

CPEB: a life in translation

Joel D. Richter

Program in Molecular Medicine, University of Massachusetts Medical School, Worcester, MA 01605, USA

Nearly two decades ago, *Xenopus* oocytes were found to contain mRNAs harboring a small sequence in their 3' untranslated regions that control cytoplasmic polyadenylation and translational activation during development. This cytoplasmic polyadenylation element (CPE) is the binding platform for CPE-binding protein (CPEB), which promotes polyadenylation-induced translation. Since then, the biochemistry and biology of CPEB has grown rather substantially: mechanistically, CPEB nucleates a complex of factors that regulates poly(A) elongation through, of all things, a deadenylating enzyme; biologically, CPEB mediates many processes including germ-cell development, cell division and cellular senescence, and synaptic plasticity and learning and memory. These observations underscore the growing complexities of CPEB involvement in cell function.

Paradigmatic translational control: from development to synaptic plasticity to cellular senescence

Early animal development is directed in part by mRNAs that are stored in the developing oocyte until subsequent use during the late stages of meiosis (maturation) or after fertilization. These mRNAs are referred to as 'masked' or maternal mRNAs and they have long been recognized as prime examples of translational control [1]. By contrast, recognition of the importance of translation in the central nervous system is relatively recent, and was given particular impetus by the observations that protein synthesis at synapses is important for synaptic plasticity and by inference, long-term memory consolidation [2]. Finally, evidence indicating that cellular senescence, a mechanism that limits cellular lifespan, is regulated in part at the translational level is quite new [3]. Whereas each of these phenomena is complex and controlled at multiple levels, one protein is involved in all three: cytoplasmic polyadenylation element-binding protein (CPEB). CPEB regulates mRNA translation and, through this activity, influences gametogenesis and early development, synaptic plasticity and cellular senescence. Here, I review the salient features of CPEB biochemistry and its influence on these biological processes.

CPEB-regulated polyadenylation-induced translation: the basics

CPEB is an RNA-recognition motif (RRM) and a zinc-finger-containing sequence-specific RNA-binding protein that is found in a wide range of vertebrates and invertebrates. Several invertebrates contain two genes

that encode CPEB-like proteins, whereas vertebrates often contain four. In vertebrates, the founding member of the CPEB proteins is sometimes referred to as CPEB1 (here, it is referred to by its more-common form 'CPEB'); other CPEBs are designated CPEB2, CPEB3 and CPEB4. Sequence comparisons within and across phyla indicate that CPEB and CPEB2–4 comprise distinct classes of proteins [4]; indeed, CPEB and CPEB2–4 interact with different RNA motifs and have unique molecular functions [5]. CPEB is discussed now, but CPEB2–4 will be mentioned later.

Much of the earlier work on CPEB control of cytoplasmic polyadenylation and translation was reviewed several years ago [4]. More recent work, however, has revealed that these processes are more complex than previously thought; thus, the present understanding of how polyadenylation induces translation is discussed here. It is likely that oocytes of all animals contain an abundance of dormant or masked mRNA that is translated only when the cell re-enters the meiotic divisions (oocyte maturation) or after fertilization. Several of the masked mRNAs have short poly(A) tails (~20–40 nucleotides), and only when these tails are elongated does translation ensue. By virtue of its recognition of the 3' untranslated region (UTR)-residing cytoplasmic polyadenylation element (CPE; with a consensus sequence of UUUUUAU), CPEB is indirectly responsible for both translational repression and translational activation by polyadenylation. CPEB accomplishes these tasks through its association with several other factors; I will first describe those involved with polyadenylation.

The termination of transcription occurs far downstream of the end of the mature mRNA; a group of proteins associated with the C-terminal domain of RNA polymerase II cleaves the primary transcript ~20–30 bases 3' of the hexanucleotide AAUAAA. Among these factors is cleavage and polyadenylation specificity factor (CPSF), a group of four polypeptides that not only mediates RNA cleavage but also subsequent nuclear polyadenylation [6]. Most RNAs, irrespective of whether they harbor a CPE, probably acquire a typically long poly(A) tail (~200–250 nucleotides) in the nucleus [7–9]. Following nuclear export, however, only the CPE-containing RNAs interact with CPEB and several interacting factors that remove most of the poly(A). These factors include: symplekin, which is possibly a platform protein upon which multi-component complexes are assembled; poly(A) ribonuclease (PARN), which is a deadenylating enzyme; and germ-line-development factor 2 (Gld2), which is a poly(A) polymerase [10–12]. Both PARN and Gld2 are active but, because PARN is more active, the poly(A) tail is removed as soon as it is added by Gld2; hence, the poly(A) tails on CPE-containing RNAs are removed and

Corresponding author: Richter, J.D. (joel.richter@umassmed.edu). Available online 4 May 2007.

