Moving Molecules: mRNA Trafficking in Mammalian Oligodendrocytes and Neurons

ROSS SMITH
Department of Biochemistry and Molecular Biology
University of Queensland

Numerous mRNA molecules are localized in regions of the dendrites of neurons, some moving along dendrites in response to synaptic activity. The proteins encoded by these RNAs have diverse functions, including participation in memory formation and long-term potentiation. Recent experiments have shown that a cytoplasmic RNA trafficking pathway described for oligodendrocytes also operates in neurons. Transported RNAs possess a *cis*-acting element that directs them to granules, which are transported along microtubules by the motor proteins kinesin and dynein. These RNA molecules are recruited to the cytoplasmic transport granules by cooperative interaction with a cognate *trans*-acting factor. mRNAs containing the 11-nucleotide A2RE11 or 21-nucleotide A2RE sequences bind heterogeneous nuclear ribonucleoproteins A2 and A3, which are abundant in the brain. Mutations in this *cis*-acting element that weaken its interaction with hnRNP A2 also interfere with RNA trafficking. Several dendritically localized mRNAs, including those encoding calcium-calmodulin-dependent protein kinase II α subunit and neurogranin, possess A2RE-like sequences, suggesting that they may be localized by interaction with these heterogeneous nuclear ribonucleoproteins. Calcium-calmodulin-dependent protein kinase II α subunit is of particular interest: Its RNA is transported in depolarized neurons, and the protein it encodes is essential for establishing long-term memory. Several other *cis*-acting sequences and *trans*-acting factors that participate in neuronal RNA localization have been discovered. NEUROSCIENTIST 10(6):495–500, 2004. DOI: 10.1177/1073858404266759

KEY WORDS *RNA localization, Neurons, Dendrites, Oligodendrocytes,* Cis-*acting sequences,* Trans-*acting factors*

Sorting Molecules

Molecular sorting is required for the development and maintenance of cellular, tissue, and organismal asymmetry. Proteins are not spread uniformly throughout cells, and their compartmentation is essential for cellular function. Many proteins have encoded within them motifs that determine where they will ply their trade. But not only proteins possess sorting motifs: Many mRNA molecules also have elements ("zipcodes"; Singer 1993) that direct them to specific subcellular locations.

Why sort RNA if the proteins they encode could instead be sorted? One of the more compelling arguments is that if the RNA is spatially restricted, the same may be true for its protein, concentrating it where it is needed and keeping it from locations where it could cause mischief. An oft-quoted example is CNS myelin basic protein (MBP). MBP is a sticky protein: It can attach to many membranes and can potentially cause indiscriminate aggregation of membranes of subcellular organelles. Colman and others (1982), however, showed that MBP mRNA is concentrated in the myelin of oligodendrocytes. This localization appears to restrict MBP translation to the region of myelin assembly where the protein is inserted directly into the nascent membrane. By translating MBP near the myelin, it has limited opportunities for attachment to inappropriate membranes.

mRNA Localization in Oligodendrocytes and Fibroblasts

The nature of RNA localization pathways has emerged primarily from studies of *Drosophila* and *Xenopus* oocytes and embryos, but in recent years, studies of somatic mammalian cells—glia, neurons, fibroblasts, and epithelia—have added considerably to the picture (Bassell and others 1999; Carson and others 2001). Again, MBP is one of the best-known examples. Ainger and colleagues (1997) identified a small segment of MBP mRNA, the 21-nucleotide heterogeneous nuclear ribonucleoproteins (hnRNP) A2 response element (A2RE), that is necessary and sufficient for its localization. Later, it was shown that this *cis*-acting element and its 5′ 11-nucleotide segment (A2RE11) preferentially

I gratefully acknowledge the contributions of my graduate students and collaborators to the work from our laboratory described here. I thank Dan Cowan for figure preparation. This research was supported by a grant from the Australian National Health and Medical Research Council.

Address correspondence to: Ross Smith, Department of Biochemistry and Molecular Biology, University of Queensland, Queensland, 4072 Australia (e-mail: ross.s@uq.edu.au).

