Two main mechanisms for delivering integral membrane proteins and secreted factors to the appropriate neuronal domain:

1. Long-range protein trafficking (from cell body to proximal/distal dendrites, axon, presynaptic terminal, etc……)

2. Local RNA translation and trafficking (within dendritic spines, growth cones, immature axon terminals and regenerating axons)

RNA localization

Sorting of mRNAs to subcellular domains is an evolutionary conserved mechanism

(from fungi to plants and animals)

local high-level production of the encoded protein at the site of mRNA localization

Spatially restricting gene expression by local translation in neurons

- ✓ **mRNA localization** and **regulated translation** provide a means of spatially restricting gene expression within each of the thousands of subcellular compartments made by a neuron, thereby vastly increasing the computational capacity of the brain.

- ✓ Recent studies reveal that local translation is **regulated by stimuli** that trigger **neurite outgrowth** and/or collapse, axon guidance, **synapse formation**, pruning, activity-dependent **synaptic plasticity**, and **injury**-induced axonal regeneration.

- ✓ Impairments in the local regulation of translation result in aberrant signaling, physiology and morphology of neurons, and are **linked to neurological disorders**.

In neurons, specific mRNAs are transported to dendritic spines

LOCALIZATION AND TRANSLATION OF mRNA IN DENDRITES AND AXONS

Christy Job and James Eberwine

The neurons of the brain extend axons and dendrites many hundreds of micrometres away from the cell body. The first electron microscope studies of these processes revealed that many of the structures that are found in the cell body are also present in dendrites. For example, particles resembling ribosomes and membrane structures like those of the endoplasmic reticulum (two structures that are important for protein synthesis) were seen in distal regions of dendrites, near synapses. Subsequent studies focused on identifying messenger RNAs in dendrites and providing evidence of dendritic protein synthesis. Transfection technologies have now been used to analyse translation within dendrites in response to pharmacological stimuli. These studies provide us with clues to the physiological role of the dendrite not just as a signal transducer, but also as a modulator of long-term synaptic efficacy.

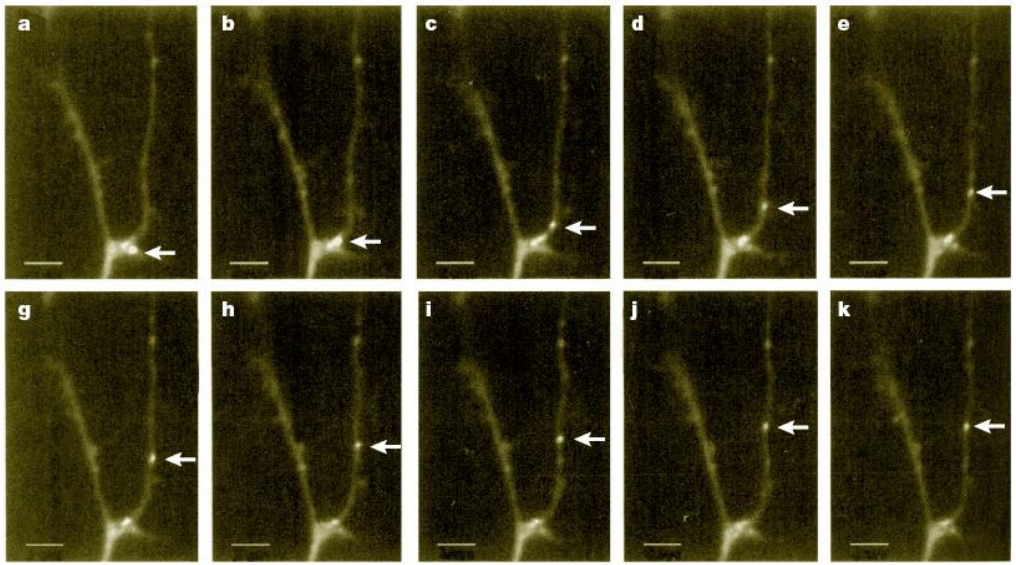


Figure 4 | **Movement of RNA-containing granules in dendrites of cultured neurons. a–k** | Time-lapse images, taken 20 s apart, of an anterograde-moving granule (arrow). The granule is detected by visualization of fluorescent SYTO-14, which binds to RNA. The granule moves more than 5 μm, with an average velocity of 0.04 μm s^{-1}. This movement was stimulated by depolarization. Reproduced with permission from REF. 34 © 2000 Society for Neuroscience.

Movement of **RNA-containing granules** in dendrites (visualized with the fluorescent dye SITO-14)

Job & Eberwine, 2001
Nature Reviews Neurosci 2:889-898

Neuronal dendrites can be isolated by mechanical dissection, this preparation can be used for further molecular analysis

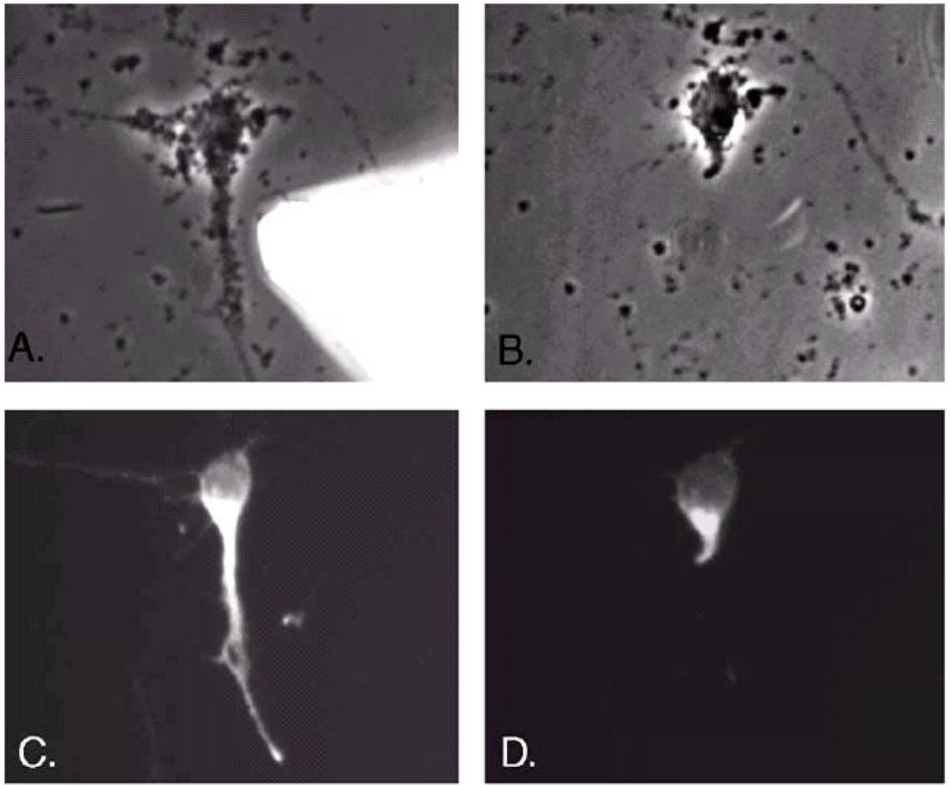
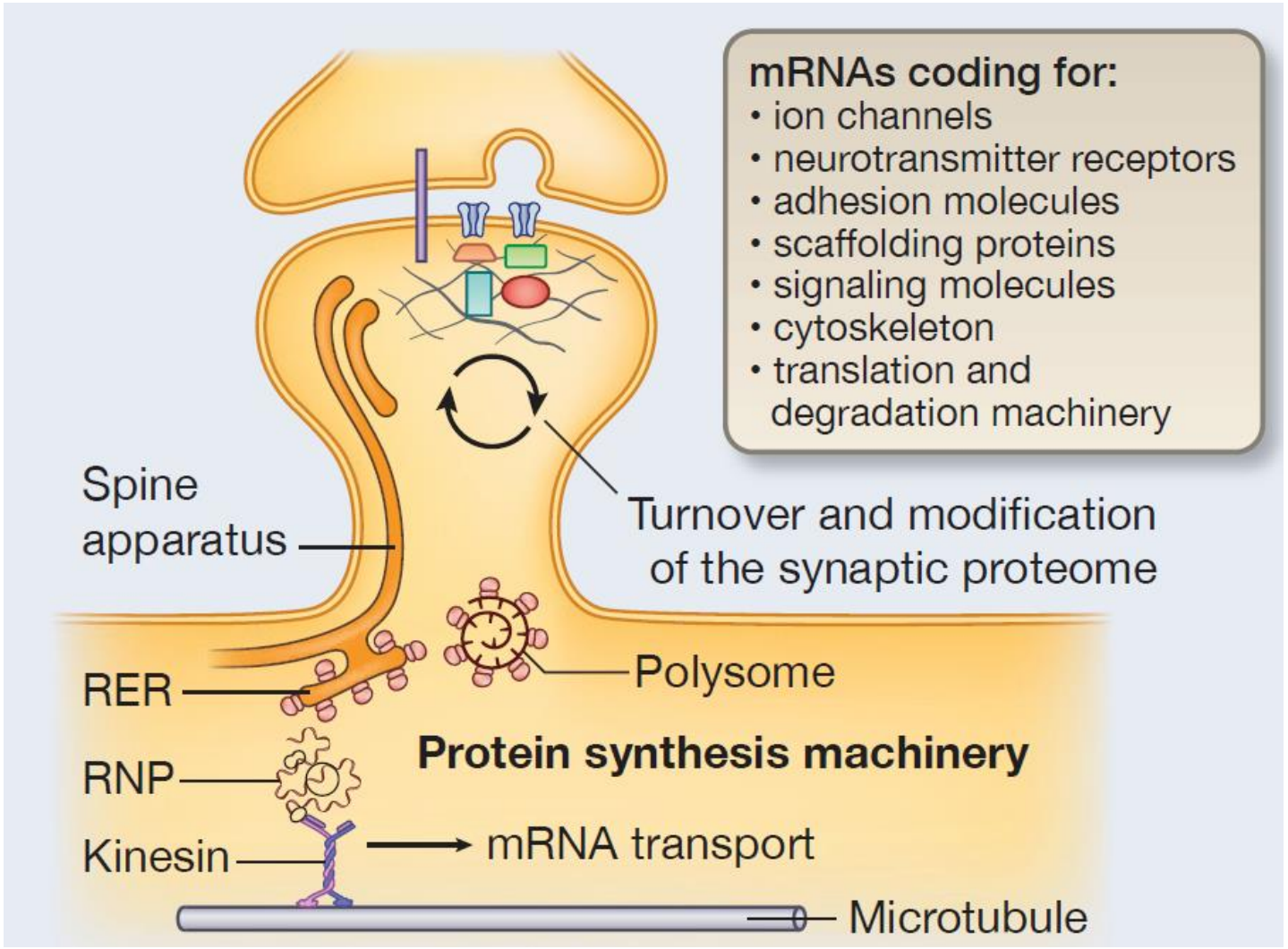


Fig. 2. The mechanical dissection of a neuronal dendrite. An individual neuron is shown in phase (panel A) and upon fluorescence from transfected GFP (panel C). The patch pipette used to sever the process is shown in panel A. Panels B and D show the remaining cell soma after the dendrite has been severed and harvested into the patch pipette. This mechanical severing is quite easy and can yield approximately 5 dendrites/min.

