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Poly(A) Binding Proteins—Are they all created equal?

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Abstract

The PABP family of proteins were originally thought of as a simple shield for the mRNA poly(A) tail. Years of research have shown that PABPs interact not only with the poly(A) tail, but also with specific sequences in the mRNA, having a general and specific role on the metabolism of different mRNAs. The complexity of PABPs function is increased by the interactions of PABPs with factors involved in different cellular functions. PABPs participate in all the metabolic pathways of the mRNA: polyadenylation/deadenylation, mRNA export, mRNA surveillance, translation, mRNA degradation, microRNA-associated regulation, and regulation of expression during development. In this review, we update information on the roles of PABPs and emerging data on the specific interactions of PABP homologues. Specific functions of individual members of PABPC family in development and viral infection are beginning to be elucidated. However, the interactions are complex and recent evidence for exchange of nuclear and cytoplasmic forms of the proteins, as well as post-translational modifications, emphasize the possibilities for fine-tuning the PABP metabolic network.

Poly(A) Binding Proteins (PABPs), represent a major class of regulatory proteins that interact with the 3' poly(A) tail of mRNA. These highly conserved polypeptides are present only in eukaryotes; vertebrates express four PABPs in the cytoplasm and Arabidopsis expresses eight, in addition one nuclear PABP is expressed[1]. These cytoplasmic PABPs contain a conserved domain organization using RNA-recognition motifs, globular domains that are also present in other RNA binding proteins. Nuclear PABPs are structurally and functionally distinct from cytoplasmic PABPs and are involved in stimulating maturation of mRNA and export.

Originally it was thought that PABPs' role was to protect the mRNA from degradation by interacting with the poly (A) tail. However, a great number of studies have shown that PABPs can interact with other regulatory sequences in the RNA and protein factors, making the PABP family a key player in numerous pathways for gene expression. In protein synthesis, PABP binds the 3' untranslated region (UTR) of mRNAs and has multiple functions in initiation of translation as well as binding to the 5' UTR of PABP mRNA to possibly regulate its own expression[2–4]. PABP also functions in polyadenlyation, export, surveillance of transcripts, microRNA (miRNA) activity, control of mRNA stability and viral infection[1, 5, 6]. PABPs appear to lack catalytic activity of their own, but mediate the interactions of factors and RNAs that affect these processes. New roles are being discovered for this multi-functional class of proteins. However, little is known about the differences among the various PABPs. This review will highlight information, where available, on the differing functions of PABPs and new information on their roles in gene expression.

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Multiple PABPs

Typically, only one gene encoding PABP is found in single cell eukaryotes, whereas multiple genes are found in metazoans and plant species. In humans, cytoplasmic PABPs (PABPC1, PABPC3, and iPABP); nuclear PABP (PABPN1); and X-linked PABP (PABPC5) have been identified (reviewed in[1]). PABPC1 and PABPC3 are most closely related. This functional diversity is increased by extensive post-translational modifications. In plants, PABP phosphorylation improves its interaction with eIF4G, and enhances the rate of mRNA translation[7, 8]. Recently, it has been shown that human PABPC1 can also be methylated and acetylated, suggesting that these dynamic modifications might also affect PABP interaction with other factors[9].

In plants, the dicot *Arabidopsis thaliana* contains eight genes encoding PABPs[10]. Four classes of PABP proteins have been identified. Class I (PABP3 and PABP5) are limited to expression in reproductive tissue: Class II (PABP2, PABP4 and PABP8) are highly and broadly expressed; Class III (PABP6 and PABP7) are weakly expressed; and Class IV (PABP1) has low tissue-specific expression. It appears that the number of PABP genes and expression patterns are similar for the monocot *O. sativa*[10, 11].

Structure of PABPs

The structure of PABPC (cytoplasmic PABP) is highly conserved[1, 5, 7, 12]. PABPCs interact with poly(A) via RNA-recognition motifs (RRMs)[5, 13], requiring a minimum binding site of 12 adenosines and multiple PABPCs can bind to the same poly(A) binding tract[14, 15]. In vitro binding affinities are of the order 2–7 nM[14–17]. PABPC binds specifically to poly(A) having lower affinity for poly(U) and poly(G) with no detectable binding to poly(C)[14, 18–20]. PABPCs consist of four RRMs and a C-terminal region containing a peptide binding region referred to as PABC domain[18, 19]. The C-terminal domain consists of five alpha-helices[21]. PABPN1 contains a single RRM domain and an arginine rich C-terminal domain[1].

