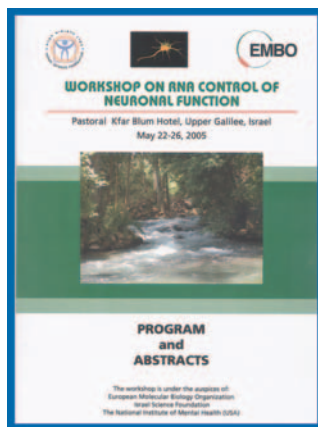


# RNA exodus to Israel: RNA controlling function in the far reaches of the neuron

## Workshop on RNA Control of Neuronal Function

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The EMBO Workshop on RNA Control of Neuronal Function took place in Kfar Blum, Israel, between 22 and 26 May 2005, and was organized by J. Richter, R. Singer and J. Yisraeli. More information about the meeting can be found at: [www.embo-rna-neurons.com](http://www.embo-rna-neurons.com)

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regulation using pharmacology and animal models that has provided proof that regulation of RNA can control neuronal function. Axonal mRNA localization has also been recognized by the neuroscience community and this meeting sought to discuss progress in identifying axonal mRNAs and their function during axon guidance and regeneration (reviewed in Piper & Holt, 2004). In this review, we present highlights of the meeting that address exciting recent reports on mechanisms, regulation and function of mRNA transport and local translation in both dendrites and axons. We also comment on several related talks that dealt with other aspects of post-transcriptional regulation of RNA and provide insight into the diversity of ribonucleo-protein (RNP) complexes and possible interrelationships with those that affect mRNA localization and translation.

### Messenger RNA regulation in dendrites and synapses

O. Steward (Irvine, CA, USA) discussed how local protein synthesis has the potential to facilitate the co-translational assembly of molecules required for postsynaptic assembly and plasticity. Steward and Worley's previous studies of dentate granule cells *in vivo* have indicated a multistep model for the glutamatergic regulation of transcription, dendritic mRNA transport and the synaptic docking of mRNAs that encode the activity-regulated cytoskeletal-associated protein Arc (Steward & Worley, 2001). In addition to the localization of mRNAs encoding structural and regulatory proteins, such as Arc and calcium/calmodulin-dependent protein kinase (CaMKII), this session also provided examples of dendrite-localized mRNAs that encode components of the translational machinery itself. Steward reported the dendritic localization of the mRNA for elongation factor 1 $\alpha$  and its regulation by signals that induce long-term depression (LTD) in the hippocampus (Huang *et al.*, 2005). D. Kuhl (Berlin, Germany) discussed progress in explaining the regulation of Arg 3.1 (Arc) mRNA localization (Waltereit *et al.*, 2001).

The role of neuronal activity and receptor signalling pathways in the regulation of local protein synthesis has been studied in single dendrites of live neurons by E. Schuman's group (Pasadena, CA, USA). Schuman presented data showing that miniature excitatory synaptic events (minis) repress dendritic protein synthesis (Sutton *et al.*, 2004). Conversely, dopamine D1/D5 receptor activation stimulated

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### Introduction

It has been 25 years since quantitative electron microscopy studies from Oswald Steward and colleagues depicted the enrichment of polyribosomes beneath synapses and dendritic spines (Steward & Levy, 1982). Now there are dozens of groups who have made important advances in identifying the many mRNAs that are localized there, the *cis*-acting sequences and *trans*-acting factors that influence mRNA localization and translation, and receptor signalling pathways that affect mRNA regulation (reviewed in Sutton & Schuman, 2005). Importantly, progress has also been made in perturbing RNA

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dendritic protein synthesis, which correlated with an increased surface expression of GluR1-containing  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and an increased frequency of minis (Smith *et al*, 2005). More recent studies from the Schuman laboratory have addressed the role of local protein synthesis regulation in the scaling of synaptic responses. These data indicate a role for local protein synthesis in the regulation and fine-tuning of basal synaptic transmission.

