Regulation of Poly(A)-binding Protein through PABP-interacting Proteins

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Translation initiation requires the participation of eukaryotic translation initiation factors (eIFs). The poly(A)-binding protein (PABP) is thought to stimulate translation by promoting mRNA circularization through simultaneous interactions with eIF4G and the 3′ poly(A) tail. PABP activity is regulated by the PABP-interacting proteins (Paips), a family of proteins consisting of Paip1, a translational stimulator, and Paip2A and Paip2B, two translational inhibitors. Paip2A controls PABP homeostasis via ubiquitination. When the cellular concentration of PABP is reduced, Paip2A becomes ubiquitinated and degraded, resulting in the relief of PABP repression. Paip1 interacts with eIF4A and eIF3, which promotes translation. The regulation of PABP activity by Paips represents the first known mechanism for controlling PABP, adding a new layer to the existing knowledge of PABP function.

Translational control is an important mechanism by which cells govern gene expression, providing a rapid response to growth and proliferation stimuli, stress, and nutrient availability. In systems with little or no transcriptional control (e.g., reticulocytes and oocytes), translation is the predominant mode of regulation of gene expression (Mathews et al. 2007). Initiation, the rate-limiting step of translation, is the main target of translational control. Translation initiation entails the recruitment of the ribosome to the mRNA, traversing of the 5′-untranslated region (5′UTR), and recognition of the initiation codon (Pestova et al. 2007). These processes are dependent on the eukaryotic translation initiation factors (eIFs). The 5′ cap structure (m7GpppN, where m is a methyl group and N is any nucleotide), which is present at the 5′ end of all nuclear-transcribed eukaryotic mRNAs, is the first mRNA structure recognized by eIFs. It is bound by the eIF4F complex, consisting of eIF4E, eIF4A, and eIF4G. eIF4E binds directly to the mRNA 5′ cap; eIF4A is an RNA helicase; and eIF4G serves as a modular scaffolding protein that binds, among other proteins, eIF4E, eIF4A, eIF3, poly(A)-binding protein (PABP), and Mnk, a serine/threonine kinase which phosphorylates eIF4E (Gingras et al. 1999; Pyronnet et al. 1999). The eIF3 complex, which contains up to 13 distinct subunits (Pestova et al. 2007), interacts with the 40S ribosomal subunit, thus serving as a link between the mRNA–eIF4F complex and the ribosome.

All eukaryotic cellular mRNAs, except those of histones, possess a poly(A) tail in their 3′UTR. Early in vitro experiments suggested a role for the poly(A) tail in translation initiation. The poly(A) tail confers a translational advantage to the mRNA in reticulocyte lysate, as addition of poly(A) RNA inhibited the translation of polyadenylated (poly(A)$^+$) mRNA (Doel and Carey 1976; Jacobson and Favreau 1983; Grossi de Sa et al. 1988). Later studies demonstrated translational stimulation by the poly(A) tail, which could not be attributed to its mRNA stabilizing effect (Munroe and Jacobson 1990a). Consistent with the importance of the poly(A) tail in translation, a positive correlation was shown between the polyadenylation state of an mRNA and translational activation during development. In many systems (e.g., *Xenopus laevis*, *Drosophila melanogaster*, mouse), the translation of a large number of maternal mRNAs is dependent on the poly(A) tail (Wickens et al. 2000).

PABP FUNCTION IN TRANSLATION

In general, PABP stimulates translation of mRNAs harboring a poly(A) tail (Sachs 2000; Kahvejian et al. 2001). PABP is an essential protein: In yeast, deletion of the Pab1 gene is lethal (Sachs et al. 1987). PABP is an abundant protein (Görlach et al. 1994) that contains, in the amino-terminal region, four phylogenetically conserved RNA recognition motifs (RRMs) (Adam et al. 1986; Sachs et al. 1987); PABP fragments containing RRMs 1 + 2 bind poly(A) RNA with an affinity similar to that of full-length PABP, whereas RRMs 3 + 4 exhibit a tenfold lower affinity for poly(A) (Burd et al. 1991; Kuhn and Pieler 1996; Deo et al. 1999).

