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The role of mammalian poly(A)-binding proteins in co-ordinating mRNA turnover

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Abstract

The function of cytoplasmic PABPs [poly(A)-binding proteins] in promoting mRNA translation has been intensively studied. However, PABPs also have less clearly defined functions in mRNA turnover including roles in default deadenylation, a major rate-limiting step in mRNA decay, as well as roles in the regulation of mRNA turnover by cis-acting control elements and in the detection of aberrant mRNA transcripts. In the present paper, we review our current understanding of the complex roles of PABP1 in mRNA turnover, focusing on recent progress in mammals and highlighting some of the major questions that remain to be addressed.

Introduction

The extent to which an mRNA is utilized is determined by its lifespan and rate of translation. These are intimately linked and can be regulated by cis-acting elements in response to the cellular context. In eukaryotes, the primary determinants of both mRNA translation and turnover are the 5’ m7GTP (7-methylguanosine triphosphate) ‘cap’ and 3’ poly(A) tail which act by binding eIF (eukaryotic initiation factor) 4F (comprising eIF4E, eIF4G and eIF4A) and PABPs [poly(A)-binding proteins] respectively. The association of these 5’- and 3’-bound factors, primarily through eIF4G–PABP interactions, forms a ‘closed-loop’ mRNA conformation (Figure 1). This enhances ribosomal recruitment [1] and protects both ends of the mRNA, most likely by increasing binding of these factors to block access of the mRNA degradation machinery.

mRNA turnover is a multi-step process in which deadenylation [shortening of the poly(A) tail] is usually the initial and primary rate-limiting step. In mammals, deadenylation is a biphasic process where poly(A) tails are shortened to ~110 nucleotides (from approximately 250 nucleotides) by the PAN [poly(A) nuclease] 2–PAN3 deadenylase complex and subsequently to oligo(A) (approximately A10–18) by the CCR4 (carbon catabolite repressor protein 4)–CAF1 (CCR4-associated factor 1) complex (reviewed in [2]). In the absence of cis-acting regulatory elements, so-called default deadenylation occurs. Initial poly(A) removal occurs at a constant low rate due to the distributive nature of PAN2–PAN3 which has a high on/off rate of RNA binding, therefore only removing exposed poly(A). In contrast, CCR4–CAF1 acts processively, presumably evicting PABP1, and rapidly removes the remaining ~110 nucleotides to leave an oligo(A) tail. This oligo(A) tail is bound by the LSm (like-Sm) 1–7–Pat1 complex which promotes removal of the 5’ cap (decapping) by the DCP (decapping protein) 1–DCP2 complex, allowing access of the 5’→3’ exonuclease XRN1 (exoribonuclease 1) which degrades the body of the mRNA in concert with 3’→5’ exoribonucleolytic activities (i.e. exosome and/or the LSm1–7–Pat1 complex) [3–5].

Cytoplasmic PABPs are conserved across eukaryotes and are best characterized as central regulators of mRNA translation (reviewed in [6–8]). Although mammals encode five PABPs, almost all studies have focused on the prototypical family member, PABP1 (also known as PABPC1). PABP1 contains four non-identical RRMs (RNA-recognition motifs) and a C-terminal region. RRMs 1 and 2 bind poly(A) with high specificity, whereas RRMs 3 and 4 bind poly(A) with reduced affinity and can bind adenine/uridine-rich RNA, although their RNA-binding specificity remains less clear [6]. Interestingly, the RRMs also mediate important protein interactions, including those with eIF4G [8]. The C-terminal region is composed of the PABC (PABP C-terminal domain)/MLLE domain which interacts with numerous PAM2 (PABP-interacting motif 2)-containing proteins [e.g. eRF (eukaryotic release factor) 3] [8], deadenylases [2,9,10] and TNRC6 (trinucleotide repeat-containing 6) [11], and a proline-rich linker that is involved in PABP1–PABP1 interactions which enhance co-operative poly(A) binding [6,12,13]. The known protein partners of PABP1 provide some insight into its complex functions in both mRNA translation and stability, and in the present paper we review the current state of knowledge regarding its role in regulating mRNA turnover in mammals.
Figure 1 | Role of PABP1 in the closed-loop mRNA conformation

mRNAs are bound at the cap by eIF4E, as part of the eIF4F complex (eIF4E, eIF4G, eIF4A) and at the poly(A) tail by PABP1, protecting the mRNA ends from decapping and deadenylation. Both eIF4E and PABP1 bind the scaffolding protein eIF4G, which effectively bridges the 5′ and 3′ ends of the mRNA to form a ‘closed-loop’. This conformation increases the affinity of eIF4E for the cap and is proposed to increase the affinity of PABP1 for the poly(A) tail, promoting small ribosomal subunit recruitment [1] and further protecting mRNAs from decay (not depicted). For simplicity, other initiation factors that interact with PABP1, including those that contribute to the closed-loop, are not shown.