In addition to the new examples of dendrite-localized mRNAs and their different types of physiological regulation, there has been equally important progress in explaining the molecular mechanisms for both mRNA transport and local translation. One well-studied example is the cytoplasmic polyadenylation element (CPE) binding protein 1 (CPEB-1) whose phosphorylation in response to *N*-methyl-D-aspartate (NMDA) receptor activation leads to the translational activation of CaMKII $\alpha$  and other CPE-containing mRNAs (Mendez & Richter, 2001). Research in J. Richter's laboratory (Worcester, MA, USA) has identified several proteins that are part of a complex with CPEB-1 and that act in a coordinated way to facilitate translation regulation through polyadenylation. One crucial factor is Maskin, which is a member of elongation factor eIF4E-binding proteins that inhibit translation (Richter & Sonenberg, 2005). Richter discussed their recent efforts to identify specific brain mRNAs that are regulated by this complex (Du & Richter, 2005). Also in progress is a study to describe phenotypes in CPEB-1-knockout mice, which include impairments in specific forms of long-term plasticity (Alarcon *et al*, 2004) and behaviour. N. Sonenberg (Montreal, Canada) presented exciting findings on a role for an eIF2 $\alpha$  kinase, GCN2, that regulates translational initiation in synaptic plasticity, learning and memory. The phenotype of Gcn2-knockout mice include deficits in late long-term potentiation (LTP) in the hippocampus and impaired performance in the Morris water maze after intense training (Cosat-Mattioli *et al*, 2005).

Important progress has also been made in explaining the functions of neuronal RNA-binding proteins in nuclear aspects of RNA processing that may be necessary for its subsequent cytoplasmic localization. R. Darnell (New York, NY, USA) presented studies on the Nova family of neuron-specific RNA-binding proteins, which regulate alternative splicing and are targeted by the immune system in some autoimmune neurological diseases. Nova-1 binding to pre-mRNA intron sequences of the glycine and GABA(A) receptor subunits has been shown to enhance exon inclusion. Using an ultraviolet-crosslinking and immunoprecipitation (CLIP) method, Darnell has now identified several Nova-1 target RNAs that encode proteins required at inhibitory synapses. In addition, recent microarray analysis of alternatively spliced RNAs from wild-type and Nova-2-knockout mice indicates that many Nova-2 targets correspond to proteins that function at synapses or in aspects of axon guidance (Ule *et al*, 2005). These studies suggest that specific mRNA-binding proteins coordinately regulate a specialized set of mRNAs.

Another family of neuronal RNA-binding proteins with important nuclear functions is the Staufen family of proteins, which are actively transported to dendrites in the form of granules and are necessary for RNA localization. M. Kiebler (Vienna, Austria) discussed nuclear transport and nucleolar localization of Staufen2 (Macchi *et al*, 2004), which may be important for the assembly of mRNP complexes that are core components of dendritic transport granules.

The laboratory of N. Hirokawa (Tokyo, Japan) has recently undertaken a *tour de force* proteomics analysis of RNA granules

and their biochemical association with the kinesin KIF5 tail domain. Hirokawa presented data showing that these large RNase-sensitive granules (1,000S) contain several known dendrite-localized mRNAs, such as CaMKII $\alpha$  and *Arc*, and many RNA-binding proteins (Kanai *et al*, 2004). Further work is needed to identify proteins of RNA granules that interact directly with the kinesin I motor. W. Sossin (Montreal, Canada) discussed a recent biochemical characterization of distinct RNA granule populations. The granules can be seen in dendrites by the distribution of different DEAD box proteins. These and other presentations of RNA transport in granules raised the interesting question of whether all neuronal RNAs move as RNPs or as granules. Further understanding of neuronal RNA motility is needed to answer this question and to show why some RNAs enter both axons and dendrites, whereas others are selectively targeted.

A main goal is to identify the molecular mechanisms involved in synapse-specific translation that can mark synapses for the long-term modifications needed for memory storage. One idea is that synapse-associated kinases could drive persistent changes in synaptic strength. H. Tiedge (Brooklyn, NY, USA) presented work performed in collaboration with T. Sactor (Brooklyn, NY, USA) on the dendritic transport of the mRNA for protein kinase M $\zeta$ , an atypical kinase that might be necessary for some forms of protein synthesis-dependent plasticity (Muslimov *et al*, 2004). Tiedge also discussed the involvement of brain cytoplasmic 1 (BC1) RNA, a small non-coding RNA, in translational regulation. J. Brosius (Münster, Germany) reported that BC1 RNA-deficient mice show reduced exploration and increased anxiety (Lewejohann *et al*, 2004).