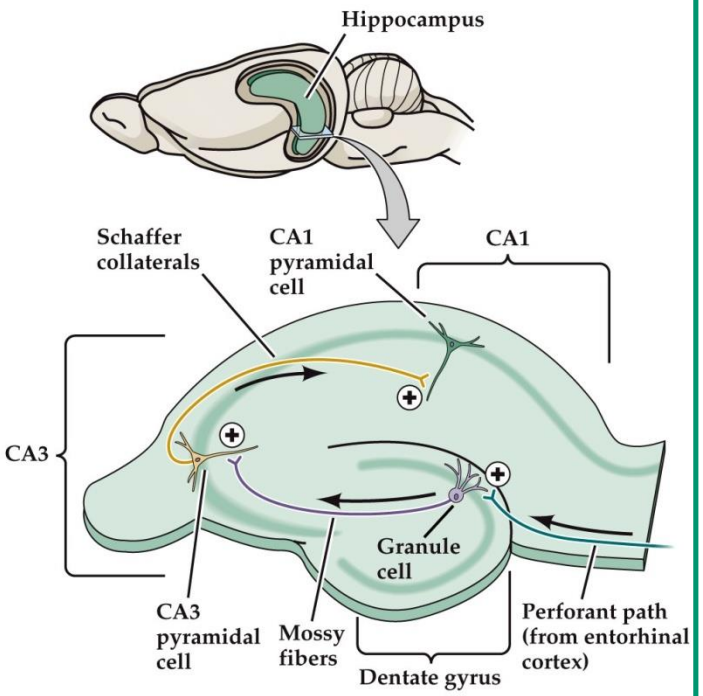
Hinkle et al., 2004
Progress In Neurobiology
doi:10.1016/j.pneurobio.2004.01.001

Which proteins can be synthesized locally in dendrites of mature neurons?

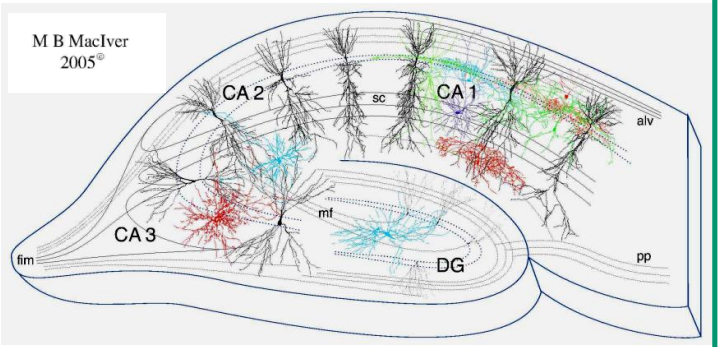


Diek et al., 2014, Neuron
http://dx.doi.org/10.1016/j.neuron.2014.02.009

Microdissection of stratum pyramidale (cell bodies) and stratum radiatum (dendritic lamina) from adult rat hippocampus to compare the mRNA expression profiles



NEUROSCIENCE 5e, Figure 8.6
© 2012 Sinauer Associates, Inc.



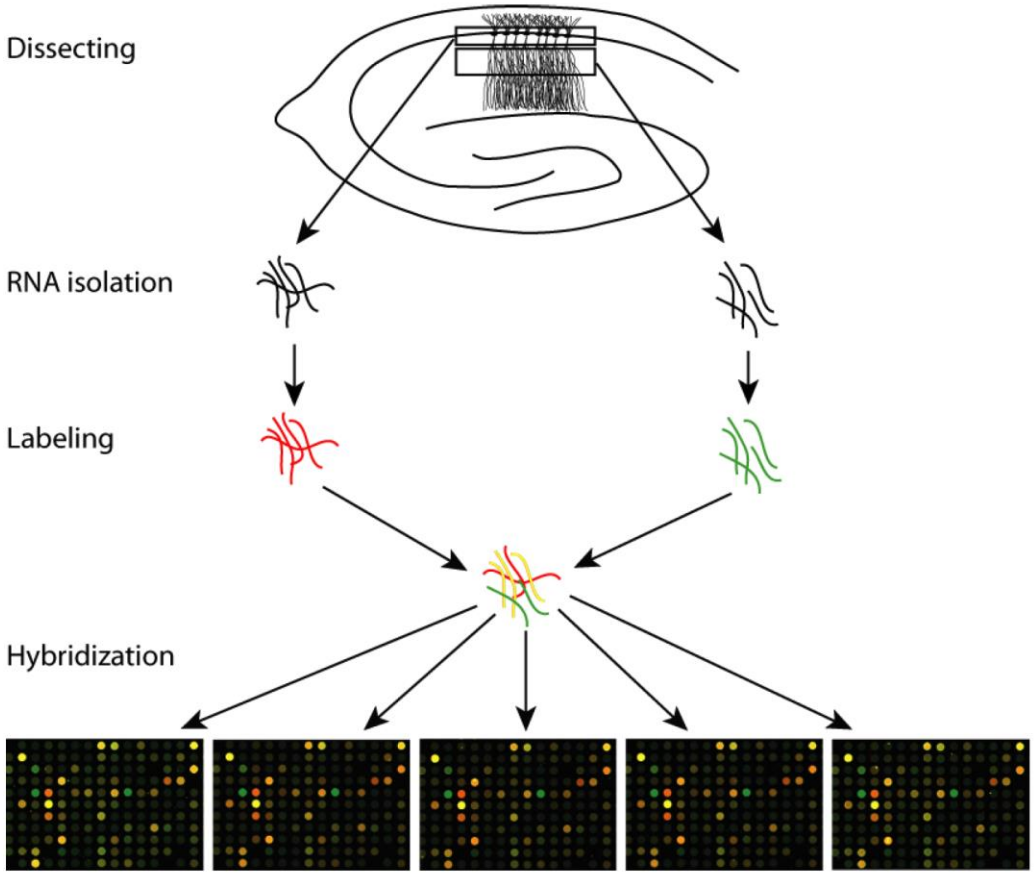


Figure 1
A schematic diagram of the experiment. Stratum pyramidale and stratum radiatum were dissected from hippocampal slices of adult rats. Total RNA extracted from each fraction was reverse primed with a T7 promoter-conjugated oligo-d(T) primer and labeled with either Cyanine 3 or Cyanine 5 through *in vitro* transcription. Equal amount of labeled probes were mixed and hybridized to a set of five replicates of the Agilent 22 K rat oligonucleotide microarray. Enlarged views of the microarrays are presented showing reproducible hybridization.

Zhong et al., 2006, BMC Neuroscience
http://www.biomedcentral.com/1471-2202/7/17

Categories of dendritic mRNAs present in hippocampal pyramidal neurons

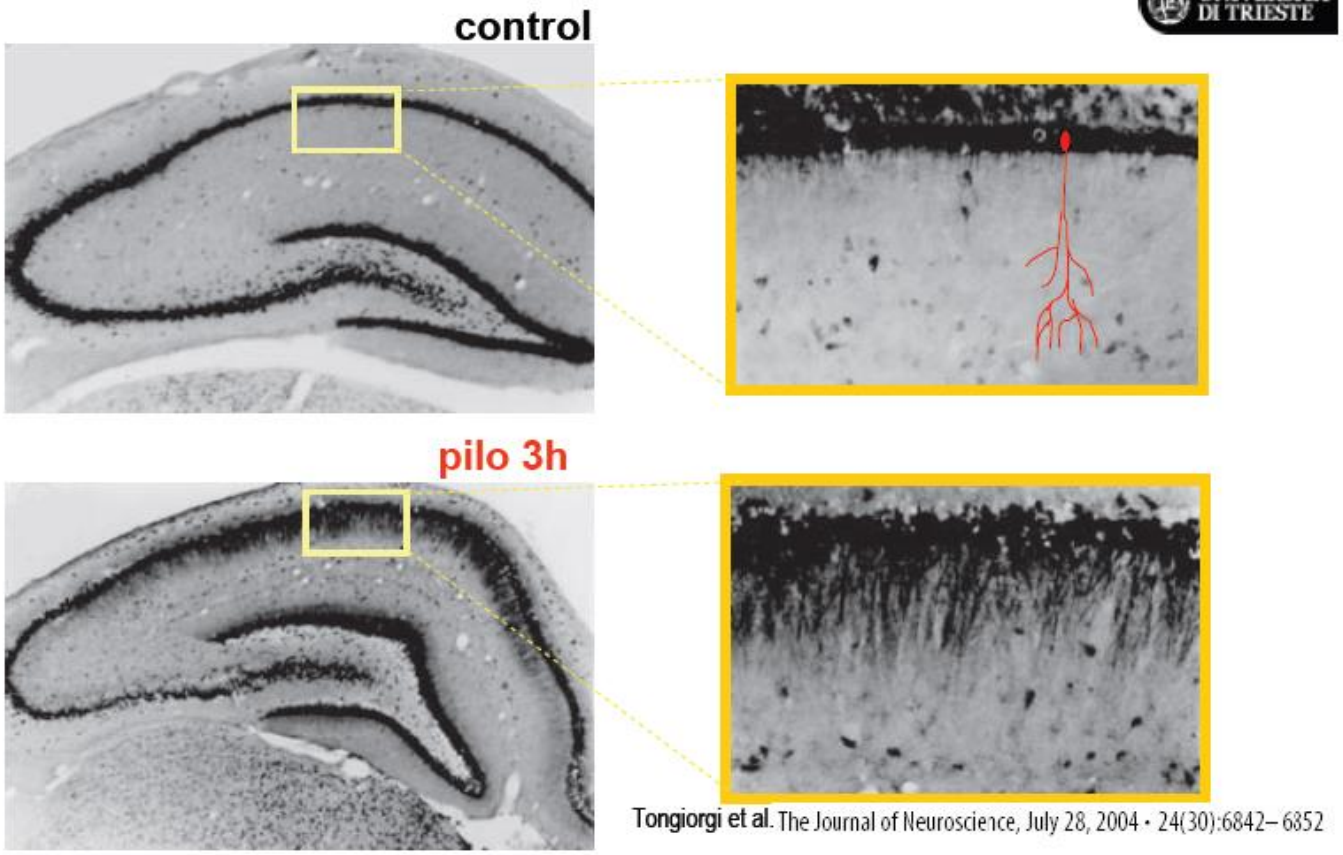
Estimated 150-400 different mRNAs (~5% expressed genes)
(Eberwine et al, 2002, Zhong et al., 2006; Poon et al., 2007)