RRM, widely distributed among proteins, is the most common motif for RNA recognition and usually consists of 90–100 amino acids[18, 19, 22]. Solution NMR and x-ray crystallography studies have shown the RRM is a globular domain composed of four anti-parallel beta sheets backed by two alpha helices[13, 21]. The central two beta strands of each RRM include two highly conserved sequence motifs which form a trough-like surface for oligonucleotide binding. Specificity for RNA binding is primarily mediated by van der Waals contacts, hydrogen bonds, and stacking interactions of aromatic residues on the beta-sheet surface[13]. The four RRM domains are conserved in the sense that each equivalent RRM from PABPC is more similar from different organisms than the RRM domains within a single organism[20, 23], arguing for different functions of the four domains. For example, in human PABPC1, RRMs 1 and 2 bind eIF4G and PAIP1[24, 25] and provide a high affinity poly(A) binding site[14]. RRMs 3 and 4 bind poly(A) with reduced affinity, but also bind AU-rich RNA and mediate protein-protein interactions, e.g eukaryotic elongation factor 1α (eEF1α)[24, 25].

Plants appear to have differing PABPs. In *A. thaliana,* it has been reported that only two of the eight PABP genes encode proteins containing four RRM domains[10]. However, a pileup analysis suggests that probably all have four RRM domains. Similarly, of the three expressed genes for PABP in *N. tabacum,* only one is reported to have four RRMs[10]. The other two contain one or two RRMs[10]. The additional genes in plants are proposed to have evolved for specialized functions in translation or mRNA metabolism.

The carboxy-terminal domain of PABPC, somewhat confusingly designated PABC, is an approximately 75 amino acid domain that folds independently into four or five alpha-

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helices[21, 26]. The human PABC is composed of five helices, while the yeast protein has only four[21, 26]. Wheat PABC shows a structure analogous to that of human PABC[11]. The PABC domain does not contact RNA, but rather serves as an additional binding surface for proteins, recognizing a 15 residue sequence "PABP interaction motif" (PAM-2)[27, 28] contained in such proteins as eukaryotic translation termination factor 3 (eRF3), PABP-interacting proteins 1 and 2 (PAIP1 and PAIP2, negative regulators of translation)[29] and PAN (poly(A) nuclease) 3 deadenylase[30]. Given the number of PAM containing proteins found in the data base, it is likely more interactions will be identified. In plants, the PABC region has a highly conserved primary sequence, indicating conserved functions. Wheat PABC structure is similar to human[11] and interacts with PAM-2 motif as do PABP2 and PABP5 from *A. thaliana*[31]. The C-terminal domain of PABP7 from *A. thaliana* has a histidine (H534) in place of tyrosine (Y577 in wheat) suggesting reduced PAM-2 binding and perhaps a different specific functional role[11, 28]. These varied interactions indicate the multiple roles PABP proteins serve. The carboxy-terminal domain is not required for cell viability in yeast and is missing from PABPC5 proteins. PABPN1 structure is not as well determined, but contains an arginine rich carboxy-terminal domain[1].