The importance of mRNA localization and local protein synthesis in neuronal function indicates that some genetic neurological diseases might be caused by loss or perturbation of the involved proteins (Bassell & Kelic, 2004). One disease that has gained attention in this respect is Fragile X syndrome (FXS), which is the most common inherited form of mental retardation and is caused by loss of an mRNA-binding protein, Fragile X mental retardation protein (FMRP). Morphological studies of human FXS patients and Fmr1-knockout mice have shown an excess of immature dendritic spines, which could result from deficiencies in synaptic protein synthesis (Bagni & Greenough, 2005). R. Darnell and J. Darnell (New York, NY, USA) have recently shown that the FMRP KH domain has a role in translation through its ability to bind to mRNA secondary structural elements (Darnell *et al*, 2005). C. Bagni (Rome, Italy) presented recent data showing that FMRP binds specifically to the RNAs BC1 and BC200 through a new RNA-binding motif (Zalfa *et al*, 2005). Bagni also presented recent evidence that an enriched environment promotes behavioural and morphological recovery in a mouse model for FXS (Restivo *et al*, 2005).

G. Bassell (Emory, GA, USA) showed how specific glutamatergic signals in cultured hippocampal neurons can drive FMRP granule transport along microtubules (Antar *et al*, 2004, 2005). These signals seem to be necessary to support the local translation of key post-synaptic regulatory molecules. Future work is needed to identify specific mRNAs whose impaired activity-dependent translation contributes to the phenotypes of FXS (Weiler *et al*, 2004). B. Oostra (Rotterdam, The Netherlands) presented results from an exciting study showing that deletion of FMRP in Purkinje cells of the cerebellum results in enhanced parallel fibre LTD and elongated spines. Moreover, these mutant mice and human patients with FXS both showed defects in cerebellar eyeblink conditioning (Koekkoek *et al*, 2005).

### Messenger RNA regulation of axonal responses

Although our understanding of dendritic mRNA localization and translation has advanced, the possibility that mRNAs extend into axons and contribute to function on this opposite side of the neuron has not received much attention. Early studies showed that invertebrate axons synthesize proteins and there were some hints that vertebrate axons might contain mRNAs and protein synthetic machinery (reviewed in Giuditta *et al*, 2002). Nevertheless, the idea that axons synthesize proteins remained controversial until the past decade. In retrospect, it is surprising that mRNA localization into the axonal compartment did not receive more consideration given the much greater distance that axons must extend compared with dendrites (Alvarez *et al*, 2000). Considerable progress has recently been made to identify mechanisms for mRNA localization and local protein synthesis in developing and regenerating axons (Piper & Holt, 2004). C. Holt's group (Cambridge, UK) has shown that developing axons require local protein synthesis to respond to extracellular guidance cues in cultured *Xenopus* retinal ganglion cells. Holt presented evidence that guidance cues stimulate the local translation of mRNAs that encode cytoskeletal proteins in growing axons, which could contribute to directional turning in growth cones. M. Fainzilber (Rehovot, Israel) showed that mRNAs are also present in uninjured vertebrate axons and, at least for importin- $\beta$  mRNA, local translation of these mRNAs is triggered by axonal injury (Hanz *et al*, 2003). This injury-induced axonal protein synthesis assembles a retrograde signalling complex that delivers a cargo of activated mitogen-activated protein (MAP) kinases to the cell body (Perlson *et al*, 2005). Continuing studies presented by Fainzilber raise the possibility that other components involved in cytoplasmic-nuclear transport are locally assembled in the axons for translation-dependent retrograde signalling.