PABP that is tethered to the 3′ end of a nonadenylated mRNA stimulates translation in *X. laevis* oocytes independently of its poly(A)-binding activity (Gray et al. 2000). A fragment containing RRMs 1 + 2 of PABP, which binds eIF4G (Imataka et al. 1998), was more effective than full-length PABP in stimulating translation (Gray et al. 2000). Fragments containing RRMs 3 + 4 or the proline-rich carboxyl terminus of PABP, termed the PABC domain, also augmented translation (Gray et al. 2000). Exogenous PABP stimulated the translation of capped poly(A)$^+$ mRNAs and, to a lesser extent, poly(A)$^-$ mRNA in yeast extracts (Otero et al. 1999) and mammalian translation systems (Kahvejian et al. 2005). These findings suggest that the mechanisms by which PABP stimulates translation are complex and may involve redundant or alternative pathways.

The PABC domain comprises a docking site for a wide range of proteins (Albrecht and Lengauer 2004). The best-characterized interactions occur with the PABP-interacting proteins (Paips), which bind to PABP and regulate its activity (Craig et al. 1998; Khaleghpour et al. 2001a; Roy et al. 2002). Other interacting proteins include the eukaryotic ribosome recycling factor (eRF3), which functions in mRNA translation termination and ribosome recycling through its interaction with PABP (Uchida et al. 2002a; Hosoda et al. 2003); deleted in azoospermia-like (DAZL) proteins, which during germ-cell development, activate silent mRNAs through binding to the 3′UTR and recruitment of PABP (Collier et al. 2005); Tob, a member of a family of proteins with antiproliferative functions (Okochi et al. 2005); and ataxin-2 homologs, which have been implicated in such cellular processes as signal transduction, embryonic development, and RNA splicing and degradation (Mangus et al. 1998; He and Parker 2000; Kiehl et al. 2000).

TRANSLATIONAL SYNERGY BETWEEN THE 5′ CAP AND THE POLY(A) TAIL

The closed-loop model for mRNA circularization was proposed more than two decades ago (Jacobson and Favreau 1983; Palatnik et al. 1984) and subsequently reiterated (Sachs and Davis 1989; Munroe and Jacobson 1990a,b; Jacobson 1996). The synergistic enhancement of translation of mRNAs that possess both a cap and a poly(A) tail further suggested a physical interaction between the two extremities of the mRNA (Gallie 1991). Electroporation of mRNAs into cells demonstrated that the translation of mRNAs was synergistically augmented by the cap and the poly(A) tail (Gallie 1991). Capped and poly(A)$^+$ mRNAs exhibited similar synergistic properties in yeast (Iizuka et al. 1994) and mammalian translation extracts (Khaleghpour et al. 2001a; Svitkin and Sonenberg 2004), indicating that the poly(A) tail plays an important role in stimulating cap-dependent translation initiation.

Proof of a direct interaction between the 5′ and 3′ ends of the mRNA was provided by the discovery of the interaction between eIF4G and PABP in yeast (Tarun and Sachs 1996) and plant systems (Le et al. 1997). In humans, a stretch of 29 amino acids in the amino terminus of eIF4G interacts with RRM 1 + 2 of PABP (Imataka et al. 1998), as in yeast PABP. However, despite its high homology with yeast PABP, human PABP does not interact with yeast eIF4G (Otero et al. 1999). The eIF4G–PABP interaction plays a critical role in *X. laevis* oocytes, since expression of an eIF4G mutant that did not bind PABP repressed translation of poly(A)$^+$ mRNAs and inhibited progesterone-induced oocyte maturation (Wakiyama et al. 2000).