PABP1 function in default mRNA deadenylation and decay

The dual role of PABP1 in both poly(A) tail protection and deadenylation

The stabilizing effect of a poly(A) tail on a reporter mRNA in vitro is negated by sequestration or depletion of PABP1, and can be rescued by addition of exogenous PABP1, with non-adenylated mRNAs being rapidly turned over independently of PABP1 status [14]. Since intermediates corresponding to the loss of footprints of consecutive PABP molecules can be observed [15,16], this led to the idea that PABP1 may act as a steric block to deadenylation (Figure 2, panel 1). Such a function will be determined by the dissociation rate \( K_d \) of PABP1 (Figure 2, panel 2) which is influenced by whether it is bound non-co-operatively or co-operatively to poly(A), with the latter exhibiting higher affinity [12]. Mammalian cells contain three major poly(A)-specific 3′ exoribonuclease activities: the CCR4–NOT (negative on TATA)–CAF1 complex, the PAN2–PAN3 complex and PARN [poly(A)-specific ribonuclease]. Intriguingly, given its poly(A)-protective effect, PABP1 interacts directly with PARN and the PAN3 subunit of the PAN2–PAN3 complex and indirectly with the CCR4–NOT–CAF1 complex via TOB (transducer of ErbB2) 1 (or TOB2) [2]. Somewhat counterintuitively, given its poly(A)-protective effect, PABP1 also appears to enhance PAN2–PAN3 complex activity and, via TOB-mediated recruitment, CCR4–CAF1 deadenylase activity [2,17] (Figure 2, panel 1). Such observations, although confusing, support complex roles for PABP1 as both as a facilitator of deadenylation and as a negative regulator of deadenylation, with its interactions with deadenylases raising the possibility that PABP1 may inhibit their function directly as well as sterically. Since it was proposed recently that only non-co-operatively bound PABP1 may be available for PABC-mediated interactions [12], it is tempting to speculate that co-operatively bound PABP1 acts as a steric block with non-co-operatively bound PABP1 recruiting/stimulating deadenylases.

Might PABP1 be removed from poly(A) tails during translation termination?

Work in yeast first highlighted potential links between deadenylation and translational termination, by showing that the translation termination factor eRF3 interacts with PAB-1. This led to a model in which eRF3–PAB–1 interaction during termination facilitates the removal of a PAB-1 molecule from the poly(A) tail, rendering the 3′ end open to limited 3′ → 5′ exonucleolytic attack [18]. Subsequently, mammalian PABP1 was shown to interact in a mutually exclusive manner with eRF3, PAN3 and TOB, and, intriguingly, switching of PABP1 from an eRF3-bound to PAN3-bound state requires active translation since it can be blocked by cycloheximide [19]. eRF3, PAN3 and TOB all contain a PAM2 motif, and ectopic expression of PAM2-mutant versions of these proteins was found to exert opposing effects on mRNA deadenylation rates [19]. Thus, similar to yeast, a model was proposed in which formation of a PABP1–eRF3–eRF1 termination complex causes PABP1 to dissociate from the poly(A) tail (Figure 2, panels 3 and 4). Displaced PABP1 leaves the PABP1–eRF3–eRF1 complex upon eRF1 stimulation of eRF3-mediated GTP hydrolysis [19,20] and, or, the 3′-most PABP1, may then recruit/stimulate PAN3 or TOB1–CCR4–CAF1.