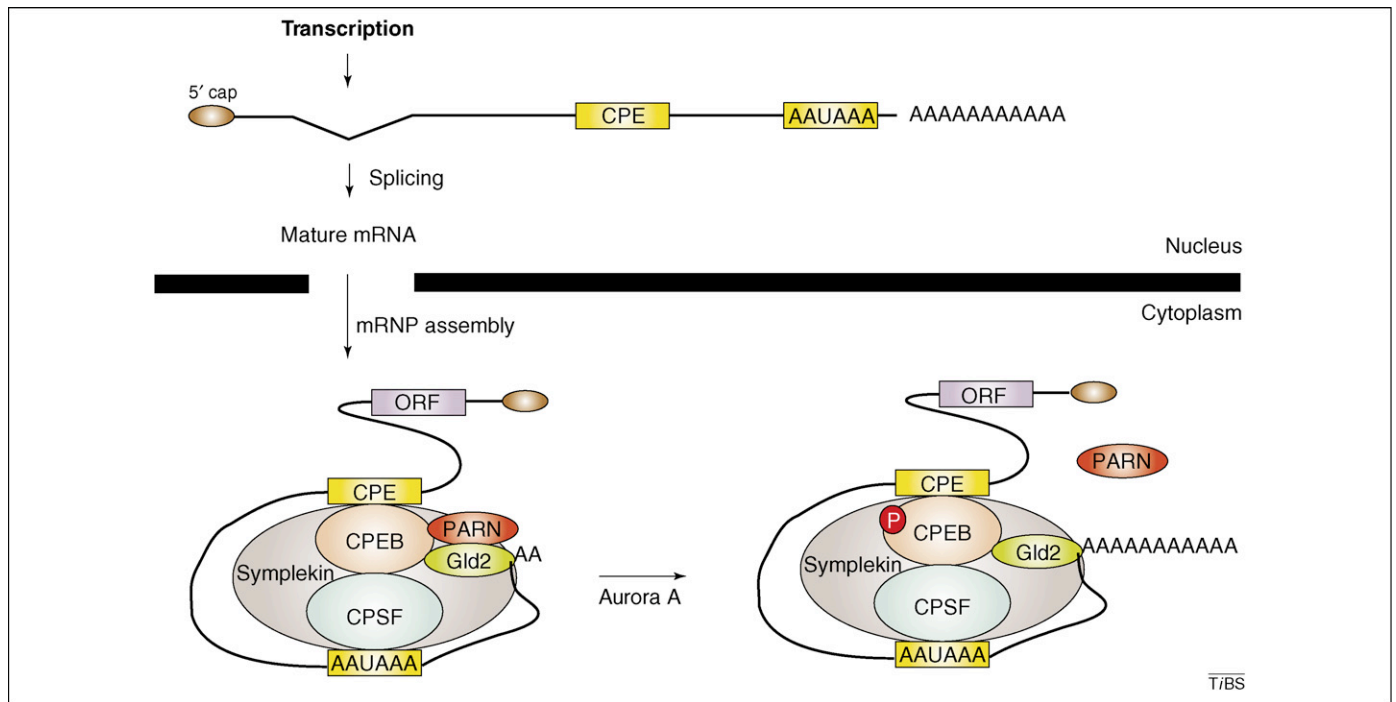


Figure 1. CPEB-regulated polyadenylation. In the nucleus, pre-RNAs containing or lacking a CPE acquire a long poly(A) tail. Following splicing and RNA export, the CPEB-containing RNAs assemble into a ribonucleoprotein (RNP) complex that is nucleated by CPEB. The other factors in this complex include: CPSF, which recognizes the AAUAAA polyadenylation hexanucleotide; PARN, a deadenylating enzyme; Gld2, a poly(A) polymerase; and symplekin, a scaffold protein. Although PARN and Gld2 are both active, PARN activity is more robust; it thus removes the poly(A) tail and keeps it short although Gld2 continues to catalyze polyadenylation. Upon the induction of oocyte maturation, the kinase Aurora A phosphorylates CPEB Ser174, which causes the expulsion of PARN from the RNP complex. Thus, by default, Gld2 elongates. Other factors such as Maskin, eIF4E and PABP have been omitted for clarity. Modified, with permission, from Ref. [8].

remain short. Following a progesterone-initiated signaling cascade emanating from the cell surface, the kinase Aurora A is activated and phosphorylates CPEB at Ser174 [13]. This event causes the expulsion of PARN from the ribonucleoprotein complex, thereby enabling Gld2 to elongate poly(A) tails by default [8] (Figure 1).

At least in some cases, CPEB-regulated translation involves both polyadenylation and the protein Maskin. Maskin is a CPEB-associated protein that also interacts with the mRNA cap-binding eukaryotic initiation factor 4E (eIF4E). Maskin binds eIF4E in the region normally occupied by another translation initiation factor, eIF4G, which is required to indirectly recruit the 40S ribosomal subunit to the 5' end of the mRNA. Therefore, competition between

eIF4G and Maskin for binding of eIF4E can inhibit translation by preventing the delivery of the 40S ribosomal subunit to the AUG start codon. While the poly(A) tail is short, Maskin remains associated with both CPEB and eIF4E; following poly(A) elongation, however, poly(A)-binding protein (PABP) is recruited to the poly(A) tail [14]. PABP, in turn, binds eIF4G [15] and helps it to displace Maskin from eIF4E, the result of which is translation initiation [16] (Figure 2).

Multiple CPEB-binding proteins

In oocytes, CPEB resides in several complexes, which indicates that it might regulate different mRNAs in a spatial and/or temporal-specific manner. The plasma membrane

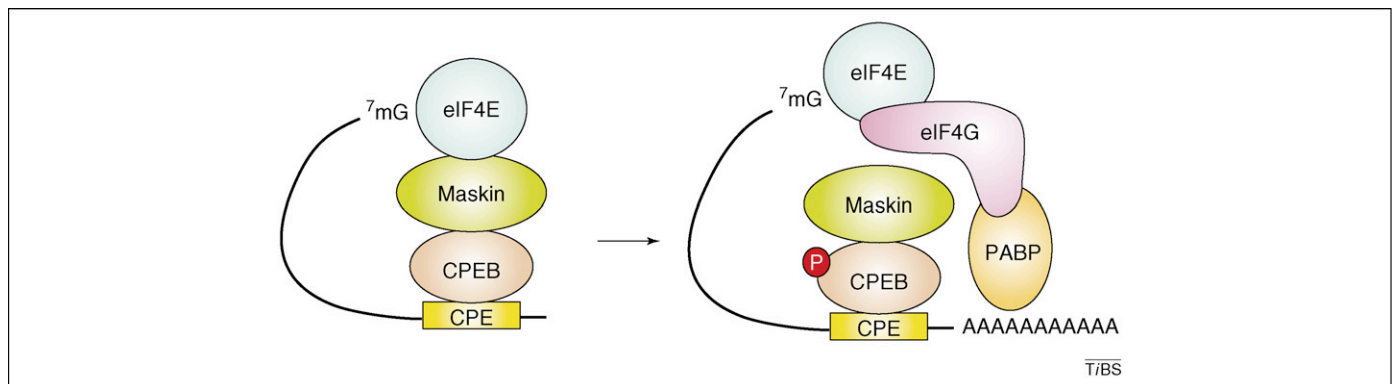


Figure 2. Translational control by Maskin. CPEB associates with both CPE-containing mRNAs and Maskin. Maskin, in turn, interacts with the cap ($7mG$)-binding factor eIF4E. In this configuration, Maskin binding to eIF4E precludes eIF4G from binding eIF4E, thus, inhibiting translation. Following CPEB phosphorylation and polyadenylation (see Figure 1), PABP binds the newly elongated poly(A) tail; PABP also binds eIF4G and helps it displace Maskin from eIF4E. Because eIF4G is indirectly associated with the 40S ribosomal subunit (not shown), translation initiation proceeds. For clarity, other polyadenylation and translation factors are omitted.