MECHANISMS OF PABP-MEDIATED TRANSLATION STIMULATION

Several models have been proposed to explain the mechanism by which PABP promotes translation. First, PABP–eIF4G binding could mediate mRNA circularization, promoting the recycling of terminating ribosomes by bridging the two ends of an mRNA, a model reinforced by the interaction between PABP and the translation termination factor eRF3 (Hoshino et al. 1999; Uchida et al. 2002a). A second model suggests that PABP stimulates 60S ribosomal subunit joining. In early experiments, mutations in a 60S ribosomal protein or in a helicase required for 60S ribosomal subunit biosynthesis partially rescued the phenotype of PABP deletion in yeast (Sachs and Davis 1989, 1990). These genetic data are consistent with biochemical experiments, in which the absence of the poly(A) tail led to a decrease in 60S ribosomal subunit joining (Munroe and Jacobson 1990a). However, other experiments support an alternative role of PABP in translation initiation, in stimulating recruitment of the 40S ribosomal subunit to the mRNA. In extracts immunodepleted of PABP, 40S ribosomal subunit recruitment was inhibited (Tarun and Sachs 1995). Consistent with these findings, in an in vitro translation system, PABP functioned as an initiation factor and stimulated both 40S initiation complex formation and 60S subunit joining (Kahvejian et al. 2005). PABP also stimulated the interaction of eIF4E with the cap structure as determined by cross-linking experiments (Kahvejian et al. 2005).

REGULATION OF PABP ACTIVITY: PABP-INTERACTING PROTEINS

In the course of searching for novel PABP-binding proteins, two novel protein partners of PABP, termed PABP-interacting proteins (Paips) were discovered: Paip1 (Craig et al. 1998) and Paip2 (Khaleghpour et al. 2001b). More recently, a homolog of Paip2 was cloned (Berlanga et al. 2006); thus, the original protein was named Paip2A and the second Paip2B.

Paip1, Paip2A, and Paip2B bind to PABP using two distinct PABP-binding motifs (PAMs; Fig. 1). PAM1 is an acidic region of approximately 25 amino acids that binds to the RRM2 in the amino terminus of PABP, whereas PAM2 is a well-defined and conserved region of approximately 15 amino acids that binds to the carboxy-terminal PABC domain of PABP (Khaleghpour et al. 2001b; Kozlov et al. 2001; Roy et al. 2002). PAM2 motifs, as well as PABC domains, have since been iden-

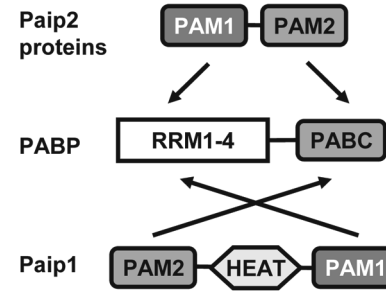

Figure 1. Structural organization of PABP interacting partners. Interactions between PABP, Paip1, and Paip2 proteins. (PAM) PABP-interacting motif; (RRM) RNA recognition motif; (PABC) PABP carboxy-terminal domain; (HEAT) heat domain (*H*untington, *e*longation factor 3, PR65/*A*, *T*OR).

tified in many different proteins of varying functions (see above), suggesting that PAM2 and PABC may play roles in protein–protein interactions in a wide range of cellular processes.

Paip1, a 75-kD protein of 479 amino acids, binds to PABP in vitro and in vivo and acts as a translational enhancer. Overexpression of Paip1 in COS-7 cells stimulated translation of a luciferase mRNA reporter (Craig et al. 1998). Deletion of the carboxyl terminus of Paip1 abrogated its ability to enhance translation. These data indicate that the PAM1 motif in Paip1 is essential for its activity (Craig et al. 1998). Amino acid sequence analysis of Paip1 revealed 25% identity and 39% similarity with the middle domain of eIF4G (Craig et al. 1998) in amino acids 619–1081 according to the new numbering system (Byrd et al. 2005). This region in eIF4G contains binding sites for eIF4A and eIF3 (Imataka and Sonenberg 1997; Morino et al. 2000). Consistent with this homology, eIF4A could be co-immunoprecipitated with Paip1 from HeLa extracts (Craig et al. 1998) and Paip1 also interacts with eIF3 (M. Derry and Y. Martineau, unpubl.) Thus, the simultaneous interactions between PABP, Paip1, eIF3, and eIF4A should facilitate the bridging of the 5′ and 3′ ends of mRNA (Fig. 2A). The existence of a complementary mode of mRNA circularization supports the importance of the circular mRNA conformation.