A link between translation termination and incremental shortening of the poly(A) tail could provide a molecular timer for mRNA lifespan, limiting the number of times that an mRNA molecule can be translated [18,19]. However, most mRNAs will be translated by many more transiting ribosomes than would be required to evict the number of PABP1 molecules bound to the poly(A) tail, suggesting that eviction does not occur at every termination event. Moreover, it is unlikely that all default deadenylation is linked to termination, since reducing the translational efficiency of a reporter mRNA by introducing a hairpin-loop into the 5′-UTR (untranslated region) does not block deadenylation [21]. As discussed above (Figure 2, panel 2), this termination-independent deadenylation may simply reflect the off rate of PABP1 and/or, since end-to-end complexes may still...
Figure 2 | Role of PABP1 in default deadenylation
(1) PABP1 bound to the poly(A) tail prevents access of deadenylases (blunted arrow), but can also recruit and stimulate
deadenylases (thin arrow), an activity that is blocked by its interaction with eRF3 which competes for the same binding site
within PABC. (2–4) Removal of PABP1 from the poly(A) tail (arrow) facilitates access of deadenylases either as a result of
(2) the inherent 'off' rate of PABP1 or (3) due to translation termination, since indirect interaction of PABP1 with terminating
ribosomes, via an eRF3-eRF1 bridge, causes (4) PABP1 to be evicted from the poly(A) tail. (5) Deadenylated mRNAs
are decapped by DCP1–DCP2 (not depicted) and degraded by XRN1 (not depicted), the exosome and/or LSm 1-7-Pat1.
TOB1–TOB2 is not depicted.

form on these mRNAs, PABP1-mediated co-ordination of
deadenylase activity.

A direct role for PABP1 in regulating decapping?
Deadenylation triggers decapping in mammalian cells ([22]
and reviewed in [23]). Both PABP1 and the poly(A)
tail are required to protect mRNAs from DCP2-mediated
decapping in vitro [24,25], suggesting that protection of
the poly(A) tail by PABP1 is likely to be sufficient to
account for this effect. Intriguingly, however, poly(A)-
bound PABP1, but not free PABP1, can bind the RNA-
incorporated cap structure, but not free cap, in vitro with
an apparent \(K_d\) of 150 nM [24], suggesting that, under certain
circumstances, poly(A) tail-associated PABP1 could directly
protect mRNAs from decapping. However, this binding only
occurs in the absence of the cap-binding factor eIF4E, thus it
is unclear whether this interaction can, or does, occur in cells.

Regulation of aberrant transcript turnover
PTCs (premature termination codons) have been described in
approximately 30% of known disease-associated mutations
[26] and promote aberrant as well as premature translation
termination. As a result of their aberrant translation
Figure 3 | PABP1 suppresses NMD

(1) mRNAs are initially bound by the nuclear CBC80–CBC20 cap-binding complex with the EJC–UPF2-containing complex marking splicing boundaries. As an mRNA emerges from the nucleus, CBC20–CBC80 is exchanged for the cytoplasmic cap-binding complex [only eIF4E and eIF4G (4G) are shown], allowing bridging interactions with PABP1. (2) During translation, the transiting ribosome displaces the EJC and PABP1–eRF3 complexes promote correct termination (+) by interacting with eRF1 (not shown). Formation of this complex blocks recruitment of the NMD factor UPF1 (blunted arrow). (3) In contrast, when PTCs occur 5′ to an EJC, the EJC is not displaced and PABP1 is not proximal to the stop codon (4). Thus normal PABP1–eRF3-mediated termination does not occur (blunted arrow) and UPF1 binds the ribosome-associated eRF3, recruiting SMG1. (5) The stalled ribosome exits the PTC and the UPF1-containing complex contacts the EJC–UPF2-containing complex and inhibits further translation initiation (blunted arrow). (6) The endonuclease SMG6 then cleaves the mRNA 3′ to the PTC with (7) the mRNA fragments then being degraded in a deadenylation-independent manner. For simplicity, not all NMD factors are depicted.

Non PTC-containing mRNA

PTC-containing mRNA

termination, PTC-containing mRNAs can be recognized by the mRNA-surveillance machinery and subjected to NMD (nonsense-mediated decay). In mammals, NMD appears to be triggered by UPF (up-frameshift) 2-containing EJCs (exon-junction complexes) located 3′ of PTCs. Prematurely terminating ribosomes undergo abnormal termination, with eRF3 being bound by UPF1, which also interacts with EJC-associated UPF2, leading to the recruitment of further NMD factors and deadenylation-independent endonucleolytic cleavage of the mRNA [27,28]. PABP1 therefore plays a role in deciding whether to commit mRNAs for NMD, since its interaction with eRF3 on the terminating ribosomes at bona fide stop codons promotes ‘normal’ termination and prevents eRF3–UPF1 interaction [29] (Figure 3). The relative proximity of PABP1 to the termination codon appears to be important in this decision,
as NMD can be suppressed by tethering PABP1 in the vicinity of PTCs but 5′ to EJC s [30–32]. However, although introduction of a PTC which creates a long ‘faux’ (or false) 3′-UTR leads to NMD, many mammalian mRNAs contain long 3′-UTRs and are not subject to NMD [27], underscoring the importance of a 3′ EJC as well as PABP1 proximity. Nonetheless, increasing the distance between poly(A)-bound PABP and a normal stop codon by extending the 3′-UTR can induce EJC-independent NMD, which is antagonized by reinstating PABP1 proximity [33]. It is not clear how this form of NMD is promoted, but one idea is that unknown 3′-UTR-associated factors prevent PABP1 from interacting with eRF3 and promote loading of UPF1 to initiate NMD [33].