Cytoplasmic functions of PABP

PABP role in translation

Virtually all eukaryotic mRNAs possess a 5' cap (m^7GpppN, where N is any nucleotide), a coding region and a poly(A) tail. During translation initiation, the 40S ribosome binds to an mRNA, scans to the initiation codon where it joins with the 60S subunit to form an 80S complex, and this complex then proceeds to translate the coding region[32, 33]. Each of these steps requires the assistance of initiation factors (eIFs). Prior to 40S binding, eIF4E (the small subunit of eIF4F) binds to the cap at the 5' terminus of RNA. eIF4G (the large subunit of eIF4F) binds and recruits additional eIFs including eIF4A which is necessary to remove secondary structure in the noncoding region which would inhibit scanning of the 40S subunit, eIF3 promotes 40S ribosomal binding to the mRNA, and the PABP stabilizes eIF4F binding to the cap. The poly(A) tail is the binding site for PABP. In plants, the interactions between PABP and eIF4G or eIF4B increase the poly(A) binding activity of PABP by 10-fold and increase the affinity of eIF4F for the 5' cap by 40-fold[34, 35]. These long distance interactions between the 5' and 3' UTRs of the mRNA stimulate efficient translation. However, there are numerous exceptions to this general description of translation initiation, such as pausing or frameshifting. A major deviation from the classical model involves those RNAs, usually viral, that lack a cap structure altogether as well as in some cases a poly(A) tail. Some of these mRNAs possess a structured, non-coding region of 5' RNA known as an internal ribosome entry site (IRES). Interestingly, IRES are also beginning to be identified in cellular mRNA[36]. These cellular mRNAs are generally those that would be advantageous to have translated under conditions where overall translation is compromised, for example mRNA coding for factors controlling growth or differentiation.

PABPs play a complex role in translation initiation which is not fully understood. In the cytoplasm PABP associates with both the mRNA poly(A) tail and eIF4G. The interaction of PABPC, eIF4E and eIF4G with the cap and poly(A) tail is an attractive mechanistic model to explain the synergistic effects on translation known to occur when mRNAs are both capped and polyadenylated[1, 37–40]. The popular "circularization model" where PABPC binds the poly(A) tail and eIF4F interacts through the eIF4E subunit with the cap to bring the two ends of the mRNA into close proximity does not fully illustrate the complexity of the reactions. Further, recent evidence suggests that PABP-eIF4G interaction serves primarily as one of several interactions to stabilize the eIF4G binding to mRNA[41], necessary for efficient recruitment of the 43S ribosome complex and translation. In plants, the cooperative interactions of eIF4F and PABP enhance the affinity of eIF4E for the 5' cap of

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the mRNA by lowering the dissociation rate[42–45], stimulate PABP binding to RNA[34], and increase the RNA helicase and ATPase activities of eIF4B, eIF4A and eIF(iso)4F[46]. Wheat germ PABP was shown to reduce the activation energy for formation of the 5'cap- eIFiso4F complex suggesting PABP interaction with eIFiso4F induces a conformational change, enhancing RNA interactions[45]. Additional interactions of PABPs in wheat germ with eIF4B[34] and the PABP-interacting proteins Paip-1 and -2 illustrate the complexity of the network[27, 29, 47, 48]. As shown in yeast, PABP1 can also influence later steps in translation including 60S subunit joining and termination which PABP1 regulates via interaction with eRF3. Most of these reactions have been described for the well characterized PABP1 and only recently have experiments explored the roles of other members of the PABP family. Further, there are few experiments to address the role of multiple PABP molecules binding to the poly(A) tail and the possible cooperative interactions. Single molecule force spectroscopy[49] revealed that carboxy-terminal domain interactions (C-C interactions) promoted cooperative binding to poly(A). However, only about 50% of the PABP molecules bound cooperatively, presumably leaving the other C-terminal domains free for other protein interactions.

Changes in gene expression have been extensively studied in vertebrate development and oocytes[24]. Recently, Gorgoni et al.[50] have established that each of the PABPs conserved in *Xenopus laevis* (PABP1, ePABP and PABP4) is essential for normal development. While all of the PABPs were able to promote global protein synthesis, knockdown or deletion of each of the PABPs showed defects in protein synthesis suggesting that they play distinct roles in specific mRNA translation and/or mRNA decay[50].