is the site where CPEB activation first occurs. Here, progesterone interaction with a surface-associated receptor causes the translational activation of RINGO (rapid inducer of G₂-M in oocytes)-Spy mRNA, which encodes a cyclin B1-like molecule [17], and glycogen synthase kinase 3 β (GSK-3 β) dissociation from Aurora A [13]; both events are required for CPEB phosphorylation and activation. Two proteins that bind CPEB also stimulate its phosphorylation: the guanine nucleotide exchange factor xGEF, which is a member of the Rho family of G proteins [18,19], and the amyloid precursor-like protein 2 (APLP2) [20]. CPEB interacts with a small intracellular domain APLP2, which is a transmembrane protein; not surprisingly, immuno-electron microscopy has revealed that both APLP2 and CPEB are closely associated with the plasma membrane and/or endo-membranes. Although the amount of CPEB associated with APLP2 is probably small, these molecules could be the earliest to be activated following progesterone stimulation of maturation because this process is thought to begin at the cell surface. Among the first RNAs to undergo polyadenylation-induced translation is *mos*, which encodes a serine/threonine kinase. *Mos*, in turn, is required for the polyadenylation-induced translation of cyclin B1 mRNA; cyclin and its binding partner cyclin-dependent kinase 1 (*cdk1*) are then responsible for many of the manifestations of oocyte maturation [21].

CPEB has also been reported to interact with p54, an RNA helicase involved in translational repression [22], and pumilio [23], another RNA-binding protein that inhibits translation [27]. In addition, CPEB resides in a complex of proteins containing the 77 000-Da subunit of cleavage stimulatory factor CstF77, which might be involved in translational repression [24]. A portion of CPEB becomes ubiquitinated in the later stages of maturation [25,26] and, thus, it presumably transiently interacts with an E3 ligase, although the identity of this enzyme is not known. *Orb*, the putative *Drosophila* homolog, also interacts with several proteins including the Fragile-X mental retardation protein (*dFMR1*) [27]. These factors reside in a complex with *orb* mRNA; whereas *Orb* stimulates the translation of its own mRNA, *dFMR1* is an inhibitor of this process.

In the oocyte, most CPEB is located in the animal pole (the pigmented portion of the oocyte in which most of the acentrically positioned nucleus is located), and it is this material that probably becomes affiliated with centrosomes and spindles in embryonic blastomeres that develop from this part of the oocyte. Maskin is also found on spindles and centrosomes where, together with CPEB, it controls local cyclin B1 mRNA translation [28]. These proteins might also be associated with *Rae1*, an RNA-export factor [29]. CPEB and Maskin are microtubule-binding proteins, and thus they probably directly anchor a large RNP complex to the mitotic apparatus. Maskin association with the mitotic apparatus, however, requires phosphorylation of Ser626; both protein kinase A and Aurora A can phosphorylate this residue [30–32].

CPEB control of oogenesis

In both invertebrates and vertebrates, CPEB regulates germ-cell development at multiple stages [33]. In CPEB knockout (KO) mice, germ-cell progression in both males and females does not proceed beyond pachytene (the stage

of the first meiotic prophase, in which the synaptonemal complex completes its formation and facilitates homologous recombination). The mRNAs encoding synaptonemal complex proteins 1 (SCP1) and 3 (SCP3) contain CPEs, and in oocytes, if the CPEB KO mouse, they are neither polyadenylated nor translated; presumably, as a consequence, further germ-cell development is inhibited in these mice [34]. Interestingly, phosphorylation of Thr171 of mouse CPEB (the equivalent residue to the Ser174 in *Xenopus*), peaks at pachytene; subsequently, the phosphatase PP1 removes this phosphate and, thus, polyadenylation and translation is inhibited. At maturation, Aurora A then rephosphorylates this residue to again induce polyadenylation [35].

However, the time between pachytene and maturation is long (months), and CPEB could mediate translation in this intervening period. To investigate this possibility, our group generated transgenic mice in which short-hairpin RNA (shRNA) against CPEB was placed under the control of the zona pellucida 3 (ZP3) promoter [36]. The zona pellucida is an extracellular glycoprotein that surrounds the oocyte and contains the sperm-binding receptor. Because the gene encoding ZP3 is transcribed after pachytene, the shRNA under its control would destroy CPEB mRNA only subsequent to this stage. In oocytes from these animals, oocyte meiosis properly progresses through pachytene; during the subsequent diakinesis period (which is the last stage of prophase); however, several phenotypes are evident. Perhaps the most striking of these is parthenogenetic activation, where ovarian oocyte cell division occurs in the absence of fertilization. One of the mRNAs of which translation is regulated by CPEB during the diakinesis period is germ-cell-derived factor 9 (GDF-9), a member of the transforming growth factor β (TGF β) family. GDF-9 is necessary for coordinating oocyte and follicle development, but its involvement in parthenogenetic activation is not known [37,38].