Paip2A, a 25-kD protein of 127 amino acids, and its recently discovered homolog Paip2B, a 25-kD protein of 123 amino acids, are antagonists of Paip1, as they inhibit the translation of poly(A)$^+$ mRNAs (Fig. 2B). Both Paip2A and Paip2B inhibit in vitro translation of a capped poly(A)$^+$ luciferase reporter mRNA in cell-free extracts (Khaleghpour et al. 2001a; Berlanga et al. 2006). In addition, overexpression of Paip2A or Paip2B in HeLa cells inhibited translation of a reporter mRNA (Khaleghpour et al. 2001a; Berlanga et al. 2006). Paip2 proteins inhibit the formation of 80S ribosomal complexes by competing with Paip1 for PABP binding, and by reducing the PABP–poly(A) interaction (Khaleghpour et al. 2001b). Paip2A further reduces translation by competing for PABP binding with eIF4G (Karim et al. 2006). Paip2 proteins therefore negate Paip1 activity by reducing mRNA circularization (Fig. 2B). The PAM1 motif confers translational inhibitory activity on Paip2 proteins (Karim et al. 2006). The *D. melanogaster* homolog dPaip2 was shown to interact with dPABP, reduce dPABP binding to poly(A), and inhibit translation in vitro. Ectopic overexpression of dPaip2 in wings and wing discs resulted in a size-reduction phenotype, due to decreased cell number, whereas overexpression of dPaip2 in postreplicative tissues reduced ommatidia size in eyes and cell size in the larval fat body (Roy et al. 2004). These data demonstrate a physiological role for Paip2 proteins in regulating cell growth and proliferation.

Although no functional differences have been observed between Paip2A and Paip2B in vitro or in vivo, Paip2A and Paip2B differ in their tissue distribution in mice at both the mRNA and protein levels (Berlanga et al. 2006). These data indicate that they may function in a tissue-specific manner or may respond to different stimuli. Three Paip2B mRNAs of different lengths were identified: one of approximately 6.5 kb, corresponding to the size of the cloned cDNA, and two other species of 1.5 kb and 0.6 kb. The longest mRNA is preferentially expressed in the brain, whereas the shortest is more abundant in liver and testis (Berlanga et al. 2006). The difference between the mRNAs is confined to the 3′UTR, possibly suggesting that the longer mRNAs are controlled differently by microRNAs or *trans*-acting factors. At the protein level, both Paip2A and Paip2B are highly expressed in testis and liver (Berlanga et al. 2006). In addition, Paip2A is expressed in the brain, whereas Paip2B is mainly expressed in the pancreas (Berlanga et al. 2006), which may suggest roles in brain function and glucose homeostasis, respectively. Another difference between Paip2A and Paip2B is their level of ubiquitination, with Paip2A being more ubiquitinated (Berlanga et al. 2006). Paip2A and Paip2B diverged early during their evolution, since mammalian Paip2B is more similar to Paip2 proteins from frog, zebra fish, and salmon than to mammalian Paip2A (Berlanga et al. 2006). Both forms modulate PABP translational activity, but other distinct functions for these proteins may yet be identified. It is therefore possible that Paip2A and Paip2B diverged during evolution to accomplish different functions.

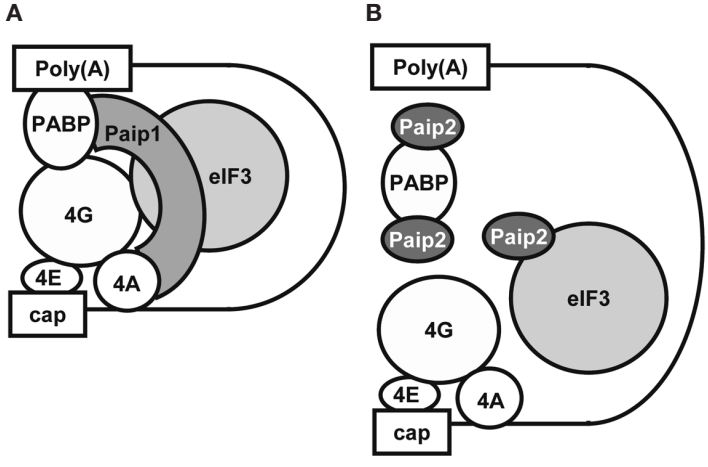

Figure 2. Model of PABP, Paip1, and Paip2 function. (*A*) Paip1 stabilizes the circularization of the mRNA by interfacing with PABP and eIF3. (*B*) Paip2 inhibits translation by reducing PABP binding to Poly(A) mRNA, Paip1, and eIF4G.

