

In addition to a role for dendritic translation during plasticity, local translation in axonal growth cones has been shown to play a role in axon guidance and synapse formation (Campbell and Holt, 2001; Ming et al., 2002; Lyles et al., 2006) and local translation in injured axons to contribute to regeneration (Zheng et al., 2001). Together, these findings indicate that mRNA localization and regulated translation provides a general mechanism whereby neurons can locally alter protein composition within discrete subcellular compartments. Understanding the mechanisms whereby mRNAs are localized and whereby their translation is locally regulated thus promises to provide important insights into many aspects of neuronal function and dysfunction.

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