CPEB control of cell division and cellular senescence

The early mitotic cell divisions in *Xenopus* embryos are very different from those of other somatic cells. First, these cells synthesize almost no RNA until there are 4000 of them; at this so-called mid-blastula transition (MBT), the zygotic genomes are transcribed for the first time. Second, the mRNAs that were synthesized in oocytes are translated in the embryonic blastomeres; at the MBT, however, many of them are destroyed. Third, the early embryonic cell cycles lack G1 and G2 phases and consist entirely of alternating S (DNA synthesis) and M (mitosis) phases. These early cell divisions are controlled most prominently by cyclin B1, a co-factor that is necessary to activate the kinase *cdk1*. Cyclin B1 peaks at M phase, after which it is destroyed; as a consequence, *cdk1* is inactivated and the cells exit M phase and enter S phase. At S phase, cyclin B1 becomes stabilized and begins to accumulate and activate *cdk1*; the cells then enter another M phase; this cycle then continues until the MBT. However, cyclin B1 levels are controlled not only at the level of protein destruction, but also at the level mRNA translation. That is, as cells enter M phase, Aurora A phosphorylates Ser174 of CPEB, which induces cyclin B1 mRNA polyadenylation and translation;

at this time Maskin dissociates from eIF4E. At the peak of M phase, CPEB is dephosphorylated, which causes poly(A) shortening and translational silencing by the re-association of Maskin with eIF4E [39].

Maskin phosphorylation-dephosphorylation also has an important role in cyclin B1 translation during the embryonic cell cycle. Maskin is phosphorylated at six residues by cdk1 as the cells re-enter the meiotic divisions (oocyte maturation, which resembles a mitotic M phase); these modifications help Maskin dissociate from eIF4E [30]. After fertilization, in embryonic cells in M phase, Maskin is hyperphosphorylated by cdk1 and dissociates from eIF4E (but not from CPEB); cyclin B1 mRNA translation is high. As the cells enter S phase, the phosphatase calcineurin dephosphorylates Maskin, thereby causing it to re-associate with eIF4E; this event abrogates the eIF4E–eIF4G interaction and inhibits the translation of cyclin B1 mRNA (recall that eIF4G indirectly recruits the 40S ribosomal subunit to the 5' end of the mRNA, hence it must associate with eIF4E to enable translation initiation). At the peak of S phase, calcineurin gradually becomes inactive, thus enabling cdk1 to again re-phosphorylate Maskin; this process induces the dissociation of Maskin from eIF4E, the re-association of eIF4G with eIF4E and translational activation of cyclin B1 mRNA. The cycle then repeats [40].

These results indicate that CPEB is important for cell division, at least in *Xenopus* embryos; however, a CPEB KO mouse is viable, albeit sterile [34], perhaps indicating that the unusual *Xenopus* embryonic cell divisions (described at the start of this section) are more reliant on CPEB than more 'typical' cell divisions. Indeed, mouse embryo fibroblasts (MEFs) prepared from wild-type (WT) and CPEB KO mice divide at similar rates. However, upon several additional passages, the WT MEFs cease to divide and enter a senescent stage, as expected. Astonishingly, however, the KO MEFs do not stop dividing but, instead, are immortal [41]! Cellular senescence is induced by many environmental stresses such as reactive oxygen species (ROS), oncogenes and UV irradiation [42–47]. Senescent cells do not divide; they express the tumor suppressors p53, p19^{INK4A} and p19^{ARF} at high levels [48], and are often detected by staining for β -galactosidase activity at acid pH. Senescence is thought to be a counterbalance to malignant transformation, and thus might prevent cells from becoming cancerous [49,50]. Whereas the lack of CPEB causes cellular immortalization, the re-introduction of CPEB into the KO MEFs via retrovirus expression rescues senescence. In MEFs, CPEB interacts with several CPE-containing mRNAs, but the most important seems to be that which encodes the proto-oncogene myc, a transcription factor. In these cells, CPEB represses myc mRNA translation and this helps drive cells into senescence; when CPEB is lacking, however, myc mRNA translation is elevated and the cells bypass senescence [41].

In MEFs, there is no evidence that CPEB promotes polyadenylation and, indeed, it might function only as an inhibitor of translation. How CPEB might repress translation in MEFs is not known, although it could interact with Neuroguidin, a Maskin-like molecule that binds both CPEB and eIF4E in mammalian cells [51]. Based on its association with the helicase p54 (also sometimes called DDX6 or RCK

[22] and its co-localization with both argonaute in p-bodies and eIF3 in stress granules [52], CPEB might also work in concert with a miRNA to repress translation (note that argonaute is the key component of the RNA-induced silencing complex, RISC, and is responsible for processing silenced mRNAs; the main function of eIF3 is as a scaffolding protein that associates with numerous factors, including eIF4G and the 40S ribosomal subunit during the initiation of translation [53,54]). How CPEB and miRNAs could work together is unclear, but it is worth noting that another sequence-specific RNA-binding protein and a miRNA modulate translation: miRNA122 represses cationic amino acid transporter-1 mRNA translation, whereas HuR alleviates this repression [55]. Moreover, recent evidence indicates that argonaute, presumably without a contribution by a miRNA, functions with the RNA-binding protein fragile-X mental retardation-related protein 1 (FXR1) to control translation [56]. This example suggests that CPEB and argonaute could control translation in a miRNA-independent manner.

CPEB control of synaptic plasticity and learning and memory

In the central nervous system, neurons communicate with one another through synaptic connections, points of contact between the axon of one neuron with the dendrite of another neuron. Pre-synaptic axon terminals release a variety of neurotransmitters that induce currents to emanate from the synaptic spines, the post-synaptic structures that protrude from the dendrites. Although neurons can have thousands of synaptic inputs, they have the capacity to distinguish between those that have been stimulated just once from those that have been stimulated multiple times. This phenomenon – the ability of synapses to undergo biochemical and morphological changes in response to stimulation – is referred to as synaptic plasticity, which is thought to underlie learning and memory.