miRNA function—PABPs are also involved in miRNA-dependent regulatory pathways. miRNA are small RNAs that regulate gene expression at the posttranscriptional level. They are involved in virtually all physiological processes, such as development, differentiation, metabolism, homeostasis, and apoptosis. miRNAs regulate gene expression through translational repression and/or mRNA deadenylation and decay[51–54]. Although deadenylation contributes to the rate of decay and the miRNA-mediated regulation, recently, it has been shown that translation repression occurs before mRNA deadenylation and decay[55, 56]. Although the molecular mechanisms involved in the coordination of these different steps of the pathway are not known, it is possible that the formation of multiprotein complexes might play an important role in the dynamic of the miRNA-mediated regulation. As miRNAs are only partially complementary to their target sequences, they function in the form of ribonucleoprotein complexes known as miRNA-induced silencing complexes (miRISCs). Argonaute (Ago) family proteins and GW182 are important factors in miRNA-mediated silencing[57–59]. Mammalian GW182 protein interacts with the C-terminal domain of PABPC1 and the CCR4–NOT deadenylase complex through independent domains to promote deadenylation[60–66]. The formation of this complex is important for miRNA-mediated deadenylation and mRNA decay, but not for translational repression[67]. On the basis of these studies, it has been proposed that the miRNA-mediated degradation of mRNAs involves the association of Ago proteins to the miRNAs and the recruitment of GW182 to the target mRNAs via its N-terminal domain; then the GW182 C-terminal silencing domain recruits the deadenylase complex through the interaction with PABPC1. The activation of deadenylation by miRISC is independent of miRNA base pairing as the direct tethering of miRISC to the mRNA is sufficient to activate deadenylase functions of CCR4-NOT[67, 68].

As PABC1 is involved in control of mRNA translation, deadenylation and mRNA stability through apparently independent molecular pathways, it is possible that changes in the PABC1-protein interactions might mechanistically connect different steps of the miRNA-mediated regulation. For example, the interaction of PABC1 with GW182 might interfere

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with PABC1 association with the poly(A) tail and eIF4G, resulting in a decrease in translational efficiency[34, 35]. On the other hand, loss of the PABC1-eIF4G interaction decreases the formation of the mRNA closed-loop, making the 5'cap and the poly(A) tail more accessible for degradation. Supporting this model, it has been shown that GW182 and eIF4G compete for PABC1 binding[61]. However, recently, it has been shown that PABPs are not essential for miRNA-mediated inhibition of translation and deadenylation[69, 70] but it is important to modulate the strength of miRNA silencing[71, 72]. Further functional studies are required to fully understand the coordination of the different steps involved in the miRNA-mediated regulation and the role of PABPs in this pathway.

Developmental function—In addition to its role in miRNA-dependent pathways, PABPs have important roles in regulating cytoplasmic mRNA stability during germ-cell development and early embryogenesis in Xenopus[73, 74]. In early development, transcription is often quiescent, so changes in protein synthesis rely on the regulation of translation of pre-existing maternal mRNAs. Some nuclear pre-mRNAs that contain specific cis-acting signals in their 3'UTRs are transported to the cytoplasm with long poly(A) tails, but once they reach the cytoplasm, their tails are shortened and those mRNAs become dormant. Once meiosis continues, the poly(A) tails are lengthened again and mRNAs are translated, allowing the egg cell to survive and grow in the absence of transcription. The effect of PABPs on the expression of mRNAs during development can be classified as general and gene-specific. The general effect of PABPs occurs on mRNAs that lack cytoplasmic polyadenylation elements (CPEs). These mRNAs undergo a default deadenylation and can remain either stable/dormant or degraded. In that scenario, the initial deadenylation process induces the lost of PABPs, resulting in further deadenylation and inhibition of translation[75]. The gene-specific effects of PABPs need cis-acting sequences in the 3'UTR of the mRNAs and involves PABPs functions other than poly(A) tail protection. Polyadenylation of dormant mRNAs is controlled by both CPEs and the hexamer AAUAAA that are the binding platforms for CPE-binding protein (CPEB) and cleavage-polyadenylation specificity factor (CPSF), respectively. Cytoplasmic polyadenylation is mechanistically different from the nuclear one (reviewed in[76]). Briefly, cytoplasmic polyadenylation starts by the binding CPEB and CPSF, both of which serve as a scaffold to bind the poly(A) polymerase Gld2 and PARN deadenylase[76–78]. PABPs interact with the polyadenylation complex components, facilitating binding of the complex to the newly synthesized poly(A) tail, promoting translation and protecting the mRNA from deadenylation[76].

