

mRNA-specific regulation of translation by poly(A)-binding proteins

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Abstract

The regulation of translation has emerged as a major determinant of gene expression and is critical for both normal cellular function and the development of disease. Numerous studies have highlighted the diverse, and sometimes related, mechanisms which underlie the regulation of global translation rates and the translational control of specific mRNAs. In the present paper, we discuss the emerging roles of the basal translation factor PABP [poly(A)-binding protein] in mRNA-specific translational control in metazoa which suggest that PABP function is more complex than first recognized.

Introduction

Cytoplasmic PABPs [poly(A)-binding proteins] are conserved throughout eukaryotes and act as central determinants of mRNA translation and stability by binding to the poly(A) tail of mRNAs (reviewed in [1,2]). Perturbation of PABP function leads to a variety of phenotypes in invertebrates [3–5], including lethality, highlighting the importance of their function. In vertebrates, the biological consequences associated with loss or perturbation of PABP function remains to be determined, but the presence of multiple PABPs with a similar domain organization [PABP1, PABP4, ePABP (embryonic PABP) and the mammalian-specific tPABP (testis-specific PABP); Figure 1A] has led to the supposition that their functions may be redundant. However, to date, most work has focused on the prototypical family member, PABP1, with little information being available for the other PABPs.

PABP1 (also referred to as PABPC1) has four non-identical RRM (RNA-recognition motifs) that are not functionally equivalent and a C-terminal region that consists of a variable protein-rich linker region and the highly conserved PABC domain [6] (Figure 1A). Whereas the RRMs mediate both RNA and protein interactions, the C-terminal region interacts only with proteins, although its role in PABP1–PABP1 interactions enhances co-operative poly(A) binding [7] (Figure 1A). When bound to the poly(A) tail, PABP1 acts as a primary determinant of translation efficiency by facilitating initiation. Initiation (reviewed in detail in [8]) starts with the binding of the

eIF (eukaryotic initiation factor) 4F complex, composed of eIF4E, eIF4G and eIF4A, to the cap at the 5'-end of the mRNA (Figure 1B; for an animation of initiation, see <http://www.biochemj.org/bj/426/0001/bj4260001add.htm> [9]). This interaction is primarily mediated by the cap-binding factor eIF4E. The cap complex facilitates the removal of secondary structure within the 5'-UTR (untranslated region), by the helicase action of eIF4A, and recruitment of the small ribosomal subunit and associated factors (eIF2–GTP–Met, eIF3, eIF1, eIF1A and eIF5), through the interaction between eIF4G and eIF3. The small ribosomal subunit subsequently scans the 5'-UTR until initiation codon recognition triggers release of initiation factors and large ribosomal subunit joining. The effects of PABP1 on metazoan initiation appear to be pleiotropic, stimulating both large and small ribosomal subunit recruitment, although our knowledge of its function is far from complete (reviewed in detail in [1,2]). Several translation initiation factors, including eIF4G, PAIP (PABP-interacting protein) 1 and eIF4B [1,2,10], have been suggested to contribute to the action of PABP (Figure 1). Of these, most attention has focused on the PABP1–eIF4G interaction which effectively circularizes mRNAs in an 'end-to-end' complex (Figure 1B) due to the simultaneous interaction of eIF4G with PABP1 and eIF4E. This complex stabilizes the association of eIF4F with the cap [11–13], resulting in enhanced small subunit joining. End-to-end complexes are thought to be further stabilized by the PABP1–PAIP1 interaction [14]. The role of the interaction of PABP1 with eIF4B, a factor that stimulates the helicase action of eIF4A, remains to be addressed. Interestingly, an interaction with the translation termination factor, eRF3 (eukaryotic release factor 3), may also contribute to initiation by increasing the pool of ribosomal subunits available for reloading [15].