Category of mRNAs in CA1 dendrites	percentage
Receptors, ion channels, and postsynaptic molecules	7.8%
Cytoskeleton	7.8%
Extracellular matrix, cell adhesion, and immuno-molecules	20.1%
Signal transduction and Protein modification	16.9%
Translation factors and RNA-binding proteins	4.5%
Ribosomal proteins	16.2%
Peptide processing and degradation	7.8%
Protein transport, membrane trafficking, endocytosis, and exocytosis	6.5%
Molecular motor	0.6%
Growth factors	2.6%
Other	9.1%

BDNF

Zhong et al., 2006, BMC Neuroscience
http://www.biomedcentral.com/1471-2202/7/17

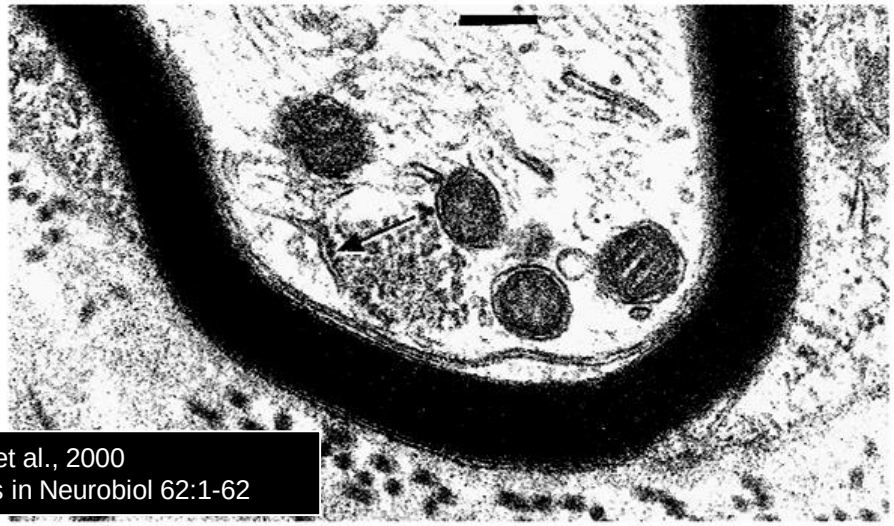
Epileptogenic seizures induce *in vivo* accumulation of BDNF mRNA in dendrites



Tongiorgi et al. The Journal of Neuroscience, July 28, 2004 • 24(30):6842–6852

mRNA transport in axons?

Polyribosomes in axons?



Alvarez et al., 2000
Progress in Neurobiol 62:1-62

Fig. 12. A conventional electron micrograph kindly provided by Prof. Ennio Pannese (University of Milan), showing a myelinated axon from the sensory portion of a rabbit spinal nerve located close to the dorsal root ganglion, in which ribosomes are clustered near the axolemma. Note that some ribosomes appear attached to a tubular endoplasmic reticulum (arrow). Reproduced from Fig. 2a in Pannese and Ledda (1991), with permission of Nuova Immagine Editrice. Calibration, 0.2 μm.

Giuditta et al., 2002
Trends in Neurosci 25:400-4

Opinion TRENDS in Neurosciences Vol.25 No.8

Axonal and presynaptic protein synthesis: new insights into the biology of the neuron

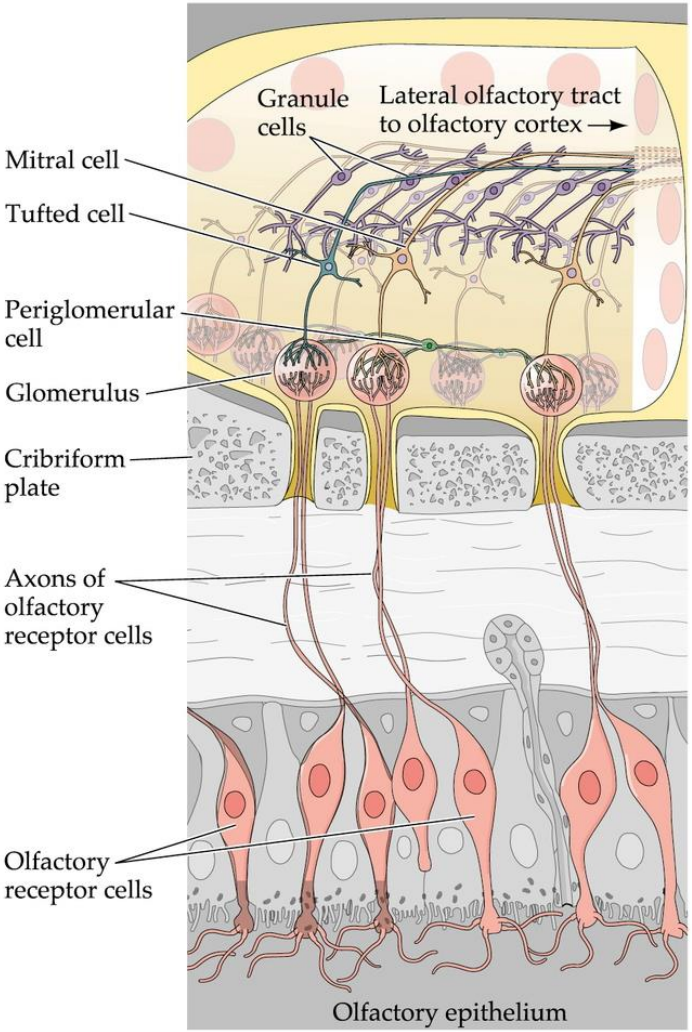
Antonio Giuditta, Barry B. Kaplan, Jan van Minnen, Jaime Alvarez and Edward Koenig

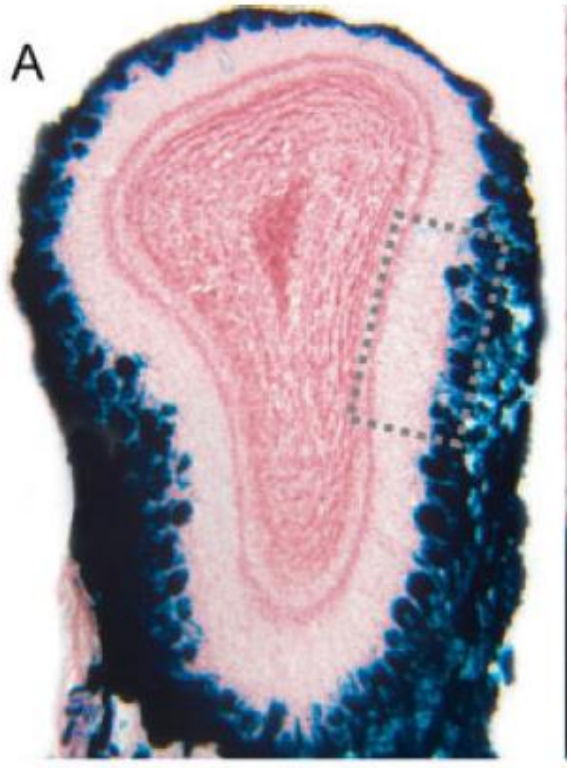
The presence of a local mRNA translation system in axons and terminals was proposed almost 40 years ago. Over the ensuing period, an impressive body of evidence has grown to support this proposal – yet the nerve cell body is still considered to be the only source of axonal and presynaptic proteins. To dispel this lingering neglect, we now present the wealth of recent observations bearing on this central idea, and consider their impact on our understanding of the biology of the neuron. We demonstrate that extrasomatic translation sites, which are now well recognized in dendrites, are also present in axonal and presynaptic compartments.

Early studies clearly indicated that presynaptic protein synthesis plays a part in the navigation of axonal growth cones in developing neurons, that presynaptic translation plays a part in invertebrate neurons and in specific classes of vertebrate neurons whose axonal/dendritic polarity might not be not fully established, and finally, that axonal protein synthesis is recruited during regeneration of injured axons.

However, in the last 2-3 years the idea that there is no mRNA transport and protein synthesis in normal mature axons has changed!!!