The cytoplasmic polyadenylation/deadenylation pathway is regulated by a combination of different cis-elements[79] and the formation of dynamic multiprotein complexes[76], all of which results in a very specific pattern of regulation for each mRNA. For example, cyclin B1 mRNA has a short poly(A) tail before maturation and is maintained translationally repressed by a complex of proteins: CPEBs bound to the CPE in the 3'UTR, eIF4E at the 5'UTR and the bridging protein maskin[80]. Upon progesterone stimulation, cyclin B1 mRNA is polyadenylated in the cytoplasm, leading to the increase in the binding of PABPs and eIF4G[81]. Another interesting mechanism of translational stimulation in oocytes and germ cells is based on the functional interaction of PABPs and deleted in azoospermia-like (DAZL) family of proteins[24]. DAZLs are RNA-binding proteins that localize in the cytoplasm throughout oogenesis and bind the 3'UTR of mRNA containing the mDAZL binding site[82]. It has been suggested that DAZL bound to the 3'UTR of the target genes recruits PABPs which, in turn, interacts with translation factors providing a mechanism of specific-control of gene expression during development in a poly(A)-independent manner[83–85]. As PABs can also bind the CPEB-containing complex, it has been suggested that both DAZL mRNA interaction and CPEB-mediated polyadenylation might be required for maximal translation activation[24]. Another example of gene-specific regulation is the RNA-dependent association of PABPs with Bic-D in Drosophila, a factor involved in the

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localization of mRNAs to specific regions during oogenesis and embryogenesis[86]. One of the PABP/Bic-D targets is osk, and this functional interaction is also poly(A) independent because PABP binds A-rich sequences in the osk 3'UTR.

Finally, the developmental functions of PABPs are in fact more complicated because each member of the cytoplasmic PABP family has distinct and essential roles in different stages. In vertebrates, depletion of either PABPC1 or ePABP is lethal and causes anterior and posterior phenotypes, and depletion of PABPC4 is lethal at later stages and causes anterior phenotypes [50]. The functional specificity of each PABP is conferred by specific domains and protein-protein interactions. PABP expression levels, which are under control of Paip2a, are also important for the regulation of translation due to changes in the interaction with eIF4E and the mRNA 5' cap during development[87].

Non-sense mediated decay (NMD)—In addition to these cytoplasmic processes, PABPs have an important role in the decay of mRNAs encoding a premature translation termination codon (PTC). mRNAs with a PTC are degraded in a pathway known as NMD[88–90]. In this pathway, which occurs in both yeast and mammalian cells, transcripts with PTCs are degraded either by deadenylation and exonucleolytic degradation or by decapping without deadenylation[88–93]. In mammalian cells, it has been shown that NMD factors, such as RNA helicases Upf1 and PABPC1, compete for binding to the translation release factors eRF1 and eRF3, representing a crucial step in the decision to decay diverse transcripts[94, 95]. Binding of PABPC1 to release factors is proposed to preserve transcript stability and translational competence. Conversely, Upf1 binding to release factors at the terminating ribosome stimulates translational repression and recruitment of decay factors[96–98]. Consistent with this idea, bringing PABPC1 in proximity to the termination codon can suppress Upf1-dependent decay[94, 99–101]. The enrichment of Upf1 on long 3′UTR-containing transcripts may increase the probability that Upf1 will out-compete PABPC1 for release factor binding and trigger NMD[95, 100, 102, 103]. Based on these studies, the model is that the distinction between PTC and normal termination codons relies on the distance between the termination ribosome and PABP. PABP promotes correct translation termination, whereas the absence of PABP-mediated signal for termination leads to the assembly of the mRNA decay complex[104].

As part of the NMD response, the proteasome is recruited to messages with PTCs as well as messages lacking a termination codon, which are degraded by nonstop decay, to degrade the aberrant protein produced by these messages. In that context, a number of PABP interacting proteins involved in mRNA translation are regulated by the proteasome in human cells, including Paip2b[105] and translation initiation factors eIF4G and eIF4E[106, 107]. The proteasome–mediated decay may constitute a primary mechanism by which cells regulate PABPs activity in translation.