Whereas the effects of poly(A) tail-bound PABP1 on initiation are essentially ubiquitous, other features of mRNAs, such as the presence of secondary structure in the 5'-UTR, can affect the extent of PABP1-dependence of individual

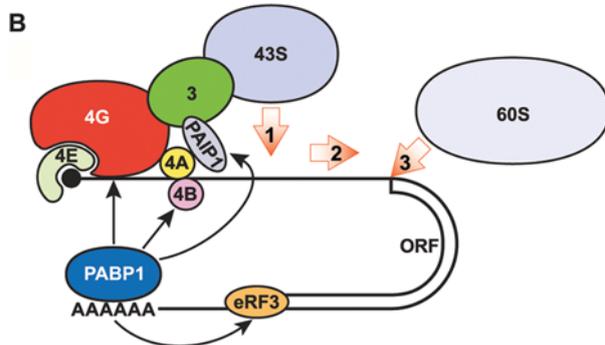
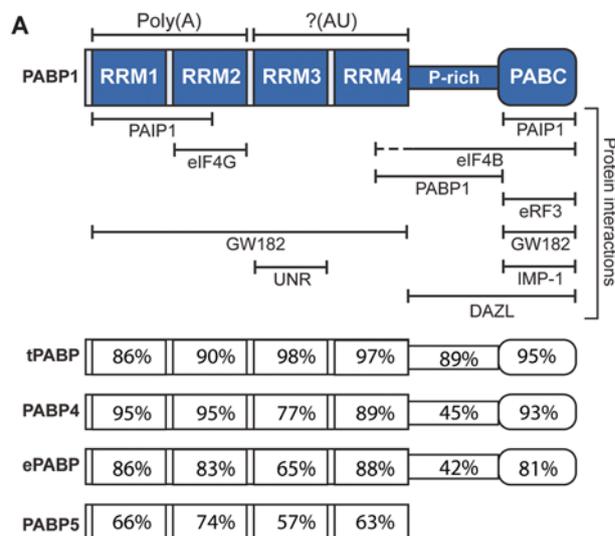
Key words: DAZ, microRNA (miRNA), mRNA-specific translational control, poly(A)-binding protein (PABP), sex-lethal, Y-box 1 (YB-1).

Abbreviations used: ARS, autoregulatory site; CAF1, CCR4-associated factor 1; DAZ, deleted in azoospermia; DAZL, DAZ-like; DV, dengue virus; eIF, eukaryotic initiation factor; eRF3, eukaryotic release factor 3; IMP-1, insulin-like growth factor II mRNA-binding protein-1; miRNA, microRNA; *msl-2*, male-specific lethal 2; PABP, poly(A)-binding protein; ePABP, embryonic PABP; PAIP, PABP-interacting protein; RRM, RNA-recognition motif; SL, stem-loop; Sxl, sex-lethal; Unr, upstream of N-ras; UTR, untranslated region; YB-1, Y-box 1.

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Figure 1 | PABPs and the cap-dependent pathway

(A) The domain structure of the human PABP family is depicted identifying the regions of PABP1 which interact with the protein partners discussed in the text. Although DAZL is depicted, all DAZ family members interact with the C-terminal region. The binding site for eIF4B is not clearly defined, but requires the C-terminus. RRM1 and 2 mediate the majority of poly(A)-binding, but the RNA-binding specificity of RRM3 and 4 remains unclear, although affinity towards AU-rich sequences has been shown. The percentage identity of each domain in other family members to PABP1 is given. PABP4 and ePABP may be represented by multiple transcripts and predicted transcripts PABPC4-002 and PABPC1L-201 were utilized. In most cases, PABP1 partner proteins have not been demonstrated to interact with the other family members. (B) Simplified overview of cap-dependent translation initiation. (1) The small ribosomal subunit and associated eIFs (43S) are recruited to the 5' end of the mRNA by the action of the eIF4F complex (see the text for details). (2) The 43S complex then scans the 5'-UTR to locate an initiation codon. (3) Following initiation codon recognition, initiation factor release and joining of the large (60S) ribosomal subunit leads to formation of a translationally competent 80S ribosome. PABP1 interactions with the scaffold protein eIF4G (4G), the eIF4G-like protein PAIP1 and the eIF4A (4A) co-factor eIF4B (4B) are thought to be important for PABP-mediated stimulation of initiation. eRF3-PABP interactions may increase the pool of available ribosomal subunits. ORF, open reading frame. The 5'-cap is depicted as a solid black spot and the poly(A) tail as AAAAAA. For clarity, not all eIFs or interactions are depicted.



mRNAs [16]. In addition, PABP1 has mRNA-specific roles in translational regulation which are mediated by the presence of defined regulatory elements within these mRNAs. In the present paper, we discuss the diversity of these emerging PABP1-regulatory mechanisms.