Transport of specific mRNAs along the axons of olfactory neurons

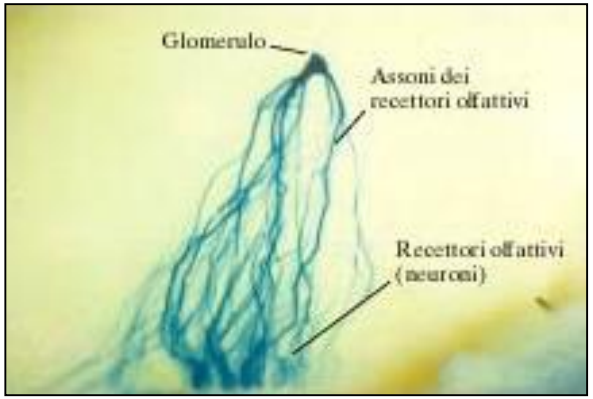


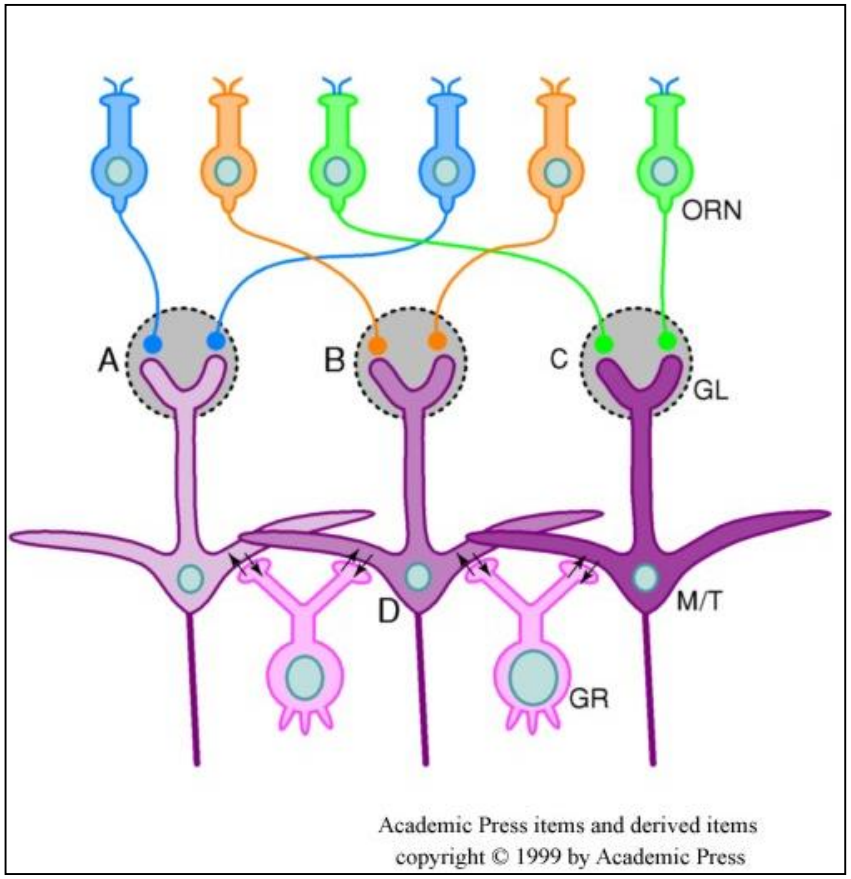


J Neurosci 1995,15:4827-37

Olfactory marker protein mRNA is found in axons of olfactory receptor neurons.
Wensley CH, Stone DM, Baker H, Kauer JS, Margolis FL, Chikaraishi DM.

The mRNA encoding each olfactory receptor is transported along the axon to a single glomerulus

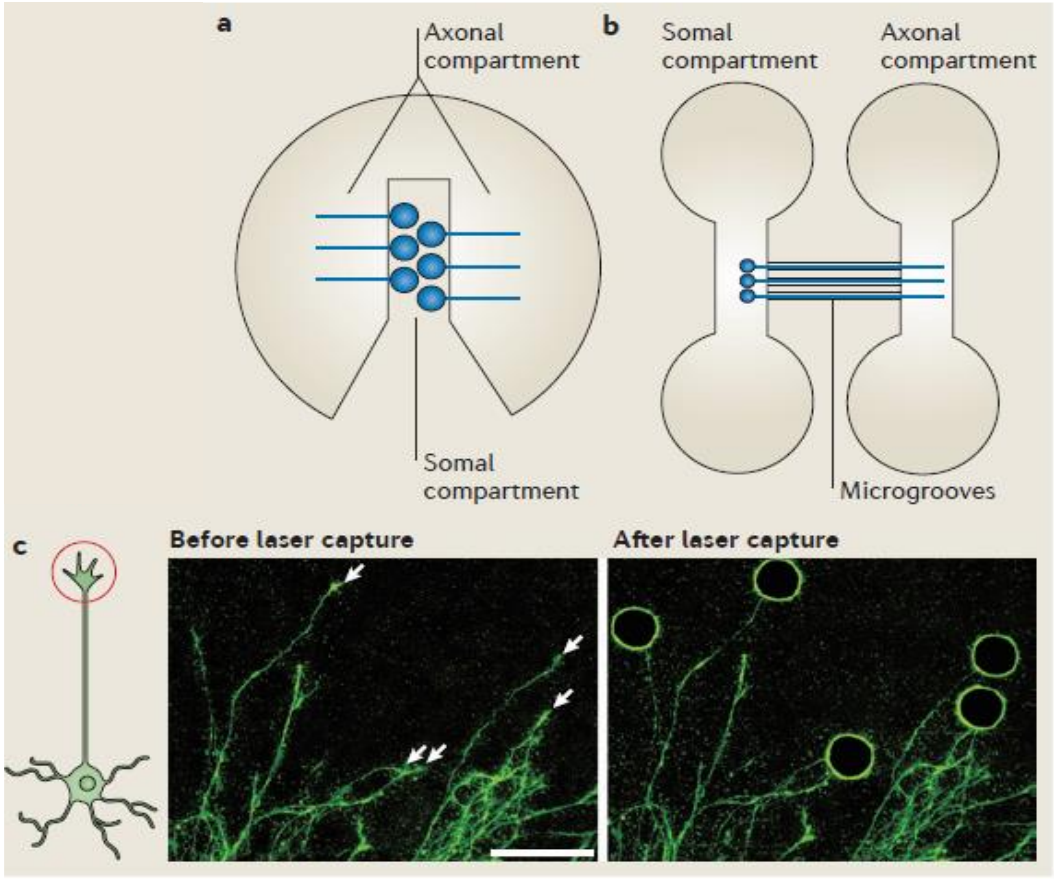




New methods used to study axonal mRNA translation and transport

- ***Axonal mRNA isolation and transcriptome analysis*** - The axons of cultured neurons are separated from their cell bodies using compartmentalized culture systems or laser-capture microdissection
- ***Live imaging of translational reporter fluorescence*** - For mRNAs whose *cis*-acting translational regulatory element is known, translation can be visualized in real-time using a fluorescent reporter whose translation is regulated by the same *cis*-acting element.
- ***Visualization of mRNAs and RNA-binding proteins*** - mRNAs can be visualized indirectly using the sequence-specific interaction of MS2 bacteriophage RNA hairpin and capsid protein (known as MS2 tagging). RNA-binding proteins fused to a fluorescent protein can also be visualized. Extracellular cue-induced changes in localization of mRNAs and RNA-binding proteins can be visualized in real-time or after fixation.
- ***Unbiased screening of* de novo *proteome or translatome*** - *De novo* proteins in axons can be metabolically labelled (i.e. using radioactive methionine), separated by two-dimensional electrophoresis, and identified by mass spectrometry. A challenge is to obtain sufficient amounts of axonally synthesized proteins (less than 5% of total protein synthesis in cultured sympathetic neurons). Alternatively, the translatome can be studied. Axonally translating mRNAs can be isolated by immunoprecipitating pre-tagged ribosomes and associated mRNAs specifically from axons. For example, a tagged ribosomal protein can be specifically expressed in the eye, and ribosome–mRNA complexes can be isolated from retinal axons

The axons of cultured neurons are separated from their cell bodies using compartmentalized culture systems:



(a) The **Campenot chamber** made of a Teflon divider attached to a petri dish, has two compartments with distinct fluid environments. The proximal compartment contains cell bodies, dendrites and proximal axons, whereas the distal compartment contains distal axons. Typically, the distal compartment is supplemented with nerve growth factor (NGF), which promotes the growth of peripheral sensory and sympathetic neurons.

(b) The **microfluidic culture platform** has two mirror-imaged compartments. Dissociated neurons are added to the somal compartment, and axons grow into the axonal compartment through microgrooves.

(c) In **laser-capture microdissection** cultured neurons labelled with a fluorescent lipophilic dye are fixed, and then axons or growth cones (indicated by white arrows in the figure) are microdissected individually. Because the amount of RNA obtained is minute, amplification is required before microarray analysis. This method, however, enables subcellular compartment-specific comparison, which is not possible in compartmentalized culture systems.

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Jung et al, 2012
Nature Reviews Neurosci
doi:10.1038/nrn3210

SCIENTIFIC REPORTS

OPEN

Messenger RNAs localized to distal projections of human stem cell derived neurons

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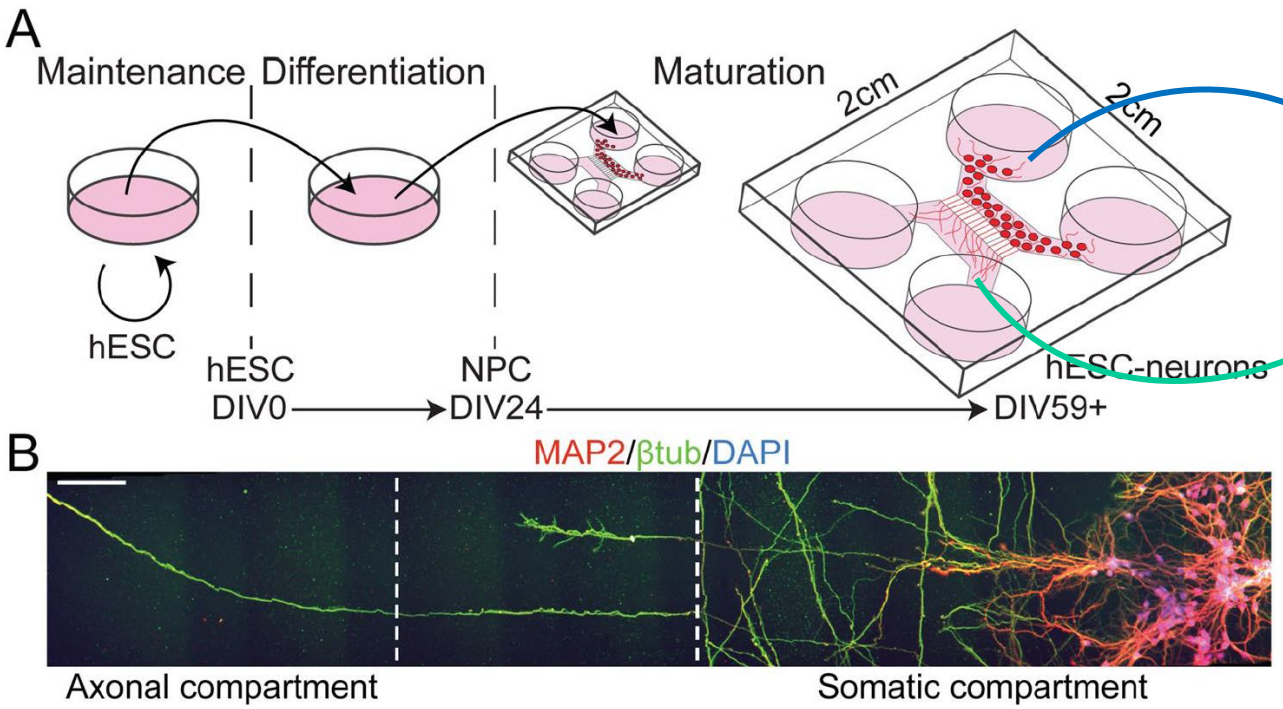
Accepted: 8 March 2017
Published online: 04 April 2017