Cellular stress conditions—As demonstrated in human cells, PABPs have a role in the cellular recovery from heat shock[108]. Following heat shock, HSP27 binds to the insoluble eIF4G and impedes its association with PABP1 and eIF4E. In those conditions, PABPC1, eIF4G and HSP27 translocate to the nucleus. During the recovery, PABPC1 expression is unregulated and it is translocated back to the cytoplasm together with eIF4G. Interestingly, in mammalian cells, UV treatment also changes the localization of both PABPC1 and PABPC4 from cytoplasmic stress granules to the nucleus[109]. PABPs' relocalization was accompanied by a reduction in protein synthesis and a change in the distribution of poly(A) mRNA in the cell. PABPs' relocalization occurs due to the UV-induced blockage of mRNA transport, indicating that nuclear export of PABPs is dependent on active mRNA export. Several studies have shown evidence that support cytoplasmic functions for PABPN1 and nuclear functions for PABPC1. Lemay et al.[110] proposed a model in which both PABPs are

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bound to the same mRNA poly(A) tail but the PABPC1:PABPN1 stoichiometry may change in each cellular compartment depending on the concentration of these PABPs in the nucleus and cytoplasm.

Nuclear functions of PABP

Polyadenylation

Almost all eukaryotic pre-mRNAs undergo polyadenylation at their 3' ends, with the exception of histone mRNAs. Polyadenylation occurs in the nucleus through a two-step reaction: an initial cleavage step, which specifies the 3′ end of the mRNA, followed by synthesis of an adenosine residue tail, which varies in length in different organisms, to the 3′ end of the upstream cleavage product (reviewed by[111]). The assembly of the polyadenylation machinery requires specific signal sequences in the pre-mRNA as well as the assembly of a large number of protein factors. The CPSF factor binds to the polyadenylation signal to cleave the mRNA, and then it associates to poly(A) polymerase (PAP) and PABPNI for the poly(A) tail synthesis, as shown in mammalian cells[111]. The binding of PABN1 to the poly(A) not only stimulates PAP processivity but also prevents degradation of mRNAs and thereby preserves the length of the poly(A)[112]. When the length of the poly(A) gets longer, the ternary complex is destabilized and PAP processivity is decreased.

PABPN1 is also a regulator of alternative cleavage and polyadenylation (APA) in mammalian cells[113]. The use of different APA signals generates a diversity of mRNA isoforms that carry different arrangements of AREs and miRNA target sites, which are involved in the regulation of mRNA stability. The relevance of these regulatory processes is highlighted by the finding of shortening in the length of the 3'UTRs of different mRNAs in cancer cells[114, 115] and during cell differentiation[116–118]. PABPN1 has been identified as an inhibitor of APA and the loss of PABPN1 results in a global enhancement of the usage of the proximal cleavage site, resulting in a shortening in the length of the 3’UTR. These studies suggest that PABPN1 functions in the recognition of the polyadenylation signal by direct interaction with the pre-mRNA 3’UTR and this interaction occurs before the synthesis of the poly(A) tail. Supporting this model, cells from patients with oculopharyngeal muscular dystrophy, which express a mutant of PABPN1, show shortening in the length of the 3’UTR, probably due to a dominant negative effect of the mutant over the wild-type PABPN1.

mRNA quality surveillance

Recent studies indicate that cytoplasmic PABPs also have nuclear roles, suggesting a more dynamic functional exchange between the different PABP forms than originally thought. Pab1p, which is the predominant cytoplasmic PABP form in yeast, participates in a nuclear surveillance pathway where incorrectly processed and defective transcripts are eliminated by 3’-end RNA degradation by the exosome, ensuring that only high-quality mRNAs are engaged in protein synthesis. Most of the exosome-activating signals come from the 3’-UTR and the poly(A) tail[119]. Interestingly, the nuclear exosome subunit Rrp6 controls the extension of the mature poly(A) tails by regulating not only the noncanonical poly(A) polymerase Trf4p but also loading the poly(A) binding proteins Pab1p and/or Nab2p onto nascent poly(A) tail[120]. In wild-type cells, the majority of mRNA poly(A) tails are Pab1p bound and destined for nuclear export and cytoplasmic translation. However, nuclear poly(A) tails harboring both Pab1p and Nab2p at their 3′ ends can target Rrp6p for trimming and mRNA degradation. Loss of Nab2 or Rrp6p results in mRNA hyperadenylation and nuclear accumulation of poly(A)+ RNA. As discussed earlier, similar surveillance pathways exist in the cytoplasm.