Changes in poly(A) tail length regulate the translation of many mRNAs

mRNAs generally exit the nucleus with a poly(A) tail of defined length (approx. 250 adenosines), which is gradually shortened until mRNA turnover is initiated. However, dynamic changes in poly(A) tail length can also regulate the translation of specific mRNAs. Such changes were originally characterized in germ cells and early embryos, where many maternal mRNAs are deadenylated as they emerge from the nucleus and then stored in a translationally silent, but stable, state until they are activated (reviewed in [17,18]). Activation of these mRNAs is often accompanied by an increase in poly(A) tail length which, in some well-studied cases, is demonstrated to be required for translational activation (reviewed in [17]). The newly synthesized poly(A) tails act as a platform to recruit PABPs [19], with each PABP covering 20–25 adenosines [1,2], thereby driving translational activation. Although the role of PABPs in activating these mRNAs is akin to their normal global role in promoting translation from the poly(A) tail, polyadenylation in the cytoplasm requires specific 3'-UTR elements [20,21], which were found to be present in approx. 30–45% of mRNAs analysed [20]. In addition to promoting the translation of these mRNAs, PABPs may also participate in the control of their poly(A) tail length by protecting the newly synthesized tails from deadenylation [22]. Interestingly, cytoplasmic polyadenylation has also been shown to occur in somatic cells such as neurons [23], indicating that the role of PABPs in this specialized form of regulation is likely to extend to other biological processes.

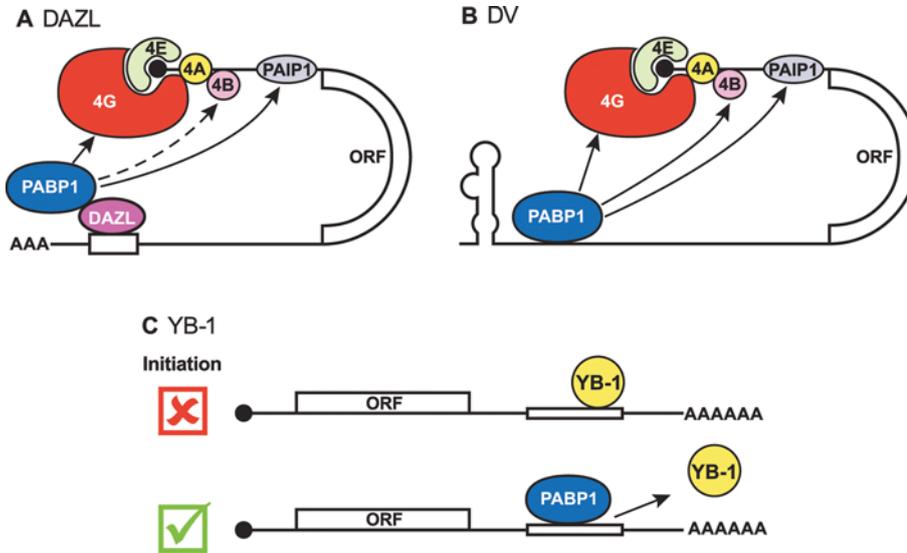
PABPs as poly(A)-tail-independent activators of mRNA-specific translation

The ability of PABPs to stimulate translation when artificially tethered to sites within the 3'-UTR of reporter mRNAs [19,24] suggested that PABPs may be able to promote translation when recruited by elements other than the poly(A) tail. Recent observations suggest that they fulfil this role in biological contexts where poly(A) tails are often short or even absent.