ISSN 1073-8584

bind the nuclear proteins hnRNPs A2 and A3, *trans*-acting factors that are particularly abundant in brain (Munro and others 1999). The specificity of this interaction is illustrated in Figure 1: A single base change within the A2RE11 element in a ~1 kb RNA eliminates its binding to hnRNP A2 and transport of the RNA in oligodendrocyte processes. In parallel studies, the central role of zipcode recognition by a *trans*-acting protein, zipcode-binding protein (ZBP), was elegantly illustrated in fibroblasts, in which a separate, microfilament-dependent pathway with different *cis* element and *trans*-acting factor mediates trafficking of β-actin mRNA (Farina and Singer 2002).

A *cis*-acting sequence that closely matches that of MBP mRNA is found in the transcript of another myelin protein, myelin-oligodendrocyte basic protein. This protein has seven isoforms: four include an A2RE-like sequence, and three lack this segment (Gould and others 1999). The RNAs encoding the former are localized to the myelin compartment, whereas the latter are found in the oligodendrocyte soma, adding to the evidence that the A2RE-like sequence is sufficient for trafficking.

Subsequent experiments with oligodendrocytes and fibroblasts led to the current model (Fig. 2) in which RNAs that are to be localized team up with their *trans*-acting factor during, or immediately following, maturation of the mRNA in the nucleus. The RNA with its cognate protein is exported to the cytoplasm, where they are incorporated into large transport granules. These granules, which have been observed in many cell types, contain multiple ribosomes and probably many of the molecules needed to translate the transported mRNA, including t-RNA synthetases and elongation factors (Barbarese and others 1995). In oligodendrocytes, they also include the molecular motors kinesin and dynein, which enable them to move along microtubules from the soma into the cell processes. It appears that translation of the RNA does not take place until it is anchored at its destination, in the distal processes for oligodendrocytes. The anchoring of the RNA, which may require attachment to microfilaments, is one of the least understood steps in this pathway.

Trafficking in Neurons

More than 20 dendritically localized mammalian mRNAs have been identified, including those encoding the proteins GAP-43 (neuromodulin), MAP2, CaMKIIα, ARC/Arg 3.1, L7, dendrin, Gly receptor α1 and α2, CREB, BDNF (neurotrophin), TrkB (BDNF receptor), β-actin, InsP3 receptor, PEP19, neurofilament protein 68, MRG15, G-protein γ subunit, calmodulin, vasopressin, oxytocin precursors, NMDAR1, ligatin, RC3 (neurogranin), fragile X mental retardation protein (FMRP), protein kinase C(γ), and the noncoding BC1 RNA. (Limitations in space preclude citation of many important contributions. The reader is directed to recent reviews by Kiebler and DesGroseillers 2000; Kindler and Monshausen 2002; Steward 2002). These RNAs are under tight spatial and temporal control: They may have

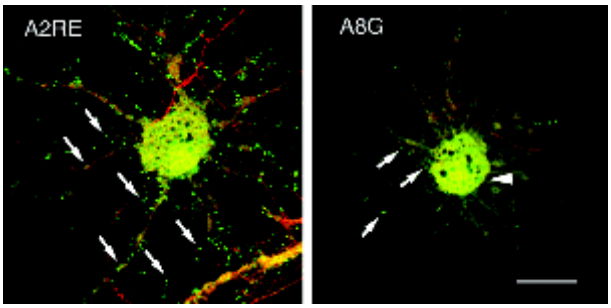

Fig. 1. RNA transport in live, cultured hippocampal neurons microinjected with fluorescently labeled A2 response element (A2RE)-containing RNA (green) and Texas Red–labeled dextran (red, to show cell morphology) and observed by confocal microscopy. The RNA assembles into granules and moves along the processes (arrows in left panel). A single nucleotide change (A8G) in the A2RE element of the ~200 nt RNA stops its assembly into granules, resulting in a diffuse RNA distribution in the soma and proximal neurites (arrowhead in right panel), with only an occasional granule visible in the processes. Scale bar = 10 μm.

different distributions in the dendritic arbor (e.g., primarily proximal), and the levels of each may vary with cell type, developmental stage, physiological state, and synaptic stimulation. They are often found co-localized with ribosomes and other components of the translation apparatus near dendritic spines where they may participate in activity-related protein synthesis (Steward and Schuman 2003), providing a mechanism for long-term potentiation (Frey and Morris 1997; Steward 2002). The proteins they encode are diverse, including cytoskeletal components, calcium-binding proteins, receptors, and kinases. The *cis*-acting elements, or regions containing these elements, have been identified for only a handful of dendritically localized RNAs (Table 1). They do not all use the same trafficking element, but several may use closely related elements.