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PABP as a viral target

Host cell translational initiation factors have long been recognized as viral targets, either to shut-off host cell protein synthesis or to circumvent host defense mechanisms. PABP has now also been recognized as a target with perhaps more complex roles in viral protein synthesis and replication (reviewed in[6]). For example, one of the strategies employed by viruses is cleavage of PABP which results in host cell translational shut-off[6]. Picornaviral (PV) proteases target eIF4G, cleaving the N-terminal region which binds eIF4E and PABP[121, 122]. Recent evidence suggests several viral proteases cleave PABPC1 in the flexible linker region eliminating interactions between PABPC1 and eIF4B and eRF3[123, 124]. Efficient translation of PV and other viruses often requires additional proteins and these viruses often use internal ribosome entry sites for translational start sites. Other viruses also cleave PABP, but some employ additional or alternative strategies which include displacement of the PABP from the eIF4G initiation complex (e.g. rotaviruses[125]), recruitment of PABP to the eIF4F complex (e.g. human cytomegalovirus and vaccinia virus) and recruitment of PABP to viral 3' UTR (e.g. dengue virus) (reviewed in[6]). PABP also plays a role in the kinetics and stability of eIF4F binding to tobacco etch virus IRES[126–129]. Further, there is evidence for nuclear relocalization of PABP during viral infection[130]. While it is clear that PABP is a common viral target, it not evident in many cases what advantage is conferred to the virus by using these tactics. There is little information on how specific PABPs, particularly in plants where multiple members of the PABP family are expressed, are exploited by viruses. Dufresne et al.[131] have shown that *A. thaliana* RNA-dependent RNA polymerase (RdRp) and VPg of turnip mosaic virus (TuMV) preferentially interact with PABP2, although RdRp and VPg were also capable of interaction with one or both of the other class II PABPs (PABP4 and PABP8). The precise functional role of these interactions remains unclear.

Perspectives and Future Directions

The PABP family of proteins has many structural and functional similarities and until recently, not much attention was paid to the different cytoplasmic homologues. Further, these homologues were thought to function only in the cytoplasm, with the nuclear protein having its own set of functions. These multifunctional proteins require complex modulation of protein/protein and protein/RNA interactions to coordinate different functions. Graded interactions and responses to environmental stimuli can be achieved by post-translational modifications and by use of different homologues. Evidence that different homologues of PABP are important comes from studies of heterologous systems where in general, PABPs from one species can only partially replace the functions of PABP from the homologous species. This suggests that while some basic functions are retained by most, if not all, of the PABPs, other perhaps more subtle functions are not. These likely include protein/protein interactions and how these protein/protein complexes interact with RNA. Further evidence for specific functions of individual members of the PABPC family arises from developmental studies where each of the cytoplasmic PABPs in Xenopus laevis was shown to have a mechanistically conserved role in translation, but knockdown studies revealed that deletion of each of the PABPs resulted in defects in translation and development suggesting different roles in mRNA-specific translation/decay. Added to this already complex network is the role of post-translational modifications, likely to play a large role in the response to environmental changes. Lastly, very little consideration has been given to the transient nature of these interactions. Recently, it has been suggested that circularization of the mRNA during translation was not essential[41]. One consideration is that mRNAs, particularly those of viruses, needs to compete for translational components. Competition is likely to involve kinetic competition with many interactions occurring only transiently and equilibrium stability playing a smaller role. Which reactions are kinetically controlled? How

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do different PABP homologues respond? How do nuclear and cytoplasmic PABPs exchange, if in fact they do? What are the roles of PABPs in miRNA-mediated regulation of mRNA expression? Is it translation or mRNA stability regulation? or both? Is the role of PABPs in control of gene expression general or is it gene specific? What are the specific targets of PABPs-mediated regulation? Could PABPs have a role in proliferation and cancer? Have all the functions of multifaceted PABPs been identified? The list of questions goes on and we are just beginning to explore the intricacies and fine tuning of this important regulatory network.