Rebecca L. Bigler[1,2], Joyce W. Kamande[2], Raluca Dumitru[3], Mark Niedringhaus[2,4] & Anne Marion Taylor[2,4,5]

The identification of mRNAs in distal projections of model organisms has led to the discovery of multiple proteins that are locally synthesized for functional roles such as axon guidance, injury signaling and regeneration. The extent to which local protein synthesis is conserved in human neurons is unknown. Here we used compartmentalized microfluidic chambers to characterize the transcriptome of distal projections of human embryonic stem cells differentiated using a protocol which enriched for glutamatergic neurons (hESC-neurons). Using gene expression analysis, we identified mRNAs proportionally enriched in these projections, representing a functionally unique local transcriptome as compared to the human neuronal transcriptome inclusive of somata. Further, we found that the most abundant mRNAs within these hESC-neuron projections were functionally similar to the axonal transcriptome of rat cortical neurons. We confirmed the presence of two well characterized axonal mRNAs in model organisms, β-actin and GAP43, within hESC-neuron projections using multiplexed single molecule RNA-FISH. Additionally, we report the novel finding that oxytocin mRNA localized to these human projections and confirmed its localization using RNA-FISH. This new evaluation of mRNA within human projections provides an important resource for studying local mRNA translation and has the potential to reveal both conserved and unique translation dependent mechanisms.

Bigler et al., 2017, Scientific Reports, DOI:10.1038/s41598-017-00676-w

Differentiation of human embryonic stem cell-derived neurons in microfluidic chambers followed by differential gene expression of axonal and somatic compartments



RNA harvesting and **microarray expression profiling** of neurons (somatodendritic compartment) and distal projections (axonal compartment)

Figure 1. Human embryonic stem cell derived neurons (hESC-neurons) matured in axon isolating microfluidic chambers. (**A**) Schematic and timeline of hESC-neuron differentiation and maturation in microfluidic chambers. (**B**) Montage image of MAP2 (dendrite), β-tubulin III (βtub, axon) and DAPI immunostaining spanning the somatic and axon compartments of DIV39 hESC-neurons cultured within a microfluidic chamber. White dashed lines delineate the boundaries of the microgroove barrier. (**C**) Representative montage

Bigler et al., 2017, Scientific Reports, DOI:10.1038/s41598-017-00676-w

New methods used to study axonal mRNA translation and transport

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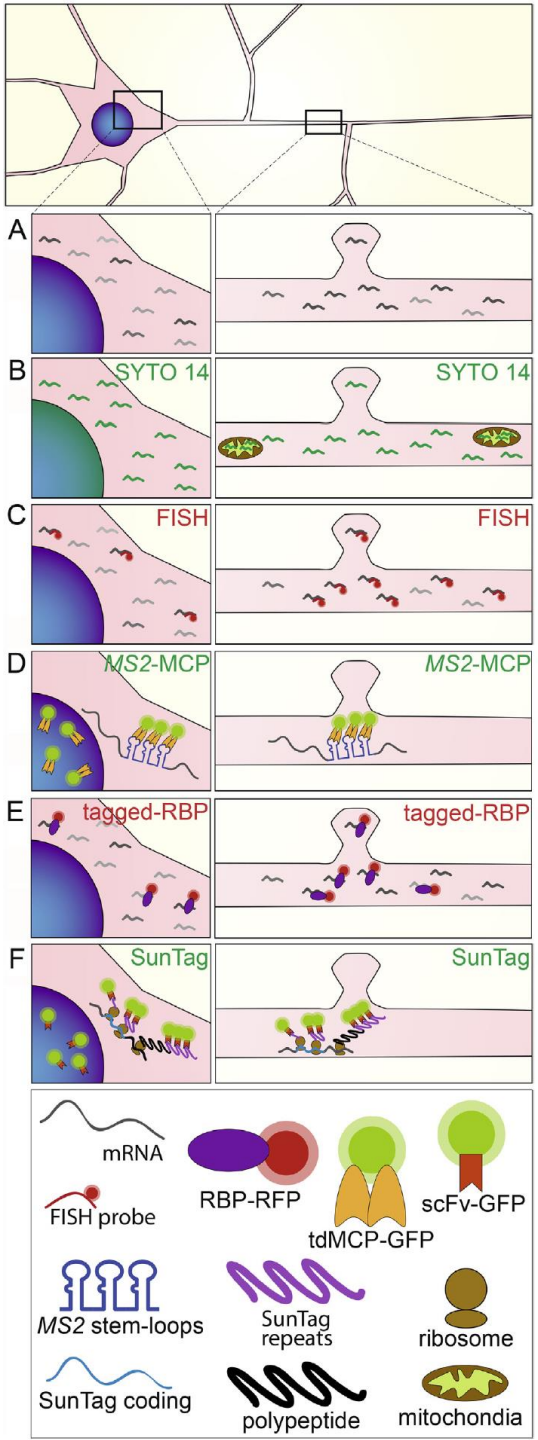
Bauer et al., 2017, Methods, http://dx.doi.org/10.1016/j.ymeth.2017.06.013

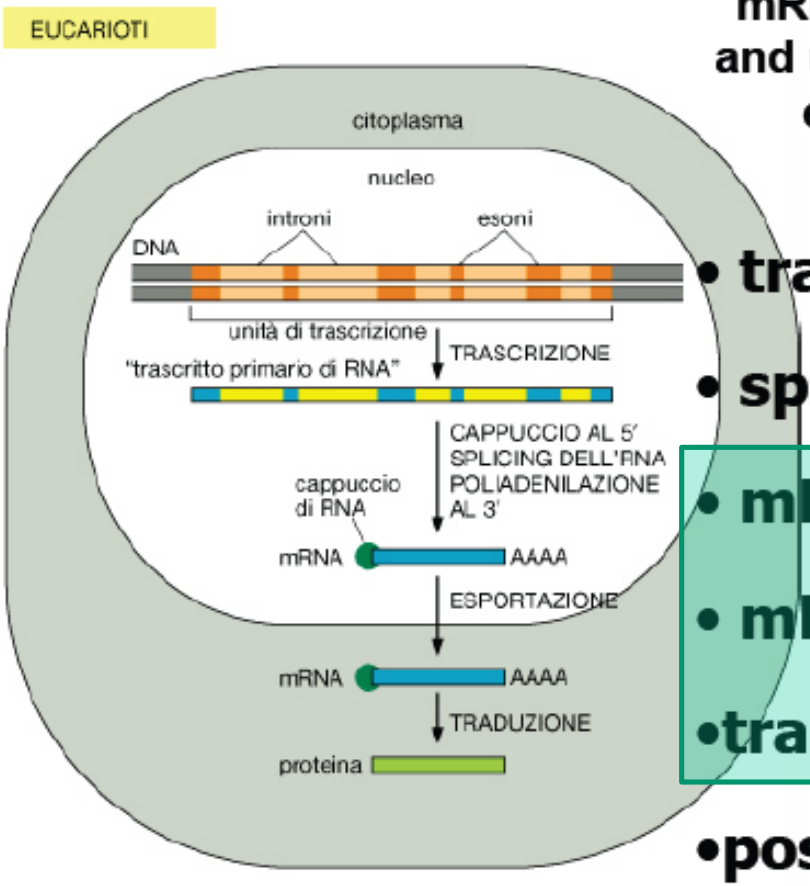


C and D: Visualization of specific mRNAs. The **MS2-MCP system** relies on the integration of an array of exogenous RNA stem-loops, derived from the MS2 phage, into the sequence of a target RNA, classically into the 3'-UTR. The stem loops are recognized by an RBP, the MS2 coat protein (MCP), with high specificity and affinity. The MCP can be tagged with a fluorescent protein (MCP-FP), thereby tethering a fluorescent signal to the target RNA carrying the MS2 stem-loops. As several repeats of the MS2 stem-loop are integrated into the target RNA, multiple MCP-FP molecules are tethered to it, leading to a local amplification of fluorescence intensity

F: Visualization of local protein synthesis. In the **SunTag technology**, the mRNA reporters include a series of SunTag repeats (24-56) at the N-terminus of the ORF. As soon as the reporter is translated, the multimerized SunTag epitopes are synthesized and immediately recognized intracellularly by a pre-formed recombinant single-chain antibody fused to GFP (scFv-sfGFP) expressed in the cell, allowing the visualization of single molecules of proteins by microscopy

Fig. 1. Methods to study mRNA granule transport and local translation. Schematic representation of a neuron, showing the soma (left panels) and a dendritic segment (right panels) in detail, indicating cytoplasmic mRNA molecules (grey) (A) that can be detected with a sequence unspecific dye for nucleic acids such as SYTO 14 (B) or, alternatively, by sequence specific fluorescent *in situ* hybridization (FISH) (C). (D) Schematic representation of the *MS2*-MCP system to visualize pre-labeled mRNAs. (E) Schematic representation of RNA granule visualization by FP-tagged RBP (in red). (F) Schematic representation of SunTag system to visualize local protein synthesis. (For interpretation of the references to colour in this figure legend, the