The DAZ (deleted in azoospermia) family of RNA-binding proteins activate the translation of a subset of mRNAs in germ cells by binding to 3'-UTR regulatory elements (reviewed in [25]) (Figure 2A). Both PABP1 and ePABP, the predominant PABP in oocytes, interact directly with DAZ family members in an RNA-independent manner [26]. Mapping of the domains that mediate the DAZ family translational activator function revealed that the PABP interaction was required for stimulation *in vivo* [26]. Location of the DAZ-binding site in the C-terminal region of PABPs

Figure 2 | Positive regulation of specific mRNAs by PABP1 independent of its poly(A)-tail-mediated functions

(A) Recruitment of PABPs to mRNAs via protein–protein interactions with DAZ family members (DAZ, BOULE and DAZL, which is depicted) can stimulate initiation independently of the poly(A) tail. The spatial arrangement of respective binding sites makes it likely that simultaneous PABP1 interactions with DAZL and eIF4G (4G) or PAIP1 can be maintained, but it is less clear whether eIF4B (4B) interaction can occur (dotted arrow). AAA depicts a short poly(A) tail. (B) PABP1 can stimulate translation of mRNAs by binding internal poly(A)-rich regions within the 3'-UTR, presumably utilizing the same initiation factor partners as PABP1 bound to the poly(A) tail. (C) *YB-1* translationally represses its own mRNA. At high concentrations, PABP1 binds to an overlapping site in the *YB-1* 3'-UTR, causing eviction of *YB-1* and relief of translational repression. PABP1 bound to the poly(A) tail of *YB-1* mRNA (AAAAAA) is not depicted for clarity. In (A–C), the spatial organization of the depicted eIFs is to facilitate the illustration of PABP1 interactions. ORF, open reading frame. The 5'-cap is depicted as a solid black spot.



suggests a model for their function in promoting initiation, as a simultaneous interaction with eIF4G and/or PAIP1 could occur allowing the formation of end-to-end complexes in a manner analogous to that of the poly(A) tail [26] (Figure 2A). In this regard, it is interesting that at least one verified *in vivo* target mRNA of DAZL (DAZ-like) is stored with a poly(A) tail of only approx. 20 nucleotides [27,28]. Furthermore, as DAZ family proteins are capable of activating the translation of unadenylated reporter mRNAs, recruitment of PABPs via protein–protein interactions is sufficient to mediate poly(A)-independent effects on initiation [26].

Although PABP1 is targeted during infection by a wide variety of viruses to achieve host cell shut-off (reviewed in [9]), a role in activating DV (dengue virus) translation has also been reported. DV has a positive-sense RNA genome with a capped 5'-UTR and a non-adenylated 3'-UTR. In the absence of a poly(A) tail, the 3'-UTR of DV appears to promote translation [29–31] with a 3'-SL (stem–loop) near the terminus of the 3'-UTR accounting for approx. 50% of the translational stimulation [30]. Viral factors do not appear to be required for this function [30,32] and, consistent with this, a number of cellular factors including PABP1 have been shown to bind the 3'-UTR [33–35]. Purified PABP1 binds to two apparently single-stranded regions containing runs of adenosines upstream of the 3'-SL (Figure 2B) [35].

The functionality of this interaction was tested in cell-free extracts using reporter mRNAs bearing the DV 5'- and 3'-UTRs, showing that their translation was sensitive to the presence of the PABP1 inhibitor PAIP2 [35], which interferes with PABP1–poly(A) and PABP1–eIF4G interactions [10]. Although the importance of PABP1, relative to other factors which bind the 3'-SL, in stimulating DV translation in infected cells remains to be determined, this observation suggests that the DV RNA may recruit PABP1 via an internal 3'-UTR-binding site to promote end-to-end complex formation (Figure 2B).

The role of PABPs in mRNA-specific translational repression

PABP1 has been shown to mediate translational repression of its own mRNA both *in vitro* and in cell lines, by binding to an approx. 60-nt element containing multiple short (six to eight) adenosine tracts within its 5'-UTR [36,37]. The affinity of PABP1 for these 5'-UTR sites appears to be lower than that for the poly(A) tail [38], such that these ARSs (autoregulatory sites) are only occupied when PABP1 levels are high. The ARS is conserved from yeast to humans, and PABP1 autoregulation is likely to be responsible for observations that overexpression of PABP1 is frequently