Recent studies suggest that a molecular mechanism of RNA targeting in neurons parallels that described for oligodendrocytes (Shan and others 2003; Tiruchinapalli and others 2003). Some features are likely to be the same for a wide range of localized neuronal RNAs: Most neuronal RNAs are probably transported along microtubules in kinesin/dynein-containing granules. It is possible, however, that different sets of *cis*-acting sequences and *trans*-acting factors are employed in trafficking, even in different neuron types.

Neuronal *Cis*-acting Sequences

A2RE-like sequences have been found by simple sequence comparisons in many localized RNAs, for example, protamine 2, MAP2, neurogranin (RC3), and ARC (Ainger and others 1997). We have shown in ultraviolet cross-linking and pull-down experiments that rat brain hnRNP A2 binds the A2RE-like sequences of MAP2 and ARC in vitro. Thus, hnRNP A2 is a potential *trans*-acting factor for several of the RNAs in Table 1, although some also bind other proteins (see below).

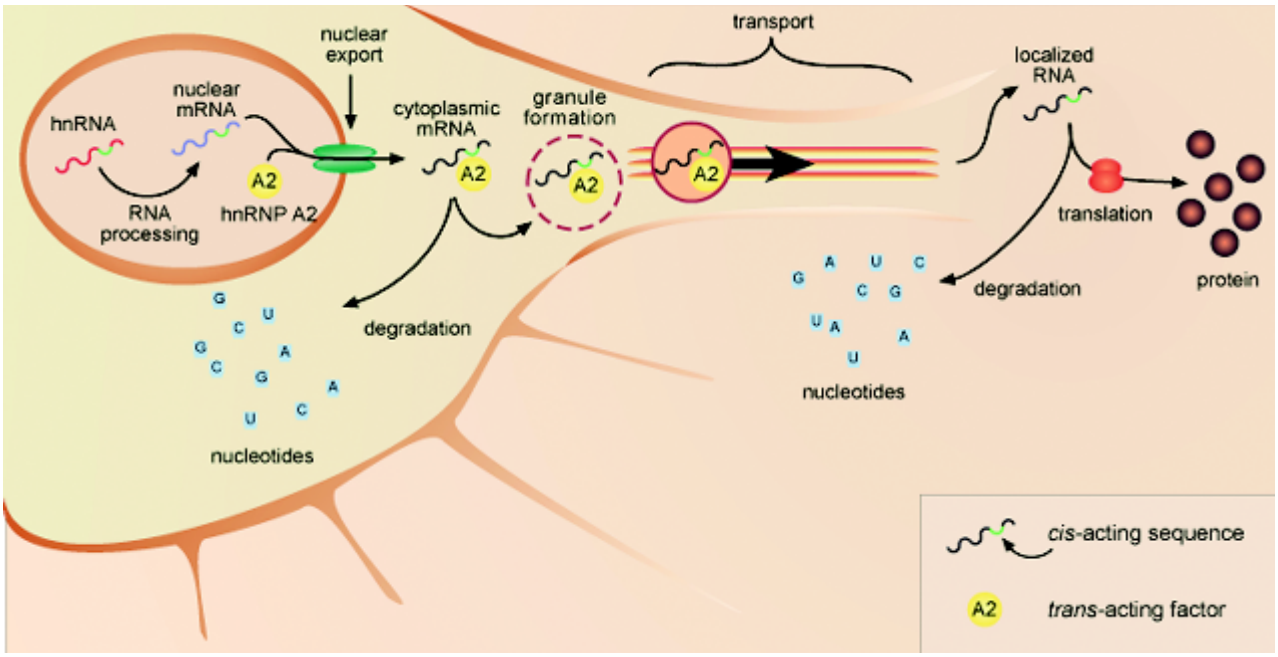

Fig. 2. Model for trafficking of A2 response element (A2RE)-containing RNAs. The A2RE, which is represented in a different color from the remainder of the mRNA, binds heterogeneous nuclear ribonucleoprotein (hnRNP) A2 or hnRNP A3 (yellow circle), and the complex is recruited to transport granules that move along the microtubules (orange unlabeled horizontal lines). The granules contain multiple copies of the RNA-protein complex. At its destination, the mRNA is anchored and translated. Each of the steps in this process, including RNA degradation, is a potential posttranscriptional control point for gene expression.

