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CPEB: a life in translation

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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

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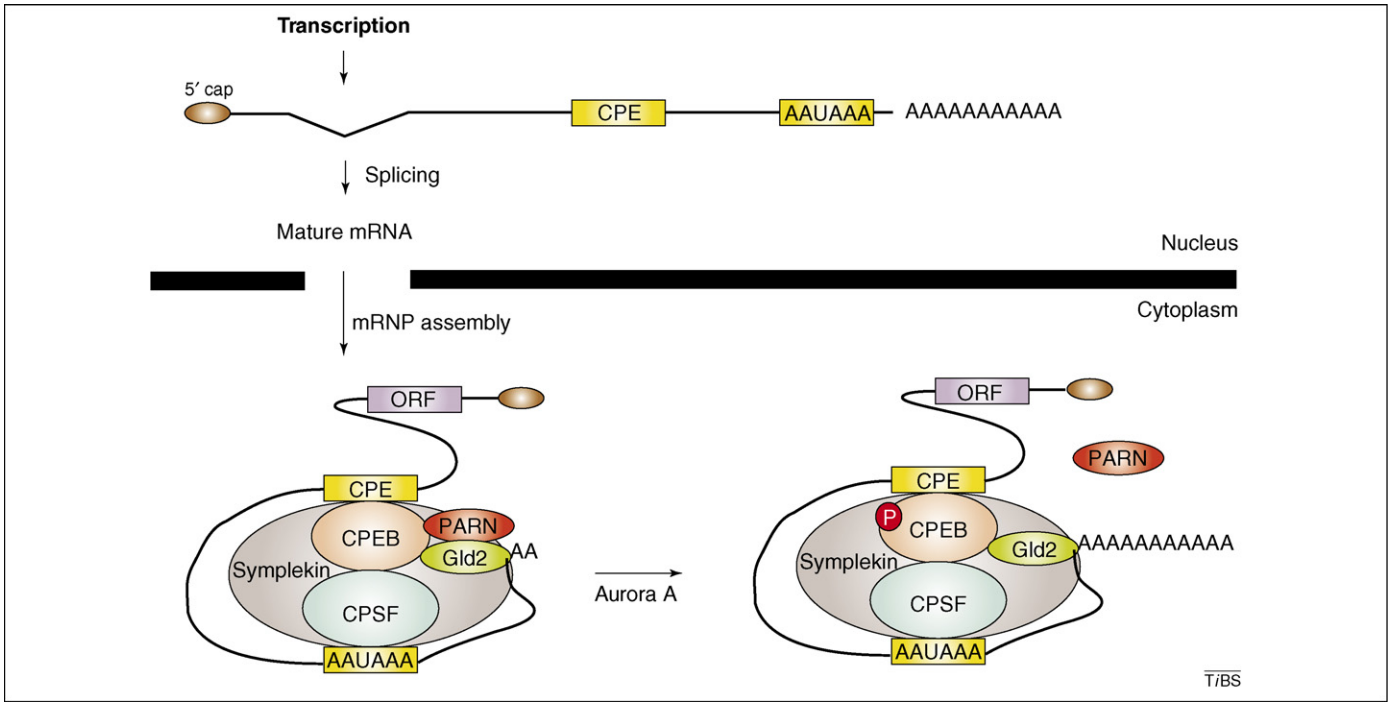

Figure 1. CPEB-regulated polyadenylation. In the nucleus, pre-RNAs containing or lacking a CPE acquire a long poly(A) tail. Following splicing and RNA export, the CPEB-containing RNAs assemble into a ribonucleoprotein (RNP) complex that is nucleated by CPEB. The other factors in this complex include: 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