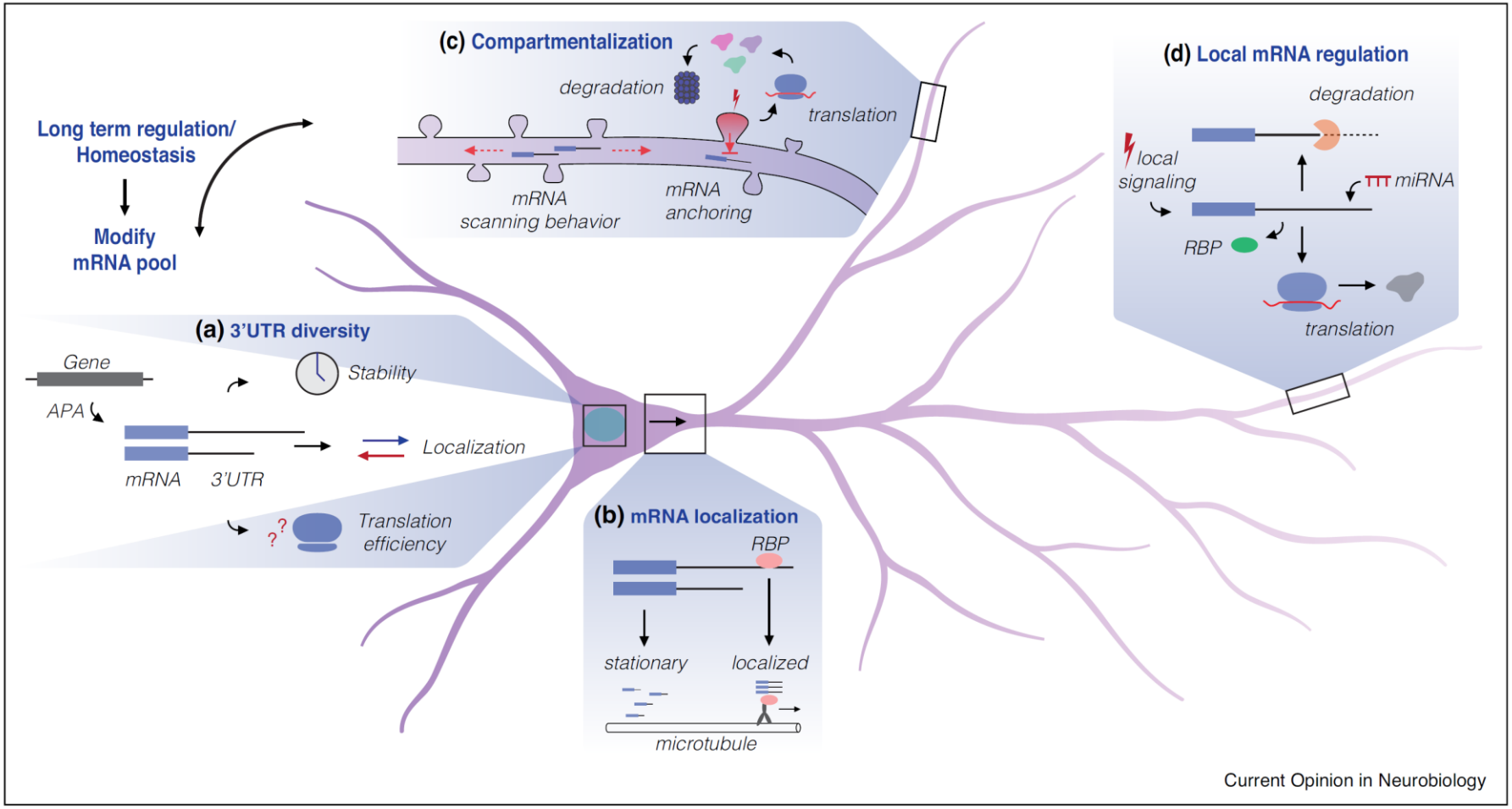
mRNAs are synthesized in the nucleus and undergo a series of regulatory steps each of which is tighly regulated



- **transcription**
- **splicing**
- **mRNA stability**
- **mRNA transport**
- **translation**
- **post-translational modifications**

Steps important in mRNA trafficking and local translation

Mechanisms of mRNA transport & local translation in neurons



Regulation of mRNA in neurons.
Alternative polyadenylation of mRNA precursors leads to the generation of an mRNA with different 3′UTRs. The 3′UTR serves as binding platform for RNA-Binding-Proteins (RBP) and other factors, which provides an opportunity for differential regulation of the same mRNA species **(a)**. Utilizing this mechanism, the cell can regulate mRNA translocation to distal dendritic/axonal parts **(b)**. mRNAs sorted into dendrites can exhibit a 'scanning' behavior and tend to be anchored close to previously activated synapses to undergo lcoal translation **(c)**. mRNAs may not only be regulated by anchoring them at sites of translation but also regulated by local translational efficiency or mRNA stability **(d)**.

Glock et al., 2017, Current Opinion in Neurobio
http://dx.doi.org/10.1016/j.conb.2017.05.005

Fragile X Syndrome: a genetic intellectual disability based on silencing of the FMR1 gene encoding for an RNA-binding protein

Fragile X Syndrome (FXS) is the most common form of inherited intellectual disability and also considered a **monogenic cause of Autism Spectrum Disorder**. FXS symptoms include neurodevelopmental delay, anxiety, hyperactivity, and autistic-like behavior.

The disease is due to the mutation or loss of the **FMRP (Fragile X Mental Retardation Protein)**, an RNA-binding protein involved in different steps of RNA metabolism, including mRNA decay, dendritic targeting of mRNAs, and protein synthesis.

FXS is due to triplet repeat expansion (90% of patients) or point mutations in the Fragile X mental retardation 1 (FMR1) gene. CGG expantion leads to hypermethylation of the CGG, transcriptional silencing, and abolished production of the Fragile X Mental Retardation Protein (FMRP)

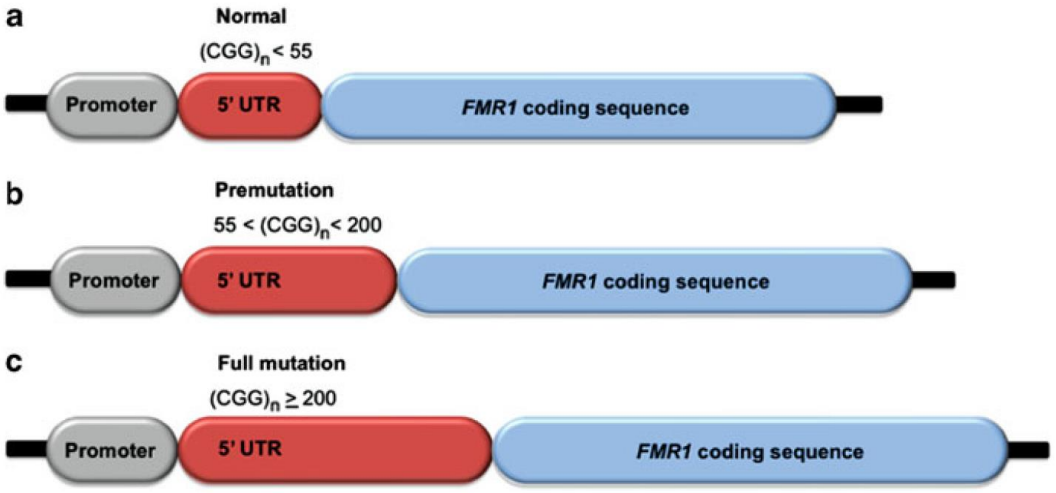


Fig. 23.1 Scheme of the *FMR1* gene which includes the promoter, the 5′ UTR, and the *FMR1*-coding sequence in a normal allele (5–44 CGG copies) (**a**), a premutated allele (55–200 copies) (**b**), and a full mutated allele (>200 repeats) (**c**)

In neurons lacking FMRP, a wide array of mRNAs encoding proteins involved in synaptic structure and function are altered. As a result of this complex dysregulation, in the absence of FMRP, **spine morphology and functioning is impaired**.

De Rubeis et al., 2012, Synaptic plasticity
DOI 10.1007/978-3-7091-0932-8_23

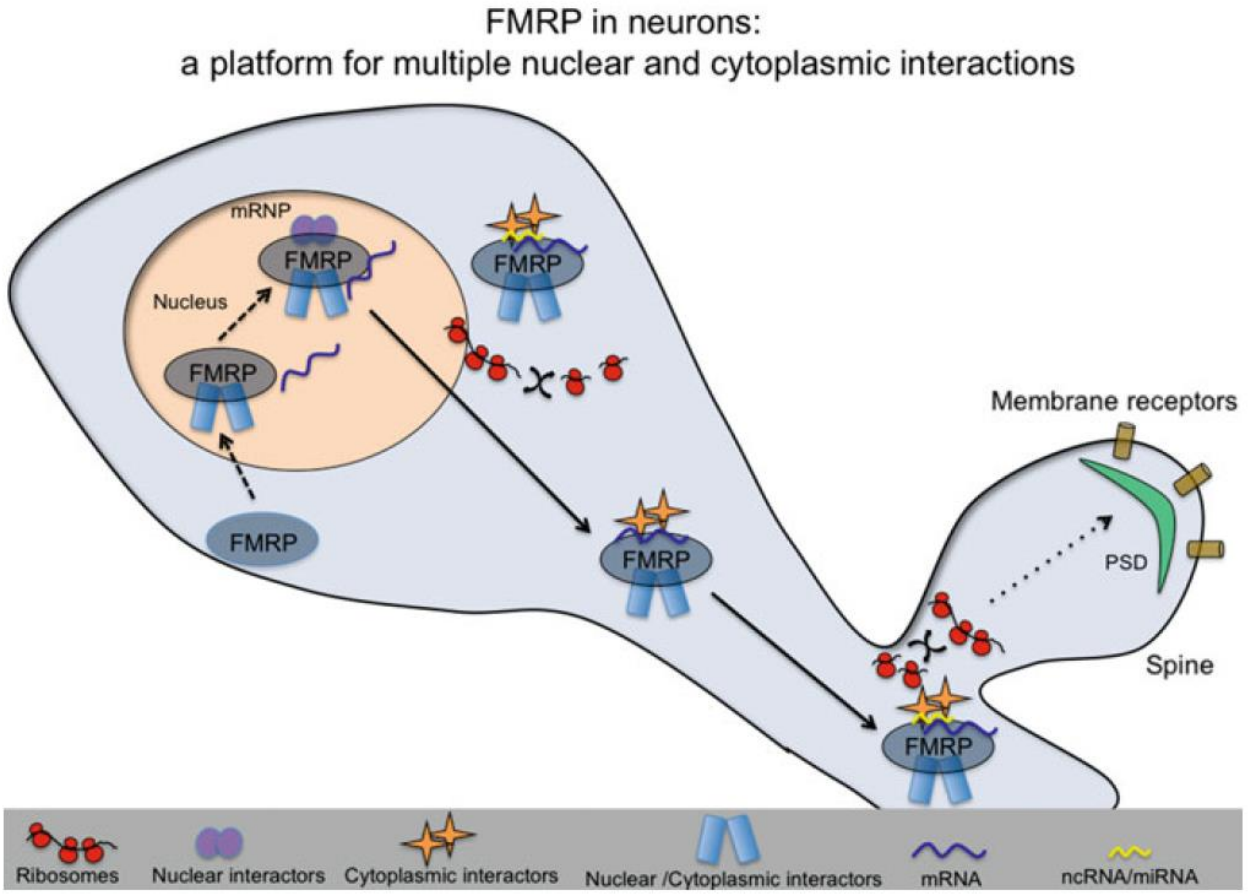


Fig. 23.3 FMRP forms part of a protein complex together with translationally arrested mRNAs. FMRP travels within an RNA–protein complex from the cell body to the synapses transporting dendritically localized mRNAs. After synaptic stimulation, FMRP liberates its mRNA targets allowing their local translation. The reversible translational repression and activation of the mRNA targets are regulated by a signaling pathway described in the text (see Sect. 23.3). Transported mRNAs are then locally translated in dendrites contributing to local protein synthesis and synaptic rearrangement that occurs after synaptic stimulation. FMRP can bind its mRNA targets through direct interaction or through noncoding RNAs such as BC1 RNA and microRNAs