While investigating the biochemical basis of synaptic plasticity, Kang and Schuman [57] found that protein synthesis in either axons or the synapto-dendritic compartment was necessary for neurotrophin-mediated plasticity in the hippocampus. Subsequent studies indicated that at least some forms of plasticity require protein synthesis in the post-synaptic compartment [2,58,59]. Although several mechanisms probably regulate synaptic protein synthesis, the identification of CPEB in the postsynaptic density (an electron dense material immediately underlying the postsynaptic membrane containing many receptors and signaling factors) indicates that cytoplasmic polyadenylation might be one of these mechanisms [60]. Indeed, synaptic stimulation induces polyadenylation and translation of α CaMKII (the α subunit of calcium-calmodulin-dependent protein kinase II) mRNA, which resides in the postsynaptic compartment [60–62] (see also Ref. [63]). Only N-methyl-D-aspartate (NMDA) receptor signaling activates CPEB and does so through its phosphorylation of Thr171 [61,64]. CPEB is now thought to modulate mRNA translation in the neurons of several invertebrate and vertebrate animals [65–67]. At least in vertebrate neurons, it also interacts with the molecular motors dynein and kinesin to control mRNA movement in

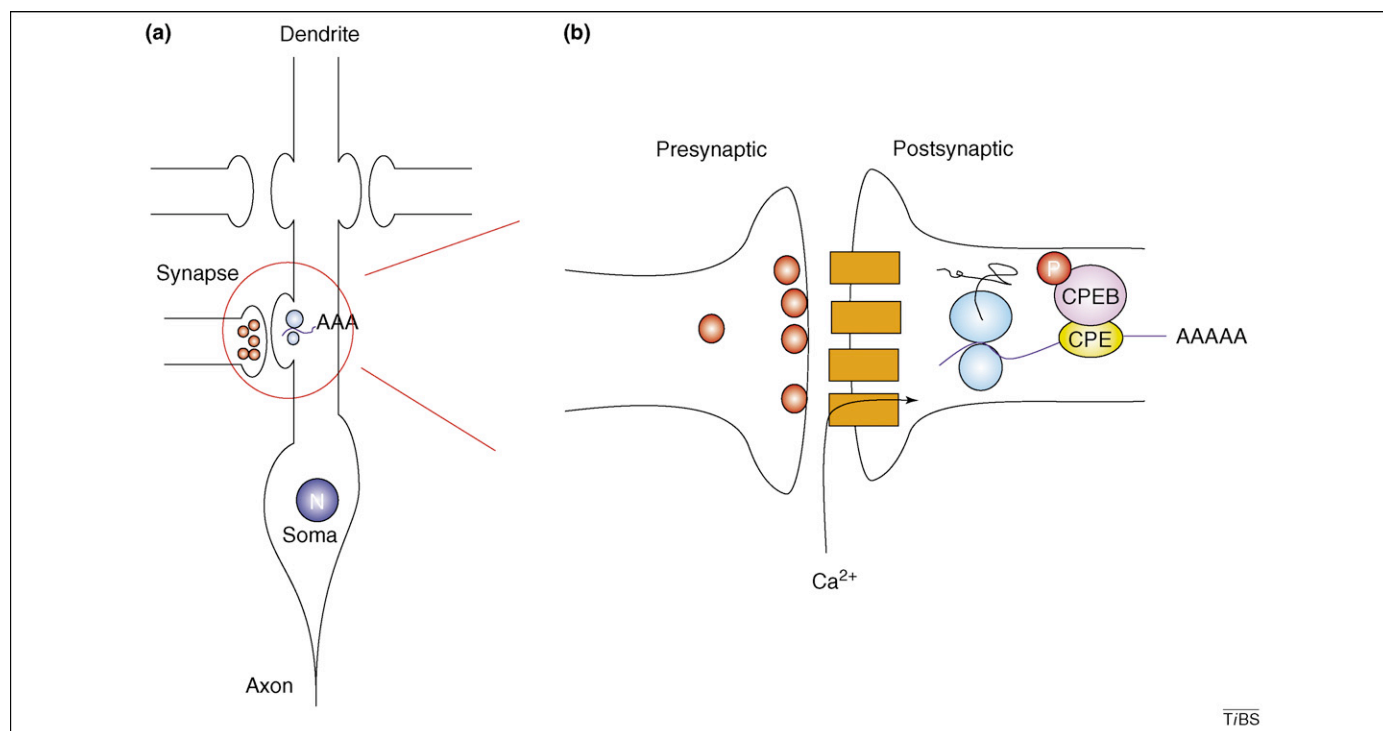


Figure 3. Translational control by CPEB at synapses. **(a)** A neuron comprising a dendrite with synapses, a soma containing the nucleus (N) and an axon. Within the synapse are neurosecretory vesicles (presynaptic, red spheres) and translating polysomes (postsynaptic). **(b)** An enlarged synaptic region: the vesicles contain NMDA, which interacts with receptors on the postsynaptic membrane (orange blocks). The NMDA receptors enable calcium entry into the synapse, which leads to CPEB phosphorylation, polyadenylation and translation of CPE-containing RNAs. The protein products of these mRNAs might then serve as synaptic tags to distinguish naïve from experienced synapses.

dendrites [68]. Figure 3 illustrates how CPEB could be involved in synaptic plasticity [69].

Is CPEB essential for proper neuronal function? Two studies indicate that it is. Under certain stimulation protocols, CPEB KO mice have a deficit in long term potentiation (LTP) and a more enduring long term depression (LTD); both are forms of synaptic plasticity that can be elicited by different stimulation protocols [70]. In addition, CPEB KO animals have an enhanced learning ability but reduced extinction, a type of hippocampal-dependent memory that refers to a behavioral response that will diminish and gradually vanish without reinforcement [71]. Extinction is not the same as forgetting and can even result in the formation of new memories [72]. Not surprisingly, LTP, LTD and extinction are protein synthesis-dependent [69].

A family of CPEB-like proteins in the brain

As noted earlier, mammals contain three additional CPEB-like proteins, all of which are expressed in the brain; one of them, CPEB4, is induced by kainate, a seizure-causing agent [73]. That these other CPEB-like proteins might mediate synaptic plasticity is indicated by a study of *Aplysia*, which, like other invertebrates, contains a single additional CPEB-like protein. An antisense oligonucleotide knockdown of *Aplysia* CPEB2 results in a failure to maintain long-term facilitation, a type of synaptic plasticity [67].