OTHER PAIP FUNCTIONS

In addition to translational regulation, evidence supporting a role for Paips in stabilization of specific mRNAs continues to accumulate. Several reports suggest a role for translation in mRNA decay. Certain nucleotide sequence elements that dictate rapid mRNA decay are located within protein-coding regions and are dependent on translation (Shyu et al. 1989; Wisdom and Lee 1991). Using the *c-fos* mRNA as a model system, a role for translation in RNA turnover has been demonstrated (Schiavi et al. 1994). Two destabilizing regions within the c-fos protein-coding region, termed protein-coding region determinants of instability (CRD), have been identified (Chen et al. 1992; Schiavi et al. 1994). Paip1 and PABP are subunits of a protein complex associated with the major CRD (mCRD) of c-fos, along with Unr, a purine-rich RNA-binding protein, hnRNP D; an AU-rich element binding protein; and NSAP1, an hnRNP R-like protein (Grosset et al. 2000). The complex stabilizes mCRD-containing mRNAs by impeding deadenylation. A bridging complex was proposed to exist between the poly(A) tail and the mCRD, which would be disrupted by ribosome transit, leading to RNA deadenylation and subsequent decay. On the basis of this report, Paip1 may be part of a decay protection complex that couples translation and mRNA decay.

Paip2A has been found in association with the 3′UTR of mRNAs known to be regulated at the level of mRNA stability. Paip2A associates with the 3′UTR of the glucose transporter GLUT5 mRNA as part of a large protein complex and is essential for the formation of this complex (Gouyon et al. 2003). Paip2A also interacts with the 3′UTR of the vascular endothelial growth factor (VEGF) mRNA. Overexpression of Paip2A led to increased stability of mRNA and increased secretion of VEGF, whereas small inhibitory RNA (siRNA)-mediated silencing of Paip2A led to decay of VEGF mRNA (Onesto et al. 2004). Surprisingly, Paip2A interacts with the VEGF mRNA in the absence of PABP (Gouyon et al. 2003) or any other proteins (Onesto et al. 2004), although Paip2A contains no known RNA-binding motif. It was suggested that in the case of VEGF mRNA, Paip2A might bind to an AU-rich region in the 3′UTR. AU-response elements (AREs) are present in the 3′UTR of many labile mRNAs and mediate their rapid degradation (Chen and Shyu 1995). Thus, Paip2A, and potentially the other Paips, may regulate mRNA stability independently of their ability to interact with and regulate PABP.

REGULATION OF PAIPS

Paips modulate PABP activity, but little data exist detailing how Paips are regulated, or under what circumstances. Paips are subject to ubiquitin-mediated degradation. Both Paip2A and Paip2B are ubiquitinated upon transfection into cells; Paip2A is modified to a greater extent than Paip2B, and thus is more rapidly degraded (Berlanga et al. 2006). The sequence in PABC that interacts with the PAM2 motif in the Paips is also present in the carboxyl terminus of EDD (Callaghan et al. 1998; Oughtred et al. 2002), a member of the *H*omologous to *E*6-AP *C*arboxyl *T*erminus (HECT) domain family (Huibregtse et al. 1995). These proteins function as E3 ubiquitin–protein ligases mediating ubiquitin-dependent proteolysis of specific protein targets. Thus, Paip2A is ubiquitinated upon binding to EDD through its PAM2 motif (Yoshida et al. 2006). The binding affinity of Paip2A to the EDD PABC domain is significantly weaker than to that of PABP, perhaps due to the absence of the first α-helix in the PABC domain from EDD (Deo et al. 2001; Kozlov et al. 2001); therefore, under physiological conditions, the higher affinity of Paip2A for PABP protects Paip2A from EDD-dependent proteolysis. However, upon reduction in PABP levels, for example through silencing by siRNA, Paip2A becomes free to associate with EDD and is subsequently ubiquitinated and degraded by the proteasome. As Paip2A protein levels decrease, the relative amount of free PABP is augmented, restoring overall PABP activity (Yoshida et al. 2006). The ubiquitin-mediated degradation of Paip2A constitutes the first evidence that Paip2A is posttranslationally regulated, thereby providing a mechanism for coordinately controlling protein levels of PABP and Paip2A and, consequently, modulating PABP function and translation (Fig. 3). Although Paip1 also possesses a PAM2 motif (Roy et al. 2002) and binds to the PABC domain of EDD (Deo et al. 2001), it is not degraded upon silencing of PABP (Yoshida et al. 2006). It is possible that the PAM2 motif is not sufficient for degradation of Paip1 or that an additional unknown factor is required for specific ubiquitination of Paip1.