Model systems to distinguish axonal from non-neuronal and even dendritic protein synthesis have been difficult to identify. However, the larger diameters of some invertebrate neurons are advantageous for manipulation in culture. M. Spira (Jerusalem, Israel) has previously used this advantage to show that an influx of calcium and localized proteolysis are needed to initiate growth cone formation in neurites of cultured *Aplysia* neurons (Spira *et al*, 2003). Although it is not clear whether local protein synthesis is needed for growth cone formation in *Aplysia*, Holt has shown that some turning responses of *Xenopus* retinal axons require both proteolysis and mRNA translation (Campbell & Holt, 2001). Fainzilber's presentation complemented this by showing that locally synthesized vimentin protein is proteolytically cleaved and that the cleavage product forms a scaffold for activated MAP kinases to bind to Importins (Perlson *et al*, 2005). Taken together, these studies suggest that translation of axonal mRNAs and proteolysis can sequentially coordinate neuronal responses to extracellular stimuli. Spira presented recent advances with microinjection of fluorescent mRNAs that encode green fluorescent protein (GFP) and other fluorescent fusion proteins into *Aplysia* neurons for analysing mechanisms of growth cone formation.

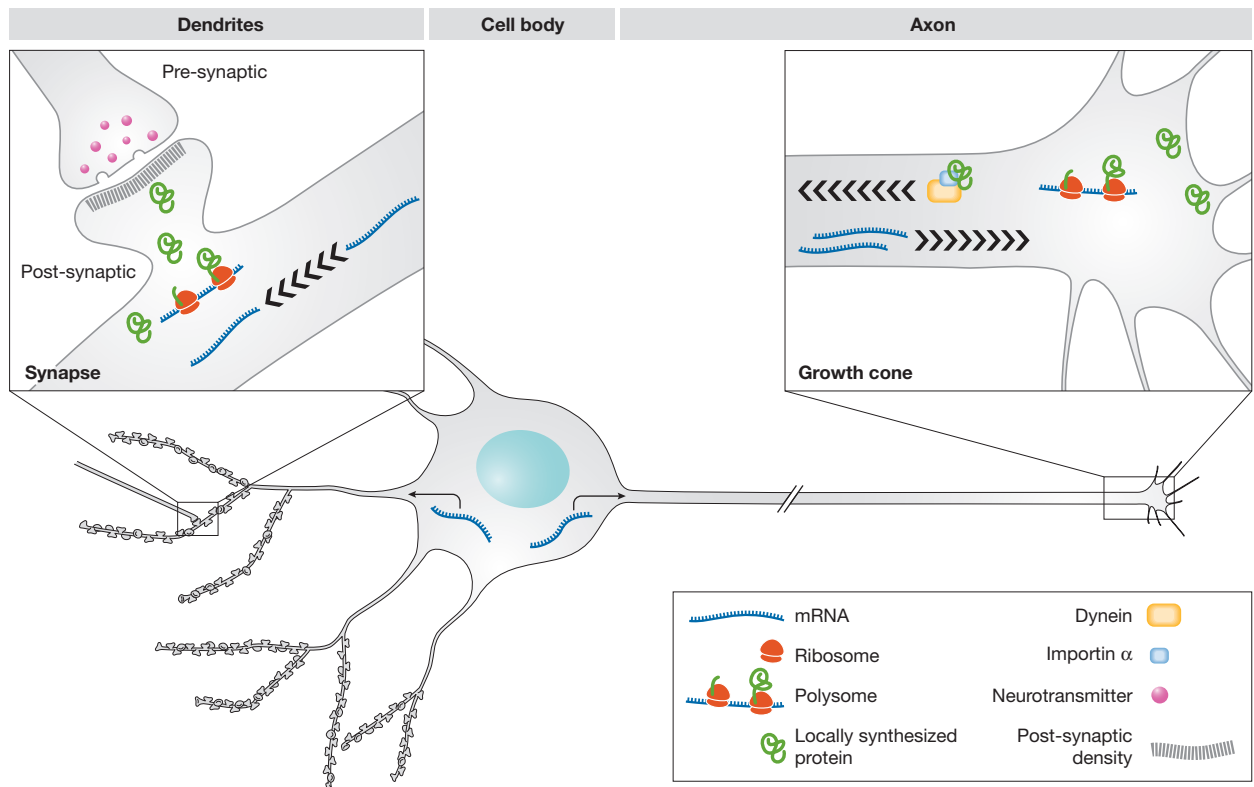
Further understanding of how the responses of growing axons are regulated by axonal mRNA translation will require determining whether there is any specificity to the axonal protein synthesis machinery. Knowledge of which mRNAs are localized to axons has so far been limited (Piper & Holt, 2004). J. Twiss's group (Wilmington, DE, USA) has recently expanded the list of known axonally synthesized proteins through a proteomics screen using the rat sensory neuron model (Willis *et al*, 2005). In addition, Twiss showed evidence for specificity of axonal mRNA transport in response to extracellular

stimuli. Using a quantitative PCR approach, he presented new data showing both increases and decreases in the transport of specific axonal mRNAs from the cell body into axons of cultured adult rat neurons. Stimuli that regulate transport included both positive and negative regulators of axonal growth. Altering the levels of particular mRNAs in the axonal compartment represents at least one way to control the specificity of axonal protein synthesis.