The extent to which the CPEB-like proteins are functionally redundant with CPEB has recently been examined. Huang *et al.* [5] used SELEX (selected evolution of ligands by exponential enrichment), an *in vitro* iterative binding assay, to demonstrate that CPEB2–4 do not interact with the CPE (at least not with a binding constant in

the sub-micromolar range) but, instead, bind another element that requires uridine residues in a stem-loop structure. Moreover, CPEB3, unlike CPEB, does not require the AAUAAA polyadenylation signal to regulate translation neither does it bind CPSF. Finally, CPEB3 binds the mRNA encoding the glutamate receptor GluR2 and represses its translation in the brain; CPEB neither binds nor regulates the translation of this mRNA. Thus, it seems reasonable to conclude that CPEB and CPEB2–4 constitute different branches of the CPEB family of proteins [4].

One unusual feature of the invertebrate CPEB proteins is the inclusion of a long stretch of glutamine residues (poly Q). Owing to a greater propensity for amyloidogenesis, the presence of poly Q in a protein can lead to prion formation, which is an epigenetic, self-seeding, protease-resistant protein polymer that is associated with some heritable neuropathies including Alzheimer's disease and Huntington's disease [74–76]. It is important to note that the correlative versus causative relationship between amyloid formation and the disease state has not yet been resolved. Si *et al.* [77], noting that *Aplysia* CPEB contains such a poly Q region, hypothesized that CPEB might assume a prion-like structure at synapses that would serve as a nearly indelible tag to distinguish experienced from naïve synapses; it would thus be a primary element in the control of synaptic plasticity. This is certainly an intriguing idea, and would fundamentally change our thinking not only as to how CPEB functions but also to how synaptic plasticity itself is regulated. By contrast, a simple model based on mechanistic work in *Xenopus* oocytes indicates that synaptic stimulation causes CPEB to become phosphorylated,

which induces polyadenylation and translation; the newly made proteins would then serve as the synaptic tags [78]. Although the prion model is elegant, consider that the degree of poly Q conservation in CPEB across phyla is not dramatic. Whereas *Aplysia* CPEB has a stretch of 65 Q residues out of 90, CPEB2 – the most Q-rich of the CPEB proteins in mammals – has a stretch in which only 12 residues out of 40 are Q. Whether this number is sufficient for prion formation is unclear but, if it is, perhaps vertebrates would use a similar mechanism under certain circumstances.

Concluding remarks and future prospects

In this review, I have tried to illustrate some of the key facts of CPEB activity, both biochemical and biological. However, because there are more features of this protein to discuss than space permits, particularly those relating invertebrate systems such as *C. elegans*, I refer you to another source for additional information [33]. But where next for CPEB research? A few questions loom especially large: if CPEB mediates cellular senescence, is it also a tumor suppressor? If CPEB represses translation in MEFs, does it do so in conjunction with miRNAs? If not, what other factors or mechanisms are involved? Is any CPEB protein a prion *in vivo*? If so, does it or how would it control translation at synapses? Irrespective of whether CPEB is a prion, what brain mRNAs does it regulate and how do the encoded proteins modulate synaptic plasticity and learning and memory? Although the answers to these questions are probably a few years away, they give us some idea of just how far CPEB has come from its initial discovery as a protein that associates with the CPE in *Xenopus* oocytes [79].