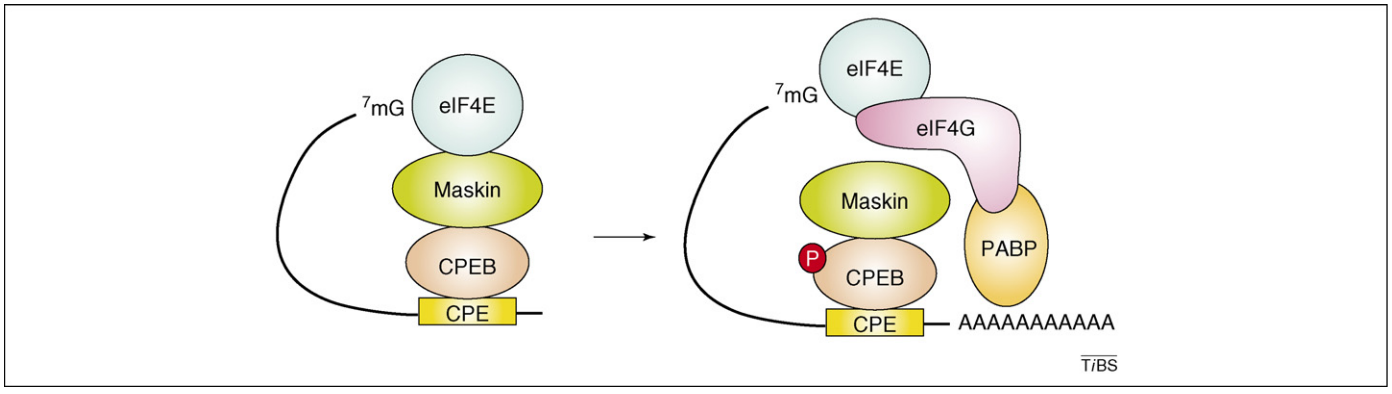

Figure 2. Translational control by Maskin. CPEB associates with both CPE-containing mRNAs and Maskin. Maskin, in turn, interacts with the cap (^{7}mG)-binding factor eIF4E. In this configuration, Maskin binding to eIF4E precludes eIF4G from binding eIF4E, thus, inhibiting translation. Following CPEB 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 G_2–M in oocytes)-Spy mRNA, which encodes a cyclin B1-like molecule [17], and glycogen synthase kinase 3β (GSK-3β) 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 ubiquitylated 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 re-phosphorylates 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 (TGFβ) 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 αCaMKII (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

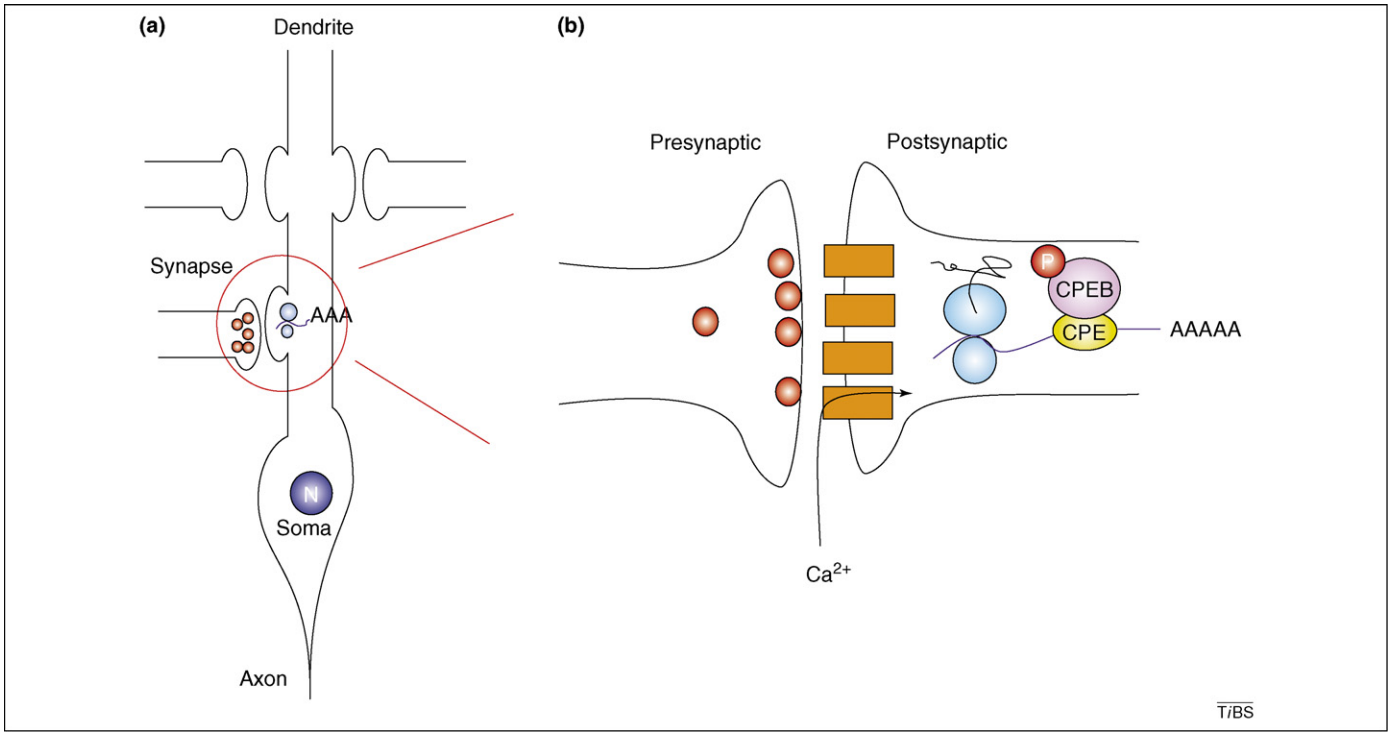

Figure 3. Translational control by CPEB at synapses. **(a)** A neuron comprising a dendrite with synapses, a soma containing the nucleus (N) and an axon. Within the synapse are neurosecretory vesicles (presynaptic, red spheres) and translating polysomes (postsynaptic). **(b)** An enlarged synaptic region: 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].

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