unsuccessful *in vivo* (e.g. [3]). PABP1 autoregulates its own translation as part of a heterotrimeric ARC (autoregulatory complex) with IMP-1 (insulin-like growth factor II mRNA-binding protein-1) and Unr (upstream of N-ras), which are suggested to increase the affinity of PABP1 for the regulatory element [38]. Since the ARS sequences are located in a cap-distal position within the 5'-UTR, this increase in RNA-binding affinity may be necessary to allow the autoregulatory complex to effectively block the scanning of ribosomal subunits through the 5'-UTR [39] (Figure 3A). Intriguingly, mammalian PABP4 appears to have an element resembling the ARS, raising the possibility that these two PABPs may be subject to co-ordinate regulation by PABP1. It remains to be established whether other PABPs also interact with Unr or IMP-1 to mediate regulation of PABP1 levels in cells where multiple PABPs are present.

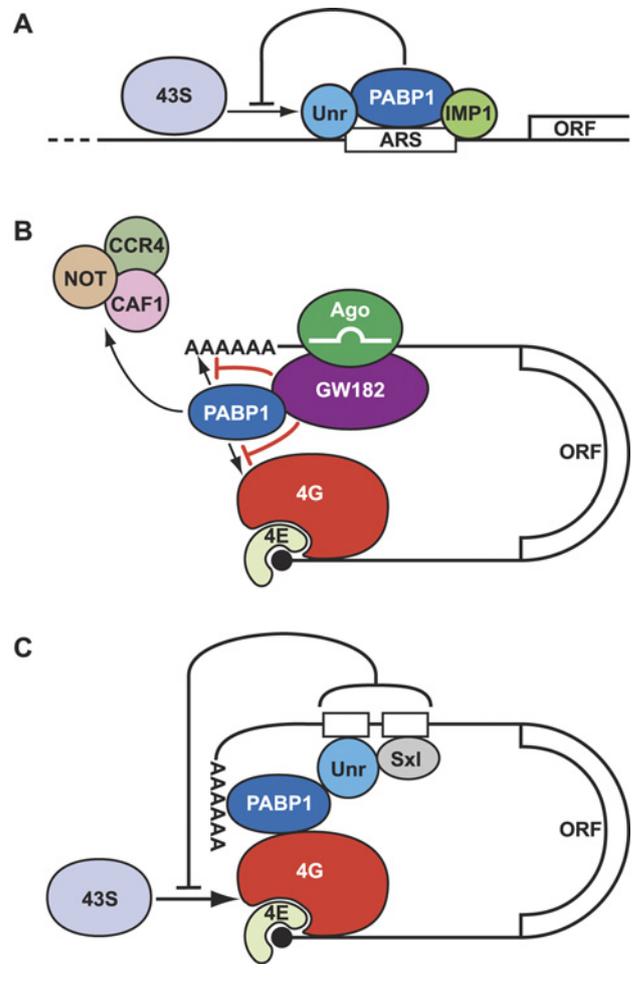
Recently, a novel activity of PABP1 in miRNA (microRNA)-mediated silencing has been shown to occur through its association with the miRISC (miRNA-induced silencing complex) (Figure 3B). PABP1 is recruited by miRISC component GW182 [40,41], which also interacts with Argonaute, and is considered to be the effector of miRNA-mediated silencing. The GW182-binding site has been reported to be in the RRM region of *Drosophila* PABP [40], but in the C-terminal region of mammalian PABP1 [41] (Figure 1A). This may reflect an ability of GW182 to interact with multiple regions of PABP, reminiscent of other PABP-interacting proteins, such as PAIP1 and PAIP2 [10]. Based in large part on the position of the GW182 interaction site, two different models for PABP action in miRNA-mediated silencing have been proposed. The first posits that GW182 binding to PABP causes translational repression as a result of reduced eIF4G interactions with the RRM [40]. The second favours a model in which deadenylation is promoted either by a PAIP2-like effect of GW182 in reducing PABP/poly(A) binding or by enhancing the activity of the CAF1 (CCR4-associated factor 1)-CCR4-Not1 deadenylase complex [41]. However, these activities may not be mutually exclusive, with both modes of regulation probably contributing to silencing (Figure 3B).