Another potential mechanism for regulation of Paips may occur through binding to as yet unknown ligands. eIF3 has recently been identified as a new ligand for Paip1

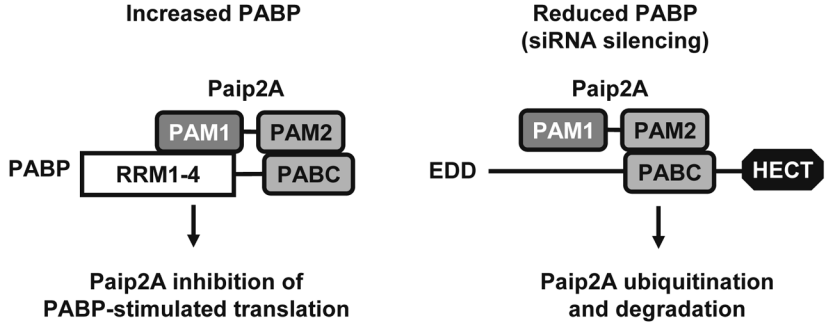

Figure 3. Model of ubiquitin-dependent degradation of Paip2A. PABP and EDD, two PABC-containing proteins, regulate the turnover of Paip2A.

(M. Derry and Y. Martineau, unpubl.). The interaction between eIF3 and Paip1 is direct and is independent of mRNA. Stimulation of cells with serum, insulin, or EGF resulted in increased eIF3–Paip1 binding, which could be reversed by wortmannin (a PI3K inhibitor), rapamycin (an mTOR inhibitor), or U0126 (a MEK1/2 inhibitor). In addition, Paip1-dependent enhancement of translation in vivo was abrogated upon co-transfection with siRNA to eIF3a. These data show that the eIF3–Paip1 interaction regulates Paip1 activity, positively correlates with increased translation in the cell, and is regulated by both the Akt-mTOR and the MEK signaling pathways.

The identification of eIF3 as a Paip1 ligand bolsters the previously proposed model (Craig et al. 1998) whereby the interaction of Paip1 with proteins, such as eIF4A, in the 5′UTR augments translation, perhaps by enhancing the activities of eIF4G or PABP or by promoting circularization. The observation that Paip1-dependent enhancement of translation is lost upon suppression of eIF3a suggests that the eIF3 may regulate Paip-dependent translational enhancement. Thus, Paip1 might be the proxy by which eIF3, and by extension the Akt/mTOR and MAPK pathways, control PABP activity.

CONCLUDING REMARKS

PABP was originally thought to enhance translation by binding to poly(A) mRNA, thus protecting it from degradation (Bernstein and Ross 1989). PABP is now known to enhance translation by direct mechanisms, including promotion of mRNA circularization through its interaction with eIF4G, ribosome recycling through its interaction with eRF3, eIF4F complex binding to the 5′ cap, and 60S subunit joining (Imataka et al. 1998; Uchida et al. 2002b; Kahvejian et al. 2005). The identification of Paips as PABP binding partners adds a new layer to the existing knowledge of PABP biochemistry, representing the first known mechanism for modulating PABP translational activity. However, how Paips act to stimulate translation, their modes of regulation, and their other potential functions are still not well understood. It is becoming clear that Paips possess activity outside the previously known scope of translation initiation regulation through PABP interactions: Paips are now known to bind to other proteins, participate in other translational activities, and even regulate other cellular processes such as mRNA stability and mRNA export. Paips exist only in metazoans (Kahvejian et al. 2001) and therefore act as regulators of translation in multicellular organisms. Further research will determine in more detail the physiological role and mechanisms of regulation of Paips in cellular processes including mRNA translation, stability, and export.

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