### mRNA-specific regulation of mRNA stability by PABP1

The rate of mRNA decay can be modulated by sequences and/or structural features within mRNAs that, most often, recruit specific trans-acting factors (reviewed in [2,23,34]). These cis-acting elements are normally located within the 3′-UTR as exemplified by AREs (adenine/uridine-rich elements) and the α-globin mRNA CRE (cytosine-rich element) or less frequently, as is the case for c-fos mRNA, in the coding region.

### PABP1-mediated regulation of endonuclease recruitment

Erythrocytes are enucleated and post-transcriptionally regulate the synthesis of α- and β-globin subunits for haemoglobin production, with an imbalance in their synthesis leading to thalassaemias, defective erythropoiesis and/or peripheral haemolysis [35,36]. The 3′-UTR of α-globin mRNA contains a CRE which is bound by the poly(C)-binding protein complex αCP1-αCP2 [15]. Interaction between PABP1 and αCP1-αCP2 causes an increase in both αCP1-αCP2 affinity for the CRE and PABP1-poly(A) tail binding, simultaneously blocking ErEN (erythroid-cell-specific endonuclease) from cleaving at the CRE [15,37] and reducing deadenylation to stabilize the mRNA (Figure 4A). A similar mechanism is employed for the stabilization of NF-L (neurofilament light) mRNA, whose misregulation results in motor neuron degeneration. PABP1 blocks aldolase C-mediated endonucleolytic cleavage within the 3′-UTR of NF-L mRNA, with in vitro studies showing that it binds a 68 nt polypyrimidine-rich region [38,39], implying that PABP1 may bind to sequences other than poly(A) or A/U.

### PABP1-mediated regulation of mRNA stability via open reading frame cis-acting elements

The c-fos mRNA mCRD (major coding-region determinant) is an 87 nt G/A-rich element that directs translationally coupled deadenylation. The c-fos mCRD binds a multiprotein complex containing UNR (upstream of N-ras), PAIP1 (PABP-interacting protein 1), AUF1 (A/U-rich RNA-binding factor 1), NSAP1 (NS1-associated protein 1) and PABP1, bridging a functional interaction between the mCRD and the poly(A) tail and preventing deadenylation [40] (Figure 4B). The key interaction in forming this bridging complex occurs between PABP1 and UNR, although PAIP1 and AUF1 are also known PABP1-interacting proteins, but it is unclear whether they interact directly with PABP1 in this context [41]. During c-fos mRNA translation, the transiting ribosome displaces the mCRD-bound complex [40,41], which may remain associated with poly(A)-bound PABP1, disrupting the association between the mCRD and the poly(A) tail and apparently permitting recruitment of the CCR4 deadenylase by UNR [41]. Thus the translation of c-fos mRNA acts as a trigger for its destruction, thereby limiting the expression of this oncogene by restricting the lifetime of its mRNA.

### PABP1, AREs and AUBPs

Although AUBPs (ARE-binding proteins) can enhance or reduce mRNA stability and/or translation, the presence of an ARE generally confers reduced basal stability to mRNAs by enhancing deadenylation [2,42]. Thus it seems likely that there is functional cross-talk between AREs and PABP, and, in support of this, PABP1 associates with AUBPs and can bind to A/U-rich RNA, including functional AREs, in vitro [43]. However, despite the large number of identified ARE-containing mRNAs and the contribution of misregulated ARE-mediated control to disease (e.g. chronic inflammatory disorders and cancer [34,44,45]), our understanding of the role of PABP1 in ARE-mediated mRNA decay is limited and its role may vary between mRNAs (Figure 4C).