Other roles of PABP in mRNA-specific repression

PABP1 appears to be present in complexes with mRNA-specific RNA-binding proteins that mediate translational repression. In *Drosophila*, Sxl (sex-lethal) regulates the splicing and translation of mRNAs such as *msl-2* (male-specific lethal 2) which is involved in dosage compensation [42]. Sxl binds both the 3'-UTR and 5'-UTR of this mRNA and analysis of initiation intermediates showed that these interactions block both small ribosomal subunit joining and scanning respectively, ensuring effective repression of *msl-2* [43]. 3'-UTR-mediated repression of small ribosomal subunit joining, but not the scanning block, also requires Unr which interacts with both Sxl and PABP1 [44,45] (Figure 3C). This repressor complex does not appear to disrupt the PABP1-

Figure 3 | PABP1 function in the negative regulation of specific mRNAs

(A) PABP1 binds to the 5'-UTR of its own mRNA as part of an autoregulatory complex with Unr and IMP-1. Located distal to the cap, the complex apparently inhibits translation by blocking scanning of the 43S complex. (B) Argonaute (Ago) bound to miRNA (white line) interacts with GW182. PABP1 acts as a co-activator of the miRNA silencing complex. GW182 is thought to compete with eIF4G and/or poly(A) for PABP1 binding (red lines). PABP1 is also thought to be important for the recruitment of the CAF1-CCR4-Not1 deadenylase complex. (C) Translational repression of *msh-2* mRNA by Sxl bound at the 3'-UTR is dependent on Unr and PABP1. Repression affects 43S complex recruitment by an unknown mechanism that does not affect the PABP1-eIF4G (4G) interaction. ORF, open reading frame. The 5'-cap is depicted as a solid black spot and the poly(A) tail as AAAAAA.



eIF4G interaction or the ability of eIF4G to bind the 5'-UTR [46]. Therefore it is unclear whether another aspect of eIF4G function, e.g. its ability to interact with eIF3, or another PABP1 interaction, e.g. PAIP1 or eRF3, is affected. However, it is possible that PABP1 may act as a cofactor of Sxl/Unr rather than a target of repression. Thus PABP1- and Unr-containing complexes mediate mRNA-specific repression from both the 5'-UTR and the 3'-UTR, albeit through

different mechanisms and partners, raising the possibility that additional regulatory events may utilize this interaction.

The general RNA-binding protein YB-1 (Y-box 1) has been suggested to render translation more PABP1-dependent, at least *in vitro*, by inhibiting the binding of eIF4G to the RNA adjacent to the cap [47,48], thereby destabilizing the eIF4F-cap interaction [49]. Interestingly, PABP1 also appears to participate in the regulation of YB-1 protein levels. Binding of YB-1 to sequences in the 3'-UTR of its own mRNA inhibits an early step in initiation, resulting in autoregulation [50,51]. PABP1 can bind an overlapping site in the *YB-1* 3'-UTR consisting of multiple short (3–4 nt) adenosine stretches, displacing YB-1 protein and relieving repression of *YB-1* translation (Figure 2C) [51]. It is suggested that this feedback mechanism contributes to the control of overall cellular translation rates, as the antagonistic action of YB-1 and PABP1 will be affected by their respective levels.

Perspectives

To date, relatively few examples of mRNA-specific regulation by PABP1 have been identified. The mechanisms by which regulation is achieved remain, for the most part, poorly defined and their delineation will require a complete understanding of how PABP1 stimulates initiation. However, the diversity of mechanisms identified raises the possibility that mRNA-specific regulation by PABP1 represents a widespread strategy of translational control. The interaction of PABP1 with a growing number of protein partners, which mediate its roles in global and mRNA-specific translation as well as mRNA turnover, raises several questions: how many of these interactions can PABP1 participate in at any given time, how dynamic are these interactions and how is its participation in different regulatory complexes regulated? Moreover, in most cases, it is unclear to what extent other PABPs share the protein interactions described in the present paper. Nonetheless, it is tempting to speculate that mRNA-specific roles may, in some cases, be mediated through PABP-specific interactions, suggesting that the multiple PABPs in vertebrates may have partially distinct functions. Unravelling the growing complexity of post-transcriptional control by the PABP family promises to be both challenging and rewarding.

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