Interaction of the A2RE-like or A2RE11-like motifs with hnRNP A2 may afford a general pathway for targeting these RNAs, but several other *cis*-acting transport elements have also been identified (Table 1).

One (constitutively expressed) localized neuronal mRNA, that encoding the calcium-calmodulin-dependent protein kinase II α subunit (CaMKIIα), has received more attention than most. It is one of several demonstrated to participate in activity-related synthesis of proteins that localize to dendritic spines or arbors (Crino and Eberwine 1996; Steward 2002). For CaMKIIα, the increased synthesis provides a mechanism for long-term potentiation and memory formation (Lisman and others 2002; Miller and others 2002), with the protein acting by several means (e.g., phosphorylation of the AMPA receptors) to strengthen synaptic transmission.

Mori and others (2000) have raised the possibility, from experiments in which they truncated the 3′UTR, that CaMKIIα RNA possesses two competing elements, one specifying retention in the perikaryon in the resting state and the other dendritic localization in depolarized neurons. The latter sequence (the calmodulin/neurogranin dendritic localization element) closely matches the 3′ half of the A2RE, as does a section of the neurogranin 3′UTR. In contrast, Kindler's laboratory has placed the targeting sequence closer to the 3′ end of the UTR (Blichenberg and others 2001), and others have shown that the cytoplasmic polyadenylation element (CPE), which is unrelated in sequence to A2RE, is sufficient to specify trafficking in neurons (Huang and others 2003).

Box 1: Protein Isoforms

Although there are of the order of 30,000 to 40,000 genes in the genomes of mammals, the number of proteins far exceeds this. Alternative splicing of the hnRNA and posttranslational modifications create a protein diversity that has received modest attention. HnRNP A2, for example, is produced in at least four isoforms through alternative splicing, each of which may be N-terminally acetylated, phosphorylated, and methylated. Evidence is emerging that these posttranslationally modified isoforms may have different locations and functions. Similarly, Staufen has two paralogues that have different spatial distributions in neurons (Mallardo and others 2003).

It is feasible for an RNA to have more than one *cis*-acting trafficking element and bind more than one *trans*-acting protein, and it would therefore be instructive to examine the ability of the sequences identified by Mori's group to independently target microinjected chimeric RNA.

Neuronal *Trans*-acting Targeting Factors

What types of proteins function as *trans*-acting targeting factors? Few neuronal factors have been identified

Table 1. Dendritic *Cis*-acting Elements and *Trans*-acting Factors

Transported RNA	*Cis*-acting Element	Location	Size	*Trans*-acting Factor	Reference
CaMKIIα, neurogranin	CNDLE	3′UTR	28–30 nt[a]	hnRNP A2	Mori and others (2000); Blichenberg and others (2001)
BC1 (noncoding)	BTE	5′ proximal	62 nt $(GGN)_n$	TB-RBP (Translin), Purα and Purβ	Muslimov and others (1997); Ohashi and others (2002)
Ligatin, CaMKIIα	Y element	Various	~14 nt	TB-RBP	Severt and others (1999)
MAP2	DTE	3′UTR	640 nt	rMARTA1/ KSRP, rMARTA2	Rehbein and others (2000, 2002)
MAP2, CaMKIIα	CPE (AU-rich)	3′UTR	6 nt	CPEB	Huang and others (2003)
A2RE-containing[b]	A2RE11	Various	11 nt	hnRNP A2	Shan and others (2003)
β-actin	β-actin zipcode	3′UTR	54 nt	ZBP1, ZBP2/ KSRP	Eom and others (2003); Tiruchinapalli and others (2003)
Many, including BC1 RNA[c]	Purine quartet and unknown elements			FMRP	Miyashiro and others (2003); Antar and others (2004)
Vasopressin precursor protein	DLS	3′UTR	395 nt	PABP	Mohr and others (2001)

CaMKIIα, calmodulin-dependent protein kinase II α subunit; CNDLE, calmodulin/neurogranin dendritic localization element; hnRNP, heterogeneous nuclear ribonucleoprotein; BTE, BC1-targeting element; TB-RBP, testis-brain RNA-binding protein; DTE, dendritic targeting element; MARTA, MAP2-RNA *trans*-acting protein; CPE, cytoplasmic polyadenylation element; CPEB, CPE-binding protein; A2RE, A2 response element; ZBP, zipcode binding protein; FMRP, Fragile X mental retardation protein; DLS, dendritic localizer sequence; PABP, poly(A)-binding protein.