De Rubeis et al., 2012, Synaptic plasticity
DOI 10.1007/978-3-7091-0932-8_23

Box 3. Outstanding questions in the field of local translation at the synapse

- What is the nature of the cis-acting RNA localization elements that target transcripts to specific subcellular compartments within a neuron?
- What are the RNA binding proteins that function to localize mRNAs within neurons and how do they mediate this localization?
- What is the composition of the RNPs that localize mRNAs to dendrites? What is the relationship between RNA transport granules, P-bodies and stress granules?
- What are the physiologically relevant stimuli that regulate local translation?
- Do/how do distinct stimuli regulate the translation of specific subsets of transcripts?
- How does the miRNA pathway contribute to local translation at synapses and thus synaptic plasticity?
- Are there differences in the mechanisms of translational regulation at the synapse as compared to in the soma?
- What mechanisms at synapses facilitate folding and maturation of the newly synthesized proteins?
- What is the nature of the secretory pathway, which is necessary for synthesis of membrane and secreted proteins, in distal dendrites?
- How does local translation of specific transcripts contribute to or alter the function of neural circuits?
- Is/how is stimulus-induced transcriptional regulation in the nucleus integrated with stimulus-induced local translation at the synapse?
- What are the proteins crucial to mGluR-LTD that accumulate at CA1 synapses of fragile X mice?
- Is PI3 kinase enhancer (PIKE) an FMRP target that is crucial for aberrant protein-synthesis-dependent synaptic plasticity observed in fragile X mice?

Wang et et al., 2010
Trends in Neurosci
doi:10.1016/j.tins.2010.01.005

Local translation in growth cones

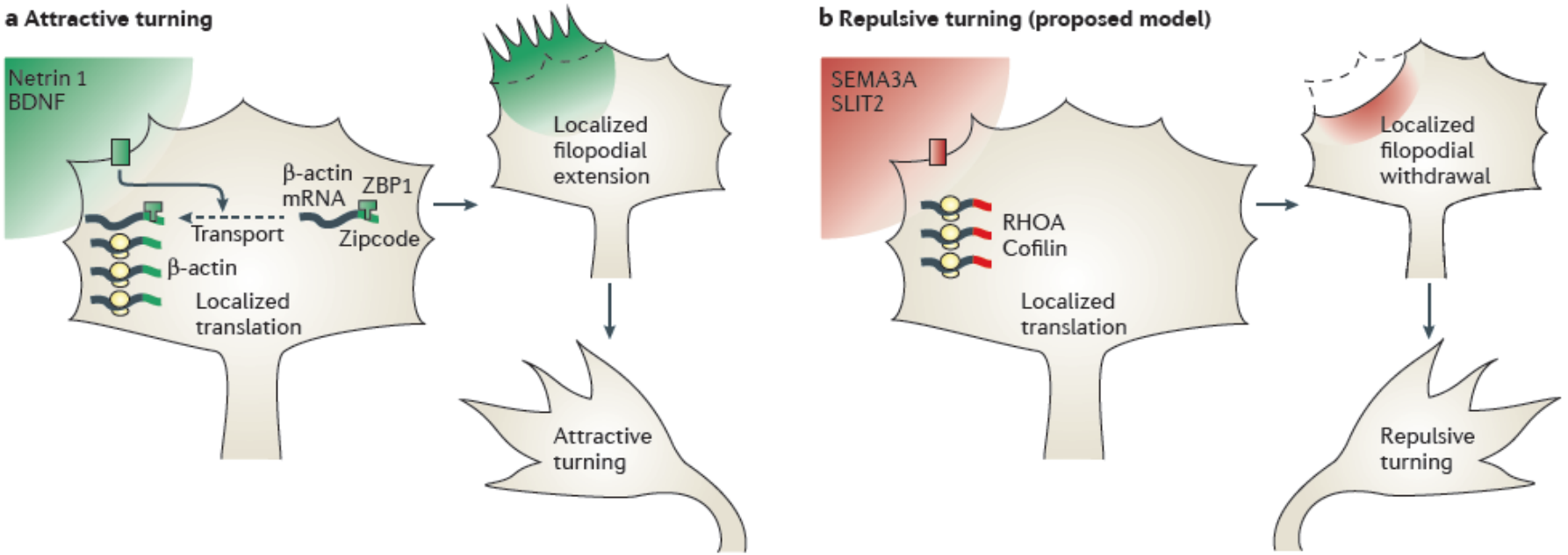
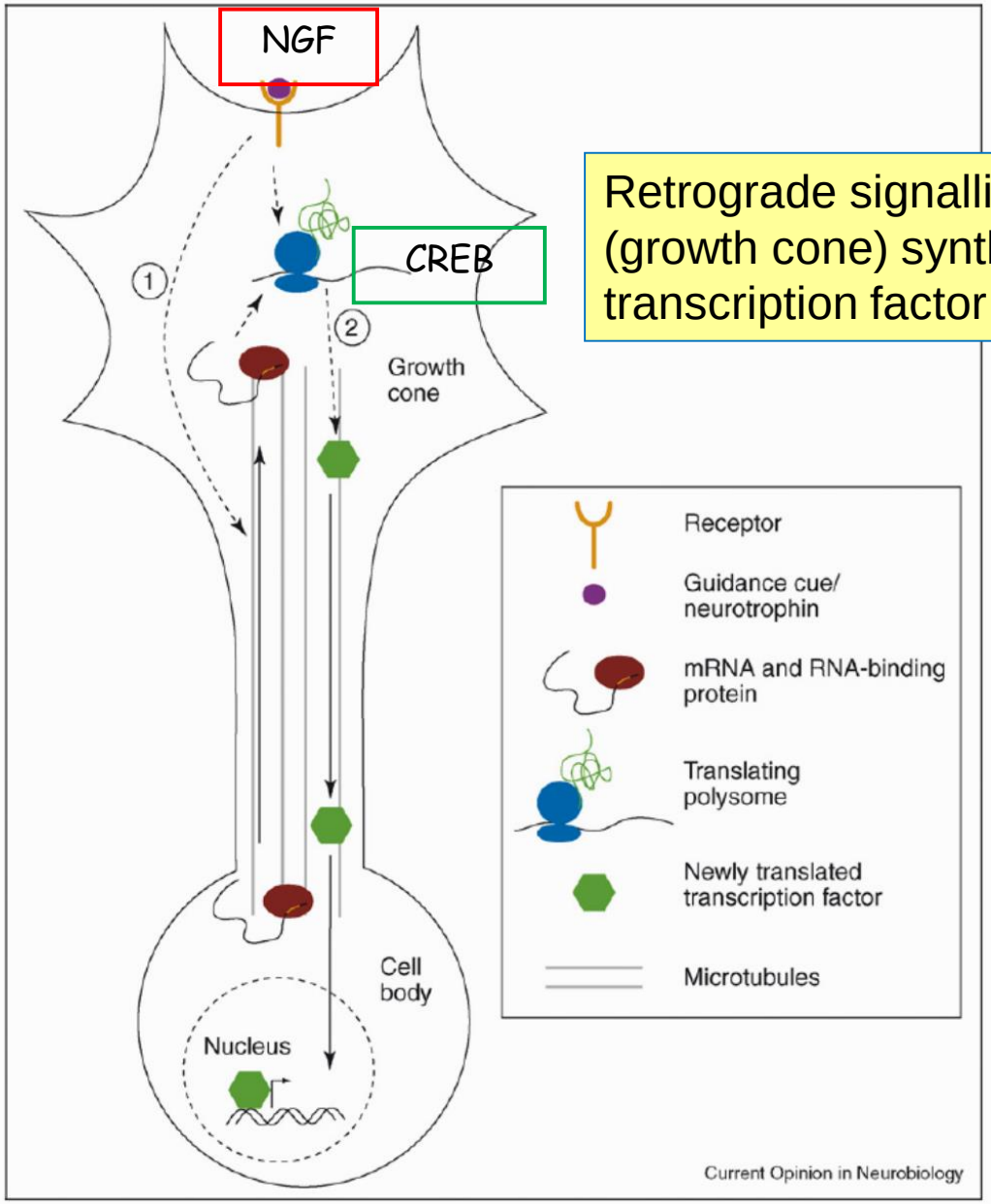


Figure 1 | **Growth cone turning regulated by differential mRNA translation.** Gradients of protein synthesis-inducing guidance cues commonly activate global translational activity on the side of the growth cone nearest to the gradient by activating mammalian target of rapamycin (mTOR). However, the specific mRNA translated in response to the cue differs depending on whether it is an attractive or repulsive cue and determines the direction of growth cone turning. **a** | Stimulation by attractive cues, such as netrin 1 and brain-derived neurotrophic factor (BDNF), leads to asymmetric synthesis of β-actin on the side near to the source of the gradient, which is mediated by β-actin mRNA transport to this region by zipcode-binding protein 1 (ZBP1)[53,54]. Spatially restricted synthesis of β-actin may lead to actin polymerization, cytoskeletal assembly and attractive turning of the growth cone. **b** | By contrast, repulsive cues, such as semaphorin 3A (SEMA3A) and SLIT2, activate the axonal translation of the actin-depolymerizing proteins RHOA[55] and cofilin[56] when uniformly applied in cell culture. A proposed model is shown, in which localized cytoskeletal disassembly may result in repulsive turning through polarized filopodial collapse. However, whether these molecules are translated asymmetrically in a repulsive gradient has not yet been tested.

http://www.youtube.com/watch?v=Wj3C6cLqXzY

Jung et al, 2012
Nature Reviews Neurosci
doi:10.1038/nrn3210



Retrograde signalling of locally (growth cone) synthesized transcription factor

Lin et al., 2008

Local translation and communication between the axon and cell body. (1) Stimulation of axons leads to transcription-independent differential localization of mRNAs to the axon through transport on microtubules, changing the population of mRNAs available for local axonal translation. (2) Newly synthesized transcription factors can be retrogradely transported on microtubules to the cell body where they influence transcription.