For instance, an interaction between ARE-bound HuR and poly(A)-bound PABP1 was posited to enhance the ability of PABP1 to protect the poly(A) tail of β-casein mRNA, contributing to its stability during lactation [46]. The underlying mechanism remains to be determined, but may reflect altered interaction of PABP1 with poly(A) or deadenylases. In contrast, the AUBP TTP (tristetraprolin) destabilizes mRNA by directly recruiting CAF1 deadenylase [47,48], with TTP–PABP1 interactions being reported to inhibit TTP-mediated deadenylation [49]. However, TTP dephosphorylation not only enhances its ability to recruit CAF1, but also enhances its interaction with PABP1, which appears to be altered under conditions of stress. Although this interaction is direct, it is thought that it may reflect the role of PABP1 in stabilizing ARE-containing mRNA translation, the expression of this oncogene by restricting the lifetime of its mRNA.
Figure 4 | Roles of PABP1 in regulating mRNA-specific mRNA turnover

(A) Left: α-globin mRNA is protected from the action of EEN and deadenylation (blunted arrows) by 3'-UTR CRE-associated αCP1-αCP2 complex which interacts with PABP1, promoting both CRE and poly(A) binding (double-headed arrow). Right: in the absence of the αCP1-αCP2 complex binding, EEN can cleave within the CRE (zigzag arrow), PABP1 poly(A) binding will be reduced (broken arrow) and the cleaved mRNA fragments will be subject to decay. (B) Left: on non-translating c-fos mRNA, the mCRD is bound by UNR in complex with AUF1, PAIP1 and NSAP1. UNR (and possibly other complex components, depicted as broken arrows) interacts with PABP1 and inhibits c-fos mRNA deadenylation (blunted arrow) by an unknown mechanism. Right: upon translation of c-fos mRNA, the transiting ribosome displaces the UNR-containing complex from the mCRD, although it may remain associated with the poly(A) tail via PABP1 (broken arrow). UNR is then able to recruit CCR4-CAF1, and possibly also PAN2-PAN3 (not shown), to promote (+) deadenylation. (C) ARE-containing mRNAs are bound by one or more AUBPs. AUBPs can promote deadenylation directly through recruitment and stimulation of deadenylases and this can be antagonized by PABP1. AUBPs may also promote deadenylation indirectly by altering PABP1 poly(A) binding or modulating PABP1-mediated stimulation of deadenylases. Conversely, AUBPs may also inhibit deadenylation by enhancing PABP1 poly(A) binding and blocking its ability to stimulate deadenylase activity. Positive and inhibitory actions are depicted by + or − respectively. (D) PABP1 function is modulated during miRNA-mediated translational repression and deadenylation. RISC (only TNRC6 and Ago shown) is brought to the mRNA via miRNA complementarity. TNRC6 interacts with PABP1 directly (shown) and indirectly (not shown) and disrupts its interaction with eIF4G (broken arrow), an interaction which promotes the closed-loop conformation and may also enhance PABP1 poly(A) binding (not depicted). This results in repressed translation (blunted arrow), facilitating deadenylation. TNRC6 also directly recruits deadenylases and may bring them into close proximity to the poly(A) tail via its interaction with PABP1, to promote mRNA deadenylation (arrows). Deadenylase (A and C, see key) denotes events in which a specific deadenylase(s) has not been implicated.
mRNAs [51], disrupts the PABP–AUF1 interaction [51]. However, ARE binding by AUF1 inhibits its interaction with PABP1 in vitro [52], suggesting that this interaction does not occur on ARE-containing mRNAs that are subject to AUF1-mediated deadenylation. Since this observation is inconsistent with an ARE-specific role for this interaction, it raises questions regarding the role of PABP1 in AUF1-mediated destabilization. Moreover, AUF1 can also bind poly(A) tails and other components of the closed-loop complex directly [52,53], emphasizing further that the role of PABP1 in AUF1-mediated mRNA turnover remains to be fully characterized.

**PABP1 and miRNAs (microRNAs)**

miRNAs play a crucial role in post-transcriptional regulation, and their dysregulation is implicated in the aetiology of a wide spectrum of human diseases (reviewed in [54]). miRNA-mediated silencing utilizes a host of protein factors, including the RISC (RNA-induced silencing complex) (reviewed extensively in [55,56]) and PABP1 and is generally considered to involve translational repression and deadenylation. To date, the order of these events and the extent to which they promote decay remain controversial.