Analyses of mRNA transport complexes suggest that mRNAs are translationally inactive while being transported from the cell body. For  $\beta$ -actin mRNA, the RNA-binding protein, ZBP1, is needed for its localization to dendrites, axons and the migratory front of fibroblasts. S. Hüttelmaier (Halle, Germany) in R. Singer's laboratory (Bronx, NY, USA) showed evidence for Src-dependent phosphorylation of ZBP1. ZBP binding to  $\beta$ -actin mRNA prevents its translation, whereas phosphorylation of ZBP1 allows translation to occur (Hüttelmaier *et al*, 2005). Therefore, the RNA transport machinery might provide a process for tight control of specific mRNA translation. ZBP1 is a member of a conserved family of RNA-binding proteins that J. Yisraeli's lab (Jerusalem, Israel) has studied. Yisraeli showed that the members of this ZBP protein family have a role in neural-crest-cell migration and carcinogenesis (Yaniv *et al*, 2003). Given that  $\beta$ -actin mRNA localization was initially demonstrated during fibroblast migration, mRNA localization in developmental and pathological forms of cell migration now seems an obvious function for these RNA-binding proteins. It is now important to determine the specific mRNAs to which these ZBP family proteins bind.

The Bassell, Beattie, and Sendtner groups have proposed the exciting possibility that alterations of axonal RNA transport might contribute to motor neuron loss in spinal muscular atrophy (SMA; Zhang *et al*, 2003; McWhorter *et al*, 2003; Rossoll *et al*, 2003). SMA develops from the inherited loss of full-length Survival of motor neuron (SMN) protein, which has diverse roles in the assembly of RNP complexes. The function of SMN in small nuclear ribonucleoprotein particle (snRNP) assembly has been well documented by G. Dreyfuss (Philadelphia, PA, USA) and colleagues, suggesting the possibility that SMA might be due, in part, to altered splicing or spliceosome availability. At the meeting, Dreyfuss presented past findings on how SMN helps to assemble the snRNPs needed for mRNA splicing. Assembly of snRNPs is directly proportionate to the amount of SMN protein available (Wan *et al*, 2005). However, as SMN is ubiquitously expressed and all cells need to assemble snRNPs, SMN might have some specific neuronal function that relates to the disease phenotype in SMA. SMN forms cytoplasmic granules that are transported into axons and neurons transfected with SMN lacking exon 7, found in SMA, show reduced neurite outgrowth (Zhang *et al*, 2003). It will be interesting to find out if this axonal sorting of SMN relates to the assembly of mRNP localization complexes that might be impaired in SMA.

As humans have two copies of the *SMN* gene, and SMA involves loss of *SMN1* gene function, altering *SMN2* splicing has been proposed as a therapeutic target in SMA. RNA transcripts of the *SMN2* gene are alternatively spliced to yield predominantly protein products lacking exon 7. These could be enhanced to be more like SMN1, which produces mostly full-length mRNAs that include exon 7. J. Manley (New York, NY, USA) showed that an exonic splicing silencer (ESS) is created by the C to T transition in exon 7 of the *SMN2* gene. Analyses of the proteins that bind to this ESS and to other elements in the SMN2 primary transcript indicate that heterogeneous nuclear RNP A1 has a key role in determining whether SMN2 mRNA contains exon 7 (Kashima & Manley, 2003).