RNA-specific transport and translation in axons

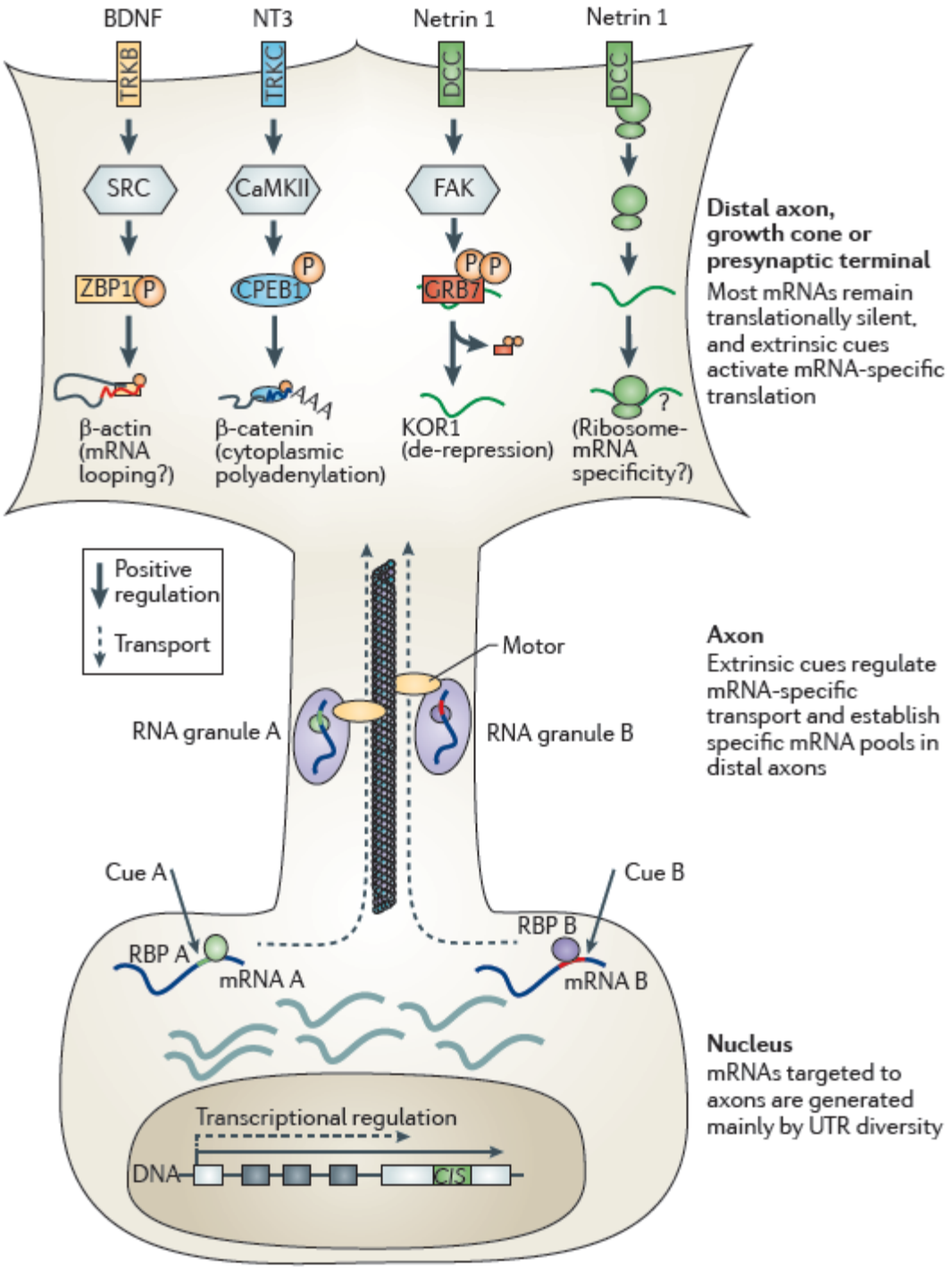


Figure 4 | **RNA-specific transport and translation.** Axonal targeting of mRNAs is directed by *cis*-acting elements that are mainly localized to the 3′-untranslated regions (UTRs) of mRNAs. Retention of these axon-targeting *cis*-acting elements is commonly regulated by the use of different transcriptional termination sites[15,66]. Extrinsic cues influence axonal mRNA repertoires by promoting transport of specific mRNAs[156]. Axonally targeted mRNAs are recruited to RNA granules (transport ribonucleoproteins (RNPs)) by specific RNA-binding proteins (RBPs) and are transported along microtubules probably by kinesin motors[157]. mRNAs remain translationally silent during transport[21]. Extracellular signals activate the translation of specific mRNAs mainly by regulating RBPs. For example, neurotrophins and guidance cues activate the kinases SRC[71], calcium/calmodulin-dependent protein kinase II (CaMKII)[174] and focal adhesion kinase (FAK)[164], which phosphorylate the RBPs, zipcode binding protein 1 (ZBP1), cytoplasmic polyadenylation element binding protein (CPEB1), and growth factor receptor-bound protein 7 (GRB7), respectively. Cell surface receptors might regulate mRNA-specific translation by directly regulating ribosomes. For example, unstimulated netrin receptor DCC directly binds to ribosomes and inhibits translation[26], and ribosome composition influences mRNA selectivity[181]. Different receptors may bind to ribosomes that are pre-tuned to specific mRNAs, and ligand stimulation might release such ribosomes and result in mRNA-specific translation. BDNF, brain-derived neurotrophic factor; KOR1, κ-type opioid receptor; NT3, neurotrophin 3; TRK, tyrosine kinase receptor.

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Model of stimulus-induced axonal translation

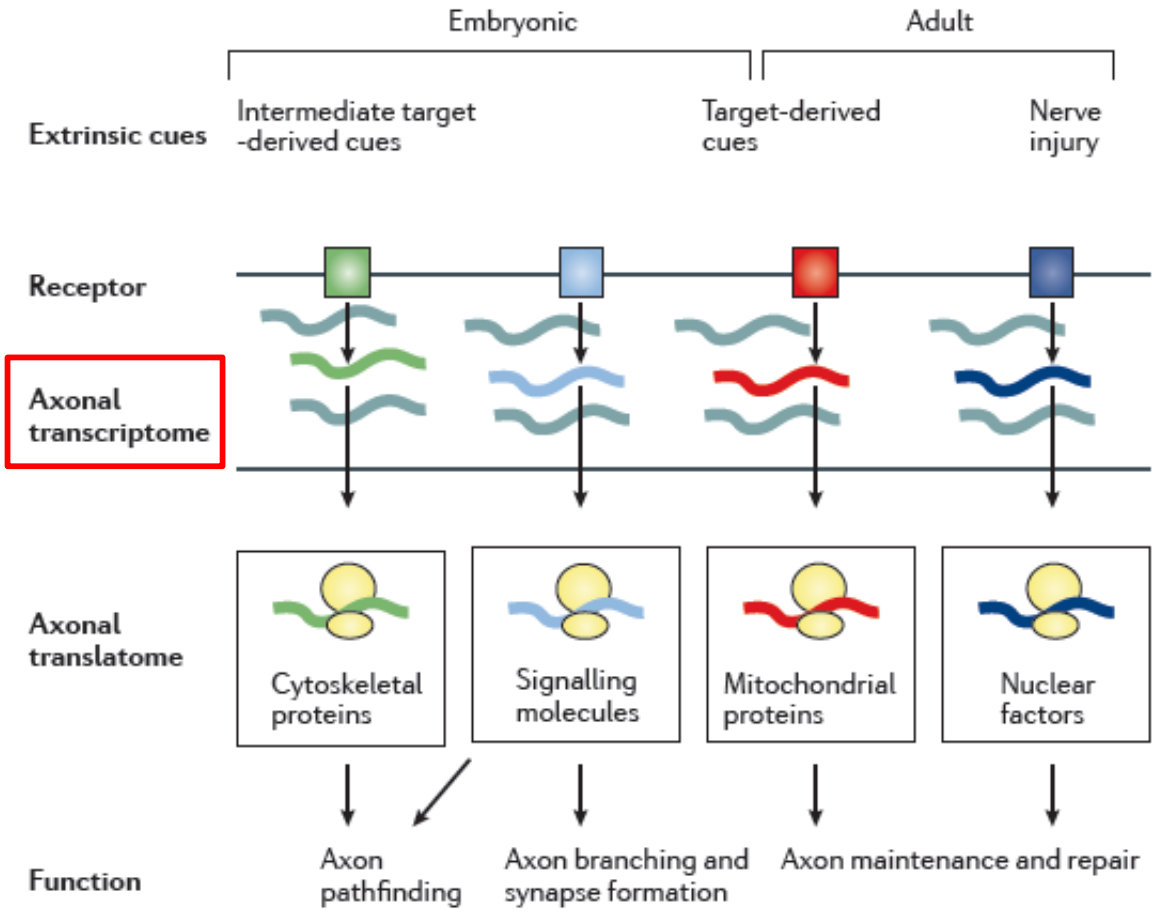

Figure 5 | **Local mRNA translation as a mediator of stimulus-induced axonal responses.** A proposed model for the function and mechanism of axonal mRNA translation. Neuronal axons contain a complex and dynamic transcriptome, and many mRNAs remain translationally silent. Various extrinsic cues stimulate translation of a distinct subset of mRNAs during development and in adulthood. For example, guidance cues induce local synthesis of cytoskeletal proteins in growing axons and regulate axon guidance and branching. Target-derived trophic factors promote local synthesis of proteins required for mitochondrial function and support the survival of distal axons. Nerve injury in adulthood stimulates local synthesis of nuclear factors that activate repair mechanisms.

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