a. Mori and others (2000) described two 3′UTR elements, one a 5′ 28 nt targeting element and a localization-suppressive element. The 28 nt localization element was initially identified by sequence comparisons as similar to those in the neurogranin and myelin basic protein (MBP) RNAs: It was shown experimentally to be sufficient for targeting to dendrites, providing the inhibitory effects of the second element are suppressed by neuronal activity. A different region, 1200 nt from the 3′UTR, was proposed by Blichenberg and others (2001), and Huang and others (2003) concluded that the short CPE element is sufficient for localization of CaMKIIα mRNA.

b. Putative A2RE-containing neuronal RNAs (see text). Shown for MBP mRNA chimera (Shan and others 2003), also CaMKIIα and neurogranin mRNAs and ARC mRNA.

c. Miyashiro and others (2003) identified more than 50 RNAs, including MBP mRNA and its own mRNA, that associated in granules with FMRP and interacted with FMRP in vitro (Brown and others 1998).

(reviewed by Kindler and Monshausen 2002). There are at least four families of *cis*-acting elements/*trans*-acting factors. One uses KH-type proteins (ZBP1, ZBP2, MAP2-RNA *trans*acting protein [MARTA]1, MARTA2, KSRP) to bind to zipcode or zipcode-like sequences (the zipcode is not well defined for MARTA/KSRP). The second uses *trans*-acting factors that possess multiple RNA recognition motifs (RRMs) and bind to elements that are related to A2RE (GCCAAGGAGCCAGAGAG-CAUG) in CaMKIIα and neurogranin mRNAs. The third, testis–brain RNA-binding protein (TB-RBP; mouse orthologue of human translin), binds the Y element (AGAAGCCCTATGCT in CaMKIIα mRNA), which is similar to the A2RE. This protein differs markedly in structure from the other A2RE-binding RRM-containing proteins: It has more than 70% of its residues in α-helical secondary structure in contrast with the α/β structure of RRMs. The fourth, CPE-binding protein (CPEB), has two zinc fingers and two RRMs and recognizes a sequence UUUUAU, unrelated to the first three. Several of these proteins (e.g., hnRNP A2, Pur, CPEB, TB-RBP, and ZBP) appear to be multifunctional. For example, hnRNP A2 is involved in RNA packaging, telomere maintenance, and alternative splicing in addition to its transport role.

HnRNP A2 has been studied intensively in oligodendrocytes. This protein recruits MBP mRNA to transport granules, causing the MBP mRNA levels in the cytoplasm to rise as the oligodendrocytes differentiate into MBP-positive cells and raising MBP mRNA and protein

levels in myelin during the period of myelination in rat spinal cords (Maggipinto and others 2004). The factors governing RNA sorting into granules have been studied in oligodendrocytes. Different A2RE-containing RNAs are sorted into the same granules. The single base change in A8G-mutated A2RE, which interferes with binding to hnRNPs A2 and A3 and RNA transport, does not stop incorporation into granules, but the mutated RNA does not partition into granules containing A2RE-RNA. In contrast, although hnRNPs A2 and A3 both bind to A2RE, have high sequence identity, and appear to be involved in RNA trafficking, they are sorted into different granules (Fig. 3). Likewise, KSRP is found in granules that lack hnRNPs A2 or A3. Thus, it appears that A2RE-containing RNAs bind cooperatively with one of the *trans*-acting factors and associate with the granules, which, as a result, may contain multiple copies of different A2RE-RNA molecules and multiple copies of one of its cognate proteins. In neurons, the A2RE is also sufficient for cytoplasmic transport and may thus mediate trafficking of RNAs, including CaMKIIα, neurogranin, and ARC, which possess an A2RE-like element.

The ZBP/zipcode transport system is one of the best understood. ZBP1 has parallel roles in oligodendrocytes and neurons, being localized to dendrites in neurons. In recent studies of rats in which ZBP1 was knocked down with morpholino antisense oligonucleotides (Eom and others 2003), there was a reduction of dendritic levels of ZBP1 and β-actin mRNA and an increased density of dendritic filopodia. By contrast, depolarization with KCl increased the level of ZBP1/β-actin mRNA granules in dendrites (Tiruchinapalli and others 2003).