References

- Tadros, W. and Lipshitz, H.D. (2005) Setting the stage for development: mRNA translation and stability during oocyte maturation and egg activation in *Drosophila*. *Dev. Dyn.* 232, 593–608
- Schuman, E.M. *et al.* (2006) Synaptic regulation of translation of dendritic mRNAs. *J. Neurosci.* 26, 7143–7146
- Ruggero, D. *et al.* (2004) The translation factor eIF-4E promotes tumor formation and cooperates with c-Myc in lymphomagenesis. *Nat. Med.* 10, 484–486
- Mendez, R. and Richter, J.D. (2001) Translational control by CPEB: a means to the end. *Nat. Rev. Mol. Cell Biol.* 2, 521–529
- Huang, Y.S. *et al.* (2006) CPEB3 and CPEB4 in neurons: analysis of RNA-binding specificity and translational control of AMPA receptor GluR2 mRNA. *EMBO J.* 25, 4865–4876
- Mandel, C.R. *et al.* (2006) Polyadenylation factor CPSF-73 is the pre-mRNA 3'-end-processing endonuclease. *Nature* 444, 953–956
- Huarte, J. *et al.* (1992) Transient translational silencing by reversible mRNA deadenylation. *Cell* 69, 1021–1030
- Kim, J.H. and Richter, J.D. (2006) Opposing polymerase-deadenylase activities regulate cytoplasmic polyadenylation. *Mol. Cell* 24, 173–183
- Sachs, A. and Wahle, E. (1993) Poly(A) tail metabolism and function in eukaryotes. *J. Biol. Chem.* 268, 22955–22958
- Barnard, D.C. *et al.* (2004) Symplekin and xGLD-2 are required for CPEB-mediated cytoplasmic polyadenylation. *Cell* 119, 641–651
- Rouhana, L. *et al.* (2005) Vertebrate GLD2 poly(A) polymerases in the germline and the brain. *RNA* 11, 1117–1130
- Rouhana, L. and Wickens, M. (2007) Autoregulation of GLD-2 cytoplasmic poly(A) polymerase. *RNA* 13, 188–199
- Sarkissian, M. *et al.* (2004) Progesterone and insulin stimulation of CPEB-dependent polyadenylation is regulated by Aurora A and glycogen synthase kinase-3. *Genes Dev.* 18, 48–61
- Cao, Q. and Richter, J.D. (2002) Dissolution of the maskin-eIF4E complex by cytoplasmic polyadenylation and poly(A)-binding protein controls cyclin B1 mRNA translation and oocyte maturation. *EMBO J.* 21, 3852–3862
- Wakiyama, M. *et al.* (2000) Interaction of eIF4G with poly(A)-binding protein stimulates translation and is critical for *Xenopus* oocyte maturation. *Curr. Biol.* 10, 1147–1150
- Richter, J.D. and Sonenberg, N. (2005) Regulation of cap-dependent translation by eIF4E inhibitory proteins. *Nature* 433, 477–478
- Padmanabhan, K. and Richter, J.D. (2006) Regulated Pumilio-2 binding controls RINGO/Spy mRNA translation and CPEB activation. *Genes Dev.* 20, 199–209
- Martinez, S.E. *et al.* (2005) XGef mediates early CPEB phosphorylation during *Xenopus* oocyte meiotic maturation. *Mol. Biol. Cell* 16, 1152–1164
- Martinez, S.E. *et al.* (2005) XGef mediates early CPEB phosphorylation during *Xenopus* oocyte meiotic maturation. *Mol. Biol.* 16, 1152–1164
- Cao, Q. *et al.* (2005) Amyloid precursor proteins anchor CPEB to membranes and promote polyadenylation-induced translation. *Mol. Cell Biol.* 25, 10930–10939
- Vasudevan, S. *et al.* (2006) Metazoan oocyte and early embryo development program: a progression through translation regulatory cascades. *Genes Dev.* 20, 138–146
- Minshall, N. *et al.* (2001) A conserved role of a DEAD box helicase in mRNA masking. *RNA* 7, 1728–1742
- Nakahata, S. *et al.* (2001) Biochemical identification of *Xenopus* Pumilio as a sequence-specific cyclin B1 mRNA-binding protein that physically interacts with a Nanos homolog, Xcat-2, and a cytoplasmic polyadenylation element-binding protein. *J. Biol. Chem.* 276, 20945–20953
- Rouget, C. *et al.* (2006) Cytoplasmic CstF-77 protein belongs to a masking complex with cytoplasmic polyadenylation element-binding protein in *Xenopus* oocytes. *J. Biol. Chem.* 281, 28687–28698
- Reverte, C.G. *et al.* (2001) CPEB degradation during *Xenopus* oocyte maturation requires a PEST domain and the 26S proteasome. *Dev. Biol.* 231, 447–458
- Mendez, R. *et al.* (2002) Differential mRNA translation and meiotic progression require Cdc2-mediated CPEB destruction. *EMBO J.* 21, 1833–1844
- Costa, A. *et al.* (2005) The *Drosophila* fragile X protein functions as a negative regulator in the orb autoregulatory pathway. *Dev. Cell* 8, 331–342
- Groisman, I. *et al.* (2000) CPEB, maskin, and cyclin B1 mRNA at the mitotic apparatus: implications for local translational control of cell division. *Cell* 103, 435–447
- Blower, M.D. *et al.* (2005) A Rae1-containing ribonucleoprotein complex is required for mitotic spindle assembly. *Cell* 121, 223–234
- Barnard, D.C. *et al.* (2005) Differential phosphorylation controls Maskin association with eukaryotic translation initiation factor 4E and localization on the mitotic apparatus. *Mol. Cell Biol.* 25, 7605–7615
- Kinoshita, K. *et al.* (2005) Aurora A phosphorylation of TACC3/maskin is required for centrosome-dependent microtubule assembly in mitosis. *J. Cell Biol.* 170, 1047–1055
- Peset, I. *et al.* (2005) Function and regulation of Maskin, a TACC family protein, in microtubule growth during mitosis. *J. Cell Biol.* 170, 1057–1066
- Thompson, B. *et al.* (2007) Translational control in development. In *Translational Control in Biology and Medicine* (Mathews, M.B., Sonenberg, N. and Hershey, J.W.B., eds), pp. 507–544, Cold Spring Harbor laboratory Press
- Tay, J. and Richter, J.D. (2001) Germ cell differentiation and synaptonemal complex formation are disrupted in CPEB knockout mice. *Dev. Cell* 1, 201–213
- Tay, J. *et al.* (2003) Regulated CPEB phosphorylation during meiotic progression suggests a mechanism for temporal control of maternal mRNA translation. *Genes Dev.* 17, 1457–1462
- Racki, W.J. and Richter, J.D. (2006) CPEB controls oocyte growth and follicle development in the mouse. *Development* 133, 4527–4537
- Matzuk, M.M. *et al.* (2002) Intercellular communication in the mammalian ovary: oocytes carry the conversation. *Science* 296, 2178–2180
- Pangas, S.A. and Matzuk, M.M. (2005) The art and artifact of GDF9 activity: cumulus expansion and the cumulus expansion-enabling factor. *Biol. Reprod.* 73, 582–585