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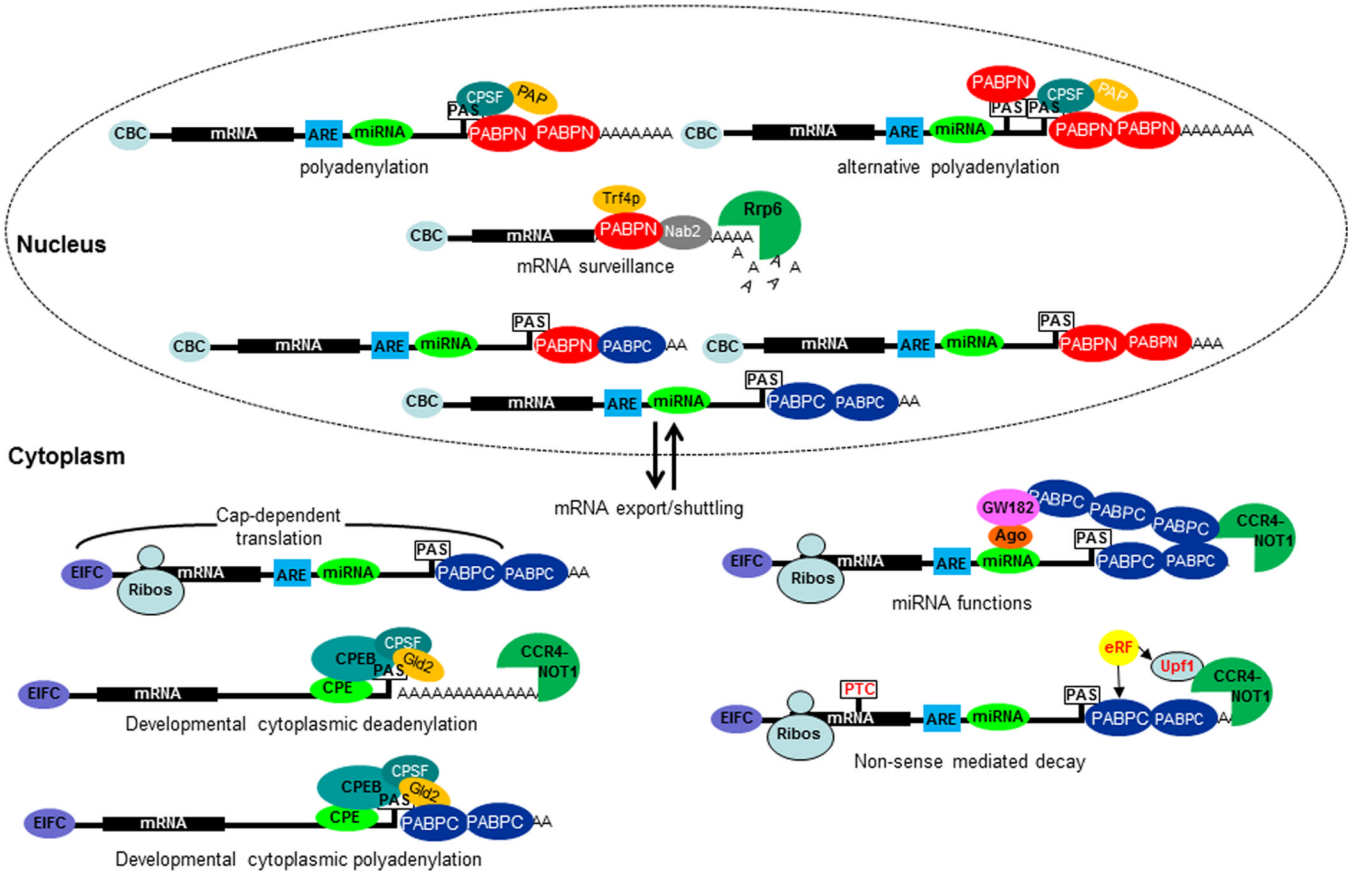

Figure 1.

Model for PABP functions in different mRNA metabolic pathways: polyadenylation, alternative polyadenylation, nuclear mRNA surveillance, mRNA export, translation, non-sense mediated decay (NMD), cytoplasmic polyadenylation/deadenylation during development. Polyadenylation signal (PAS), cleavage-polyadenylation specificity factor (CPSF), poly(A) polymerase (PAP), AU-rich element (ARE, microRNA (miRNA), Cap-binding complex (CBC), ribosome (Ribos), eukaryotic translation initiation factor complex (EIFC), eukaryotic translation termination factor (eRF).