In addition to the translation components identified in granules, there are a few other proteins that may have a more general function in granule assembly or transport, for example, Staufen (Köhrmann and others 1999). Other proteins that coprecipitate with mammalian Staufen include Purα, FMRP, ELAV/Hu, Barentsz, and myosin Va (Ohashi and others 2002). Purα, ELAV/Hu, and FMRP are thought to bind to different *cis*-acting sequences. The noncoding transcript BC1 is also expressed at high levels in synaptodendritic domains and found in transport granules (Skryabin and others 2003).

Prospects and Conclusions

For most dendritically localized RNAs, the *cis*-acting sequences and *trans*-acting factors are unknown or poorly defined. We need to know how each RNA is recognized by its cognate *trans*-acting factor; how the RNA-protein complex is recruited to granules, transported, anchored, translated, and released; and, where relevant, the effects of synaptic activity on these processes.

Identifying *trans*-acting proteins has become a less demanding task in the past few years. The high sensitivity of current mass spectrometers has greatly simplified the critical phase of protein isolation: Proteins excised from 1D or 2D polyacrylamide gels can readily be identified by mass analysis of enzymatic digests ("mass fingerprinting"). Under favorable circumstances, hundreds of proteins may be identified in a day by comparison of their mass fingerprints with those predicted from the DNA databases. Identification of transported RNAs in complex structures or measurement of changes in RNA levels (e.g., in response to a learning task) have also been simplified by recent advances in microarray technology.

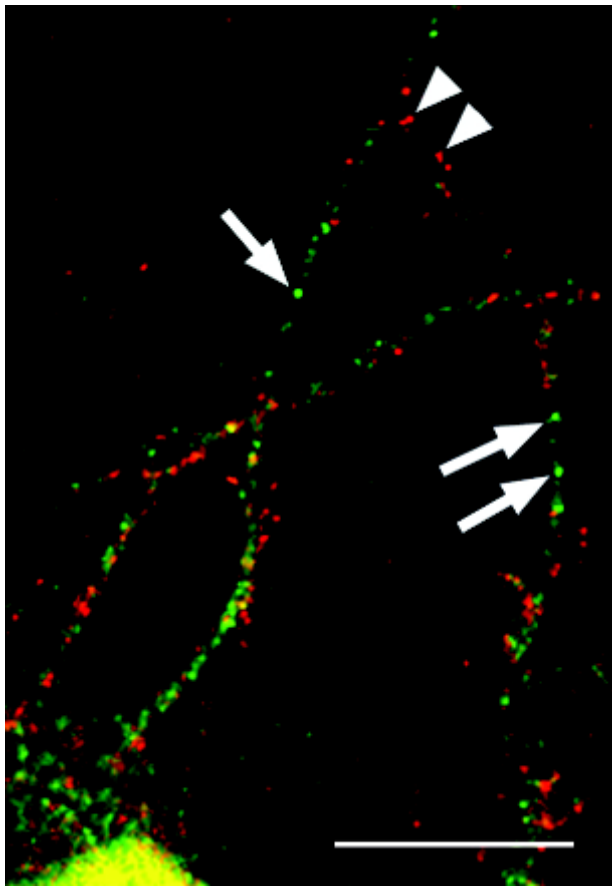

Fig. 3. Confocal laser scanning microscopy image of the neurites of a cultured hippocampal neuron showing granules containing heterogeneous nuclear ribonucleoprotein (hnRNP) A2 (green, arrows) and hnRNP A3 (red, arrowheads). Statistical analysis of the fluorescence of individual granules showed that the majority of granules in the neurites contained either hnRNP A2 or hnRNP A3. Only a small number of granules were yellow, indicating the presence of both proteins. Scale bar = 5 μm.

Co-localization of an RNA and its cognate protein in granules constitutes support for protein-RNA interaction, but multiple experimental approaches are needed to establish that such co-localization is functionally significant. However, the biggest challenge at present is in identifying the minimum requirements in the RNA for binding the *trans*-acting factor(s). Typically, an ssRNA will have a protein-binding surface formed by 6 to 10 nucleotides, but these nucleotides need not be contiguous. At present, however, our knowledge of the principles governing ssRNA-protein interactions is rudimentary: There are few published three-dimensional structures for RNA-protein complexes.