PABP1 interacts with TNRC6 [56] (Figure 4D), the RISC component parologue of GW182, of which there are isoforms A–C in mammals. TNRC6 interacts with PABC via a non-canonical PAM2 motif and indirectly with the RRM region that binds eIF4G, via an unknown partner [56–58]. The TNRC6–PABP1 interaction is required for effective miRNA-mediated silencing [58,59], but, intriguingly, TNRC6 recruits both CCR4–CAF1 and PAN2–PAN3 deadenylase complexes directly, and PABP1–independently, to effect deadenylation [60–62]. Thus TNRC6 may disrupt the PABP1–eIF4G interaction, which is important for the closed-loop conformation and may also strengthen PABP1 poly(A) binding, to repress translation and enhance deadenylation. Alternatively, TNRC6 may utilize its interaction with PABP1 to bring the poly(A) tail into proximity of its associated deadenylases [63]. These models are not mutually exclusive.

**How do other PABP family members contribute to mRNA turnover?**

PABP1 is the only one of five mammalian PABPs for which there is extensive functional information available. However, the *Xenopus laevis* homologue of PABP4 has been shown to stimulate translation in vitro [64], and, consistent with a similar role, mammalian PABP4 (also known as PABPC4 or iPABP) binds poly(A) [43] and is found on polysomes [65], suggesting that PABP4 may share roles with PABP1 in protecting mRNAs from deadenylation. Moreover, mammalian PABP4 is known to exhibit an increased affinity for adenine/uridine-rich RNA in vitro relative to PABP1 [43], raising the possibility that it may bind AREs in vivo, although this remains to be established. ePABP (embryonic PABP) (also known as ePAB or PABPC1L) is the predominant PABP in oocytes and early embryos [66,67] and has mainly been studied in *X. laevis*, where it is required for both oocyte maturation [68] and early development [64]. *X. laevis* ePABP binds poly(A) [64,66] and has been shown to promote mRNA-specific cytoplasmic polyadenylation by protecting newly synthesized poly(A) tails in vitro and in vivo [68,69] and to prevent deadenylation of ARE-containing mRNAs in vitro [66]. It is also likely to inhibit default deadenylation via its ability to promote translation initiation through eIF4F interaction [67] and translation termination through interaction with eRF3 [70]. Recent studies in mice have shown that mammalian ePABP shares the ability to promote cytoplasmic polyadenylation and is required for oocyte maturation [71].

**Perspectives**

Although it is apparent that PABP1 has pleiotropic roles in mRNA turnover, it is also clear that there are currently more questions pertaining to those roles than answers. One reason for the current lack of clarity likely stems from the use of multiple experimental systems, each optimized to analyse specific steps in the mRNA translation/turnover pathway. Thus the development of an *in vitro* system that retains regulated coupled mRNA translation/turnover would be a boon for studies of post-transcriptional control, and PABPs in particular. Another reason may be an overreliance on a small number of reporter miRNAs (e.g. β-globin reporter), which are often used in cell types for which they may be inappropriate.

A major question pertaining to PABP1 function in default deadenylation relates to understanding the apparent fundamental contradiction between the abilities of poly(A)-bound PABP1 to both protect an mRNA from deadenylation and to recruit/enhance deadenylase activities. It is tempting to speculate that this may be controlled, at least in part, by competition between PAN2–PAN3, the TOB1–TOB2–CCR4–CAF1 complex and other PABC partners, which have differing affinities (e.g. eRF3<<PAN3<TOB1/2) [9], with all of these interactions potentially being in competition with PABP1–PABP1 co-operative interaction [12]. This raises the possibility that, during the lifetime of an mRNA, co-operativity, which also affects PABP1 poly(A) binding, could be modulated to alter overall or mRNA-specific deadenylation rates (e.g. by a trans-acting factor). Moreover, it is also possible that PABP1 poly(A) binding and/or these PABC interactions are modulated by PABP1 PTMs (post-translational modifications). PTMs have been identified throughout the functional domains of PABP1 and are predicted to alter PABC–PAM2 interaction specificity [72]. Therefore PTMs provide an additional mechanism by which the poly(A)-protective and deadenylation-promoting functions of PABP1 may be co-ordinated. Such putative regulatory events may also contribute to the poorly understood switch between the distinct phases of mRNA deadenylation.
Although even less well understood, mRNA-specific roles for PABP1 in mRNA turnover are fast emerging and supported by multiple findings, although such roles remain to be demonstrated in vivo. However, a better understanding of the role of PABP1 in global mRNA turnover may first be necessary to inform studies of its mRNA-specific functions. Thus whether PABP1 contributes to the regulation of specific mRNAs in multiple ways or whether a unifying mechanism exists remains an important question. A final important, and extremely challenging, question pertains to the contribution of PABP1-mediated regulation of both default deadenylation/mRNA stabilization and mRNA-specific decay to mammalian physiology.

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