**Fig 1** | Regulation of neuronal functions by localized mRNAs. Schematic of a polarized neuron. For dendrites, translationally active mRNAs (polysomes) are concentrated at the base of the dendritic spines. Post-synaptic protein synthesis is regulated by trans-synaptic stimuli where the locally synthesized proteins contribute to synaptic components of the dendritic spine, translational machinery and cytoskeleton. Activity also selectively targets some dendritic mRNAs (for example, Arc) to activated synapses. For axons, ribosomes appear uniquely concentrated in growth cones. Axonal protein synthesis is regulated by guidance cues in growing axons and by injury in mature axons. Guidance cues also modulate anterograde transport of axonal mRNAs. In addition to synthesis of cytoskeletal elements, axonally synthesized importin-β and vimentin proteins assemble into a retrograde signalling complex with existing axonal proteins.

**Future directions**

In *Aplysia* sensory-motor neuron co-cultures, rapamycin-sensitive protein synthesis in presynaptic terminals is required for LTF—a form of plasticity thought to underlie learning and memory. E. Kandel’s (New York, NY, USA) work in *Aplysia* and mammalian systems has made seminal advances in our understanding of the molecular mechanisms involved in these processes. Studies from the Kandel group, using both *Aplysia* and mouse models, support the concept that local protein synthesis controls synapse-specific plasticity. Kandel discussed recent work showing that the neuronal-specific isoform of the CPEB protein is locally synthesized in *Aplysia* neurites and is required to maintain LTF stably at synapses (Si *et al*, 2003a). This neuronal CPEB has a unique folding capability, which is conferred by its amino-terminus and is self-perpetuating, similar to prion proteins (Si *et al*, 2003b). Kandel proposed that this could provide a unique conformational state of CPEB at the synapse that is maintained by virtue of the prion-like quality (Si *et al*, 2003b). Homology to this unique amino-terminal region of the *Aplysia* neuronal CPEB is apparently seen in CPEB isoforms that are expressed in mouse CNS neurons (Theis *et al*, 2003), suggesting that this prion-like property may extend to mammalian CPEBs. It is intriguing to speculate that distinct qualities of locally synthesized proteins, either in

dendrites or axons, could provide long-lasting modifications at the subcellular site of their synthesis.

In closing comments, O. Steward (Irvine, CA) provided a perspective for future directions of mRNA control of neuronal function (Fig 1). Indeed, the field has grown substantially since Steward’s classical observations of polysomes at the base of dendritic spines. Whereas mRNA control of dendritic function, particularly synaptic plasticity, has received much attention during the past three decades, localized mRNAs regulating axonal function is now taking centre stage. The possibility that mRNA localization and translation defects can contribute to human diseases such as SMA and FXS is an area of intense study (Bassell & Kelic, 2004). Steward suggested that we might see therapeutic strategies for modifying neuronal mRNA localization and protein synthesis for diseases such as SMA and FXS, and even for restoring axonal or dendritic potential for regrowth during the next decade.