We can anticipate the identification of many more localized RNAs in neurons. These RNAs are likely to contain many different *cis*-acting elements that will bind an array of *trans*-acting factors, with the *cis*-*trans* combination determining what aspect of RNA metabolism is influenced. For transport, the RNA–*trans*-acting factor combination results in attachment to a granule destined to bind the cytoskeleton, or the act of binding to the granule causes changes that determine granule fate. Some of the components of granules have been identified, but a complete inventory and knowledge of the extent of compositional variation are needed. This is probably going to require isolation of these very large and non-electron-dense particles: This will be no trivial task, but important advances in this direction have recently been made.

References

Ainger K, Avossa D, Diana AS, Barry C, Barbarese E, Carson JH. 1997. Transport and localization elements in myelin basic protein mRNA. J Cell Biol 138:1077–87.

Antar LN, Afroz R, Dicterberg JB, Carroll RC, Bassell GJ. 2004. Metabotropic glutamate receptor activation regulates fragile X mental retardation protein and *Fmr1* mRNA localization differentially in dendrites and at synapses. J Neurosci 24:2648–55.

Barbarese E, Koppel DE, Deutscher MP, Smith CL, Ainger K, Morgan F, and others. 1995. Protein translation components are colocalized in granules in oligodendrocytes. J Cell Sci 108:2781–90.

Bassell GJ, Oleynikov Y, Singer RH. 1999. The travels of mRNAs through all cells large and small. FASEB J 13:447–54.

Blichenberg A, Rehbein M, Muller R, Garner CC, Richter D, Kindler S. 2001. Identification of a *cis*-acting dendritic targeting element in the mRNA encoding the alpha subunit of Ca^{2+}/calmodulin-dependent protein kinase II. Eur J Neurosci 13:1881–8.

Brown V, Small K, Lakkis L, Feng Y, Gunter C, Wilkinson KD, and others. 1998. Purified recombinant Fmrp exhibits selective RNA binding as an intrinsic property of the fragile X mental retardation protein. J Biol Chem 273:15521–7.

Carson JH, Cui H, Kreuger W, Schlepchenko B, Brumwell C, Barbarese E. 2001. RNA trafficking in oligodendrocytes. Results Probl Cell Differ 34:69–8.

Colman DR, Kreibich G, Frey AB, Sabatini DD. 1982. Synthesis and incorporation of myelin polypeptides into CNS myelin. J Cell Biol 95:598–608.

Crino PB, Eberwine J. 1996. Molecular characterization of the dendritic growth cone: regulated mRNA transport and local protein synthesis. Neuron 17:1173–87.

Eom T, Antar LN, Singer RH, Bassell GJ. 2003. Localization of a beta-actin mRNP complex with zipcode-binding protein modulates the density of dendritic filopodia and filopodial synapses. J Neurosci 23:10433–44.

Farina KL, Singer RH. 2002. The nuclear connection in RNA transport and localization. Trends Cell Biol 12:466–72.

Frey U, Morris RGM. 1997. Synaptic tagging and long-term potentiation. Nature 385:533–6.

Gould RM, Freund CM, Barbarese E. 1999. Myelin-associated oligodendrocytic basic protein mRNAs reside at different subcellular locations. J Neurochem 73:1913–24.

Huang Y-S, Carson JH, Barbarese E, Richter JD. 2003. Facilitation of dendritic mRNA transport by CPEB. Genes Dev 17:638–53.

Kiebler MA, DesGroseillers L. 2000. Molecular insights into mRNA transport and local translation in the mammalian nervous system. Neuron 25:19–28.

Kindler S, Monshausen M. 2002. Candidate RNA-binding proteins regulating extrasomatic mRNA targeting and translation in mammalian neurons. Mol Neurobiol 25:149–65.

Köhrmann M, Luo M, Kaether C, DesGroseillers L, Dotti CG, Kiebler MA. 1999. Microtubule-dependent recruitment of Staufen-green fluorescent protein into large RNA-containing granules and subsequent dendritic transport in living hippocampal neurons. Mol Biol Cell 10:2945–53.