- 39 Groisman, I. *et al.* (2002) Translational control of the embryonic cell cycle. *Cell* 109, 473–483
- 40 Cao, Q. *et al.* (2006) CDK1 and calcineurin regulate Maskin association with eIF4E and translational control of cell cycle progression. *Nat. Struct. Mol. Biol.* 13, 1128–1134
- 41 Groisman, I. *et al.* (2006) Control of cellular senescence by CPEB. *Genes Dev.* 20, 2701–2712
- 42 Ben-Porath, I. and Weinberg, R.A. (2005) The signals and pathways activating cellular senescence. *Int. J. Biochem. Cell Biol.* 37, 961–976
- 43 Lowe, S.W. *et al.* (2004) Intrinsic tumour suppression. *Nature* 432, 307–315
- 44 Narita, M. and Lowe, S.W. (2005) Senescence comes of age. *Nat. Med.* 11, 920–922
- 45 Sherr, C.J. (2004) Principles of tumor suppression. *Cell* 116, 235–246
- 46 Bardeesy, N. and Sharpless, N.E. (2006) RAS unplugged: negative feedback and oncogene-induced senescence. *Cancer Cell* 10, 451–453
- 47 Ramsey, M.R. and Sharpless, N.E. (2006) ROS as a tumour suppressor? *Nat. Cell Biol.* 8, 1213–1235
- 48 Kim, W.Y. and Sharpless, N.E. (2006) The regulation of INK4/ARF in cancer and aging. *Cell* 127, 265–275
- 49 Campisi, J. (2005) Senescent cells, tumor suppression, and organismal aging: good citizens, bad neighbors. *Cell* 120, 513–522
- 50 Campisi, J. (2005) Suppressing cancer: the importance of being senescent. *Science* 309, 886–887
- 51 Jung, M.Y. *et al.* (2005) Translational control by neuroguidin, a eukaryotic initiation factor 4E and CPEB binding protein. *Mol. Cell Biol.* 26, 4277–4287
- 52 Wilczynska, A. *et al.* (2005) The translational regulator CPEB1 provides a link between dcp1 bodies and stress granules. *J. Cell Sci.* 118, 981–992
- 53 Parker, J.S. and Barford, D. (2006) Argonaute: a scaffold for the function of short regulatory RNAs. *Trends Biochem. Sci.* 31, 622–630
- 54 Hinnebusch, A.G. (2006) eIF3: a versatile scaffold for translation initiation complexes. *Trends Biochem. Sci.* 31, 553–562
- 55 Bhattacharyya, S.N. *et al.* (2006) Relief of microRNA-mediated translational repression in human cells subjected to stress. *Cell* 125, 1111–1124
- 56 Vasudevan, S. and Steitz, J. (2007) AU-rich-element-mediated upregulation of translation by FXR1 and argonaute 2. *Cell* 128, 1105–1118
- 57 Kang, H. and Schuman, E.M. (1996) A requirement for local protein synthesis in neurotrophin-induced hippocampal synaptic plasticity. *Science* 273, 1402–1406
- 58 Huber, K.M. *et al.* (2000) Role for rapid dendritic protein synthesis in hippocampal mGluR-dependent long-term depression. *Science* 288, 1254–1257
- 59 Sutton, M.A. and Schuman, E.M. (2006) Dendritic protein synthesis, synaptic plasticity, and memory. *Cell* 127, 49–58
- 60 Wu, L. *et al.* (1998) CPEB-mediated cytoplasmic polyadenylation and the regulation of experience-dependent translation of α -CaMKII mRNA at synapses. *Neuron* 21, 1129–1139
- 61 Huang, Y.S. *et al.* (2002) N-methyl-D-aspartate receptor signaling results in Aurora kinase-catalyzed CPEB phosphorylation and alpha CaMKII mRNA polyadenylation at synapses. *EMBO J.* 21, 2139–2148
- 62 Shin, C.Y. *et al.* (2004) Rapid, activity-induced increase in tissue plasminogen activator is mediated by metabotropic glutamate receptor-dependent mRNA translation. *J. Neurosci.* 24, 9425–9433
- 63 Miller, S. *et al.* (2002) Disruption of dendritic translation of CaMKII α impairs stabilization of synaptic plasticity and memory consolidation. *Neuron* 36, 507–519
- 64 Atkins, C.M. *et al.* (2004) Cytoplasmic polyadenylation element binding protein-dependent protein synthesis is regulated by calcium/calmodulin-dependent protein kinase II. *J. Neurosci.* 24, 5193–5201
- 65 Liu, J. and Schwartz, J.H. (2003) The cytoplasmic polyadenylation element binding protein and polyadenylation of messenger RNA in *Aplysia* neurons. *Brain Res.* 959, 68–76
- 66 Liu, L.O. *et al.* (2000) Photoreceptor regulated expression of Ca²⁺/calmodulin-dependent protein kinase II in the mouse retina. *Brain Res. Mol. Brain Res.* 82, 150–166
- 67 Si, K. *et al.* (2003) A neuronal isoform of CPEB regulates local protein synthesis and stabilizes synapse-specific long-term facilitation in *Aplysia*. *Cell* 115, 893–904
- 68 Huang, Y.S. *et al.* (2003) Facilitation of dendritic mRNA transport by CPEB. *Genes Dev.* 17, 638–653
- 69 Klann, E. and Richter, J.D. (2007) Translational control of synaptic plasticity and learning and memory. In *Translational Control in Biology and Medicine* (Mathews, M.B., Sonenberg, N. and Hershey, J.W.B., eds), pp. 485–506, Cold Spring Harbor Laboratory Press
- 70 Alarcon, J.M. *et al.* (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
- 71 Berger-Sweeney, J. *et al.* (2006) Reduced extinction of hippocampal-dependent memories in CPEB knockout mice. *Learn. Mem.* 13, 4–7
- 72 Abel, T. and Lattal, K.M. (2001) Molecular mechanisms of memory acquisition, consolidation and retrieval. *Curr. Opin. Neurobiol.* 11, 180–187
- 73 Theis, M. *et al.* (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. U. S. A.* 100, 9602–9607
- 74 Osherovich, L.Z. and Weissman, J.S. (2001) Multiple Gln/Asn-rich prion domains confer susceptibility to induction of the yeast (PSI⁺) prion. *Cell* 106, 183–194
- 75 Osherovich, L.Z. *et al.* (2004) Dissection and design of yeast prions. *PLoS Biol.* 2, E86
- 76 Tuite, M.F. and Cox, B.S. (2003) Propagation of yeast prions. *Nat. Rev. Mol. Cell Biol.* 4, 878–890
- 77 Si, K. *et al.* (2003) A neuronal isoform of the *Aplysia* CPEB has prion-like properties. *Cell* 115, 879–891
- 78 Richter, J.D. and Lorenz, L.J. (2002) Selective translation of mRNAs at synapses. *Curr. Opin. Neurobiol.* 12, 300–304
- 79 Paris, J. *et al.* (1991) Maturation-specific polyadenylation: *in vitro* activation by p34cdc2 and phosphorylation of a 58-kD CPE-binding protein. *Genes Dev.* 5, 1697–1708

The ScienceDirect collection

ScienceDirect's extensive and unique full-text collection covers more than 1900 journals, including titles such as *The Lancet*, *Cell*, *Tetrahedron* and the full suite of *Trends*, *Current Opinion* and *Drug Discovery Today* journals. With ScienceDirect, the research process is enhanced with unsurpassed searching and linking functionality, all on a single, intuitive interface.

The rapid growth of the ScienceDirect collection is a result of the integration of several prestigious publications and the ongoing addition to the Backfiles – heritage collections in a number of disciplines. The latest step in this ambitious project to digitize all of Elsevier's journals back to volume one, issue one, is the addition of the highly cited *Cell Press* journal collection on ScienceDirect. Also available online for the first time are six *Cell* titles' long-awaited Backfiles, containing more than 12,000 articles that highlight important historic developments in the field of life sciences.

For more information, visit www.sciencedirect.com