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## REFERENCES

- Alarcon JM, Hodgman R, Theis M, Huang YS, Kandel ER, Richter JD (2004) Selective modulation of some forms of Schaffer collateral-CA1 synaptic plasticity in mice with a disruption of the CPEB-1 gene. *Learn Mem* **11**: 318–327
- Alvarez J, Giuditta A, Koenig E (2000) Protein synthesis in axons and terminals: significance for maintenance, plasticity and regulation of phenotype. With a critique of slow transport theory. *Prog Neurobiol* **62**: 1–62
- Antar LN, Afroz R, Dichtenberg 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**: 2648–2655
- Antar LN, Dichtenberg JB, Plociniak M, Afroz R, Bassell GJ (2005) Localization of FMRP-associated mRNA granules and requirement of microtubules for activity-dependent trafficking in hippocampal neurons. *Genes Brain Behav* **4**: 350–359
- Bagni C, Greenough WT (2005) From mRNP trafficking to spine dysmorphogenesis: the roots of fragile X syndrome. *Nat Rev Neurosci* **6**: 376–387
- Bassell GJ, Kelic S (2004) Binding proteins for mRNA localization and local translation, and their dysfunction in genetic neurological disease. *Curr Opin Neurobiol* **14**: 574–581
- Campbell D, Holt C (2001) Chemotropic responses of reginal growth cones mediated by rapid local protein synthesis and degradation. *Neuron* **32**: 1013–1016
- Costa-Mattioli M *et al* (2005) Translational control of hippocampal synaptic plasticity and memory by the eIF2 $\alpha$  kinase GCN2. *Nature* **436**: 1166–1173
- Darnell JC, Fraser CE, Mostovetsky O, Stefani G, Jones TA, Eddy SR, Darnell RB (2005) Kissing complex RNAs mediate interaction between the Fragile-X mental retardation protein KH2 domain and brain polyribosomes. *Genes Dev* **19**: 903–918
- Du L, Richter JD (2005) Activity-dependent polyadenylation in neurons. *RNA* **11**: 1340–1347
- Giuditta A, Kaplan BB, van Minnen J, Alvarez J, Koenig E (2002) Axonal and presynaptic protein synthesis: new insights into the biology of the neuron. *Trends Neurosci* **25**: 400–404
- Hanz S *et al* (2003) Axoplasmic importins enable retrograde injury signalling in lesioned nerve. *Neuron* **40**: 1095–1104
- Huang F, Chotiner JK, Steward O (2005) The mRNA for elongation factor 1 $\alpha$  is localized in dendrites and translated in response to treatments that induce long-term depression. *J Neurosci* **25**: 7199–7209
- Huttelmaier S, Zenklusen D, Lederer M, Dichtenberg J, Lorenz M, Meng X, Bassell GJ, Condeelis J, Singer RH (2005) Spatial regulation of  $\beta$ -actin mRNA translation by Src-dependent phosphorylation of ZBP1. *Nature* **438**: 512–515
- Kanai Y, Dohmae N, Hirokawa N (2004) Kinesin transports RNA: isolation and characterization of an RNA-transporting granule. *Neuron* **43**: 513–525
- Kashima T, Manley JL (2003) A negative element in SMN2 exon 7 inhibits splicing in spinal muscular atrophy. *Nat Genet* **34**: 460–463
- Koekoek SK *et al* (2005) Deletion of FMR1 in Purkinje cells enhances parallel fiber LTD, enlarges spines, and attenuates cerebellar eyelid conditioning in fragile X syndrome. *Neuron* **47**: 339–352
- Lewejohann L *et al* (2004) Role of a neuronal small non-messenger RNA: behavioural alterations in BC1 RNA-deleted mice. *Behav Brain Res* **154**: 273–289
- Macchi P, Brownawell AM, Grunewald B, DesGroseillers L, Macara IG, Kiebler MA (2004) The brain-specific double-stranded RNA-binding protein Staufen2: nucleolar accumulation and isoform-specific exportin-5-dependent export. *J Biol Chem* **279**: 31440–31444
- McWhorter ML, Monani UR, Burghes AH, Beattie CE (2003) Knockdown of the survival motor neuron (Smn) protein in zebrafish causes defects in motor axon outgrowth and pathfinding. *J Cell Biol* **162**: 919–931
- Mendez R, Richter JD (2001) Translational control by CPEB: a means to the end. *Nat Rev Mol Cell Biol* **2**: 521–529
- Muslimov IA, Nimrich V, Hernandez AI, Tcherepanov A, Sacktor TC, Tiedge H (2004) Dendritic transport and localization of protein kinase M $\zeta$  mRNA: implications for molecular memory consolidation. *J Biol Chem* **279**: 52613–52622
- Perlson E, Hanz S, Ben-Yaakov K, Segal-Ruder Y, Seger R, Fainzilber M (2005) Vimentin-dependent spatial translocation of an activated MAP kinase in injured nerve. *Neuron* **45**: 715–726