Lisman J, Schulman H, Cline H. 2002. The molecular basis of CaMKII function in synaptic and behavioural memory. Nat Rev Neurosci 3:175–90.

Maggipinto M, Rabiner C, Kidd GJ, Hawkins AJ, Smith R, Barbarese E. 2004. Increased expression of the MBP mRNA binding protein hnRNP A2 during oligodendrocyte differentiation. J Neurosci Res 75:614–23.

Mallardo M, Deitinghoff A, Muller J, Goetze B, Macchi P, Peters C, and others. 2003. Isolation and characterization of Staufen-containing ribonucleoprotein particles from rat brain. Proc Natl Acad Sci U S A 100:2100–5.

Miller S, Yasuda M, Coats JK, Jones Y, Martone ME, Mayford M. 2002. Disruption of dendritic translation of CaMKIIα impairs stabilization of synaptic plasticity and memory consolidation. Neuron 36:507–19.

Miyashiro KY, Beckel-Mitchener A, Purk TP, Becker KG, Barret T, Liu L, and others. 2003. RNA cargoes associating with FMRP reveal deficits in cellular functioning in *Fmr1* null mice. Neuron 37:417–31.

Mohr E, Fuhrmann C, Richter D. 2001. VP-RBP, a protein enriched in brain tissue, specifically interacts with the dendritic localizer sequence of rat vasopressin mRNA. Eur J Neurosci 13:1107–12.

Mori Y, Imaizumi K, Katayama T, Yoneda T, Tohyama M. 2000. Two *cis*-acting elements in the 3′ untranslated region of alpha-CaMKII regulate its dendritic targeting. Nat Neurosci 3:1079–84.

Munro TP, Magee RJ, Kidd GJ, Carson JH, Barbarese L, Smith LM, and others. 1999. Mutational analysis of a heterogeneous nuclear ribonucleoprotein A2 response element for RNA trafficking. J Biol Chem 274:34389–95.

Muslimov IA, Santi E, Homel P, Perini S, Higgins D, Tiedge H. 1997. RNA transport in dendrites: a *cis*-acting targeting element is contained within neuronal BC1 RNA. J Neurosci 17:4722–33.

Ohashi S, Koike K, Omori A, Ichinose S, Ohara T, Kobayashi S, and others. 2002. Identification of mRNA/protein (mRNP) complexes containing Pura, mStaufen, fragile X protein, and myosin Va and their association with rough endoplasmic reticulum equipped with a kinesin motor. J Biol Chem 277:37804–10.

Rehbein M, Kindler S, Horke S, Richter D. 2000. Two *trans*-acting rat-brain proteins, MARTA1 and MARTA2, interact specifically with the dendritic targeting element in MAP2 mRNAs. Mol Brain Res 79:192–201.

Rehbein M, Wege K, Buck F, Schweizer M, Richter D, Kindler S. 2002. Molecular characterisation of MARTA1, a protein interacting with the dendritic targeting element of MAP2 mRNAs. J Neurochem 82:1039–46.

Severt WL, Biber TUL, Wu X-W, Hecht NB, DeLorenzo RJ, Jakoi ER. 1999. The suppression of testis-brain RNA binding protein and kinesin heavy chain disrupts mRNA sorting in dendrites. J Cell Sci 112:3691–702.

Shan J, Munro TP, Barbarese E, Carson JH, Smith R. 2003. A molecular mechanism for mRNA trafficking in neuronal dendrites. J Neurosci 23:8859–66.

Singer RH. 1993. RNA zipcodes for cytoplasmic addresses. Curr Biol 3:719–21.

Skryabin BV, Sukonina V, Jordan U, Lewejohann L, Sachser N, Muslimov IA, and others. 2003. Neuronal untranslated BC1 RNA: targeted gene elimination in mice. Mol Cell Biol 23:6435–41.

Steward O. 2002. mRNA at synapses, synaptic plasticity, and memory consolidation. Neuron 36:338–40.

Steward O, Schuman EM. 2003. Compartmentalized synthesis and degradation of proteins in neurons. Neuron 40:347–59.

Tiruchinapalli DM, Oleynikov Y, Kelic S, Shenoy SM, Hartley A, Stanton PK, and others. 2003. Activity-dependent trafficking and dynamic localization of zipcode binding protein 1 and β-actin mRNA in dendrites and spines of hippocampal neurons. J Neurosci 23:3251–61.