- Piper M, Holt C (2004) RNA translation in axons. *Annu Rev Dev Biol* **20**: 505–523
- Piper M, Salih S, Weint C, Holt CE, Harris WA (2005) Endocytosis dependent desensitization and protein synthesis-dependent resensitization in retinal growth cone adaptation. *Nat Neurosci* **8**: 179–186
- Restivo L, Ferrari F, Passino E, Sgobio C, Bock J, Oostra BA, Bagni C, Ammassari-Teule M (2005) Enriched environment promotes behavioral and morphological recovery in a mouse model for the fragile X syndrome. *Proc Natl Acad Sci USA* **102**: 11557–11562
- Richter JD, Sonenberg N (2005) Regulation of cap-dependent translation by eIF4E inhibitory proteins. *Nature* **433**: 477–480
- Rossoll W, Jablonka S, Andreassi C, Kroning AK, Karle K, Monani UR, Sendtner M (2003) Smn, the spinal muscular atrophy-determining gene product, modulates axon growth and localization of  $\beta$ -actin mRNA in growth cones of motoneurons. *J Cell Biol* **163**: 801–812
- Si K, Giustetto M, Etkin A, Hsu R, Janisiewicz AM, Miniaci MC, Kim JH, Zhu H, Kandel ER (2003a) A neuronal isoform of CPEB regulates local protein synthesis and stabilizes synapse-specific long-term facilitation in *Aplysia*. *Cell* **115**: 893–904
- Si K, Lindquist S, Kandel ER (2003b) A neuronal isoform of the *Aplysia* CPEB has prion-like properties. *Cell* **115**: 879–891
- Smith WB, Starck S, Roberts RW, Schuman EM (2005) Dopaminergic stimulation of local protein synthesis enhances surface expression of GluR1 and synaptic transmission in hippocampal neurons. *Neuron* **45**: 765–779
- Spira ME, Oren R, Dormann A, Gitler D (2003) Critical calpain-dependent ultrastructural alterations underlie the transformation of an axonal segment into a growth cone after axotomy of cultured *Aplysia* neurons. *J Comp Neurol* **457**: 293–312
- Steward O, Levy WB (1982) Preferential localization of polysomes under the base of dendritic spines in granule cells of the dentate gyrus. *J Neurosci* **2**: 248–291
- Steward O, Worley PF (2001) A cellular mechanism for targeting newly synthesized mRNAs to synaptic sites on dendrites. *Proc Natl Acad Sci USA* **98**: 7062–7068
- Sutton MA, Schuman EM (2005) Local translational control in dendrites and its role in long-term synaptic plasticity. *J Neurobiol* **64**: 116–131
- Sutton MA, Wall NR, Aakalu GN, Schuman EM (2004) Regulation of dendritic protein synthesis by miniature synaptic events. *Science* **304**: 1979–1983
- Theis M, Si K, Kandel ER (2003) Two previously undescribed members of the mouse CPEB family of genes and their inducible expression in the principal cell layers of the hippocampus. *Proc Natl Acad Sci USA* **100**: 9602–9607
- Ule J *et al* (2005) Nova regulates brain-specific splicing to shape the synapse. *Nat Genet* **37**: 844–852
- Waltereit R, Dammermann B, Wulff P, Scafidi J, Staubli U, Kauselmann G, Bundman M, Kuhl D (2001) Arg3.1/Arc mRNA induction by Ca<sup>2+</sup> and cAMP requires protein kinase A and mitogen-activated protein kinase/extracellular regulated kinase activation. *J Neurosci* **21**: 5484–5493
- Wan L, Battle DJ, Yong J, Gubitza AK, Kolb SJ, Wang J, Dreyfuss G (2005) The survival of motor neurons protein determines the capacity for snRNP assembly: biochemical deficiency in spinal muscular atrophy. *Mol Cell Biol* **25**: 5543–5551
- Weiler JJ *et al* (2004) Fragile X mental retardation protein is necessary for neurotransmitter-activated protein translation at synapses. *Proc Natl Acad Sci USA* **101**: 17504–17509
- Willis D, Li KW, Zheng JQ, Chang JH, Smit A, Kelly T, Merianda TT, Sylvester J, van Minnen J, Twiss JL (2005) Differential transport and local translation of cytoskeletal, injury-response, and neurodegeneration protein mRNAs in axons. *J Neurosci* **25**: 778–791
- Yaniv K, Fainsod A, Kalcheim C, Yisraeli JK (2003) The RNA-binding protein Vg1 RBP is required for cell migration during early neural development. *Development* **130**: 5649–5661
- Zalfa F, Adinolfi S, Napoli I, Kuhn-Holsken E, Urlaub H, Achsel T, Pastore A, Bagni C (2005) FMRP binds specifically to the brain cytoplasmic RNAs BC1/BC200 via a novel RNA binding motif. *J Biol Chem* **280**: 33403–33410
- Zhang HL, Pan F, Hong D, Shenoy SM, Singer RH, Bassell GJ (2003) Active transport of the survival motor neuron protein and the role of exon-7 in cytoplasmic localization. *J Neurosci* **23**: 6627–6637