Poly(A)-binding proteins and mRNA localization: who rules the roost?

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Abstract

RNA-binding proteins are often multifunctional, interact with a variety of protein partners and display complex localizations within cells. Mammalian cytoplasmic poly(A)-binding proteins (PABPs) are multifunctional RNA-binding proteins that regulate multiple aspects of mRNA translation and stability. Although predominantly diffusely cytoplasmic at steady state, they shuttle through the nucleus and can be localized to a variety of cytoplasmic foci, including those associated with mRNA storage and localized translation. Intriguingly, PABP sub-cellular distribution can alter dramatically in response to cellular stress or viral infection, becoming predominantly nuclear and/or being enriched in induced cytoplasmic foci. However, relatively little is known about the mechanisms that govern this distribution/relocalization and in many cases PABP functions within specific sites remain unclear. Here we discuss the emerging evidence with respect to these questions in mammals.

Introduction

Eukaryotic cells rely on post-transcriptional control of gene expression to ensure the tight spatiotemporal control of protein production needed to fulfil their functions. One key feature of eukaryotic mRNAs is the co-transcriptionally added 3'-poly(A) tail which is important for their nuclear export, translation and stability. Poly(A)-binding proteins (PABPs) are thought to mediate the functions of the poly(A) tail and accompany mRNAs from their birth in the nucleus until their eventual destruction [1–4]. In contrast with budding yeast, metazoans encode distinct nuclear (PABPN) and cytoplasmic PABPs (PABPC, referred to as PABPs hereafter), which share an ability to bind the poly(A) tail, but bear virtually no sequence or other functional similarity [2]. At steady state, PABP1 (also called PABPC1), the prototypical PABP, is diffusely cytoplasmic. However both PABP1 and PABPN1 shuttle between nucleus and cytoplasm making the timing of their exchange on mRNA poly(A) tails unclear, although PABPN1 appears required for mRNA export into the cytoplasm [5].

PABP1 is considered to be a central regulator of cytoplasmic mRNA fate, controlling rates of mRNA translation and decay, as well as controlling mRNA-specific translation and stability, in some cases poly(A)-tail independently. Additionally, PABP1 has roles in miRNA-mediated repression/silencing and in the nonsense-mediated decay (NMD) mRNA surveillance pathway [6]. In mammals, three other family members, testis-specific (t)PABP (also called PABPC2/PABPC3) and embryonic (e)PABP (also known as ePAB/PABP1L), both of which are restricted to the germ line and PABP4 (also referred to as inducible (i)PABP), share the domain organization of PABP1 (Figure 1) [1]. Mammals also harbour an additional family member, PABP5 (also called PABPC5), which has only some of the PABP1 domains and whose function has not been addressed. Although the functions of the PABP1-like family members have been considerably less well-studied, they appear to have a predominantly diffused cytoplasmic localization [7–11]. PABP4 is known to undergo nucleocytoplasmic shuttling [10,12] but it is unknown whether tPABP and ePABP share this property. Moreover, PABPs also accumulate at specific locations within the cytoplasm, such as foci implicated in the storage of translationally silent mRNAs or sites associated with localized translation. Since PABPs play a central regulatory role, it is not surprising that their nucleocytoplasmic distribution and localization within the cytoplasm are dynamically regulated, e.g. in response to cell stress. However, the mechanisms by which their sub-cellular distribution is controlled are only now becoming clear. Here we explore the evidence that mRNA distribution, which largely mirrors that of PABP, is a major driver of PABP localization and discuss our current understanding of the role of PABP in the site-specific regulation of mRNA fate.

Key words: chromatoid body, cytoplasmic poly(A)-binding protein 1 (PABPC1), localized translation, messenger ribonucleoprotein (mRNP) granules, nucleocytoplasmic, poly(A)-binding protein (PABP), stress granule.

Abbreviations: ALS, amyotrophic lateral sclerosis; BC, brain cytoplasmic; CB, chromatoid body; CRM, chromosomal maintenance; eEF, eukaryotic translation elongation factor; ePABP, embryonic PABP; FTLD, frontotemporal lobar degeneration; FUS, fused in sarcoma; G3BP, GTPase-activating protein SH3-domain-binding protein; HSV-1, herpes simplex virus 1; LMB, leptomycin B; NES, nuclear export signal; NLS, nuclear localization signal; NMD, nonsense-mediated decay; NSP, non-structural protein; PABP, poly(A)-binding protein; PABPC, cytoplasmic poly(A)-binding protein; PABPN, nuclear poly(A)-binding protein; PB, processing body; RRM, RNA-recognition motif; RUBV, rubella virus; SG, stress granule; TAP, Tip-associated protein; TD-NEM, transcription-dependent nuclear export motif; TDP, transactive response DNA-binding protein; TIA, T-cell internal antigen; TIAR, TIA-1 related protein; tPABP, testis-specific PABP.

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PABP nucleocytoplasmic distribution

Determinants of the steady state

Although PABP1 and PABP4 are nucleocytoplasmic shuttling proteins [7–11], they lack the classical nuclear

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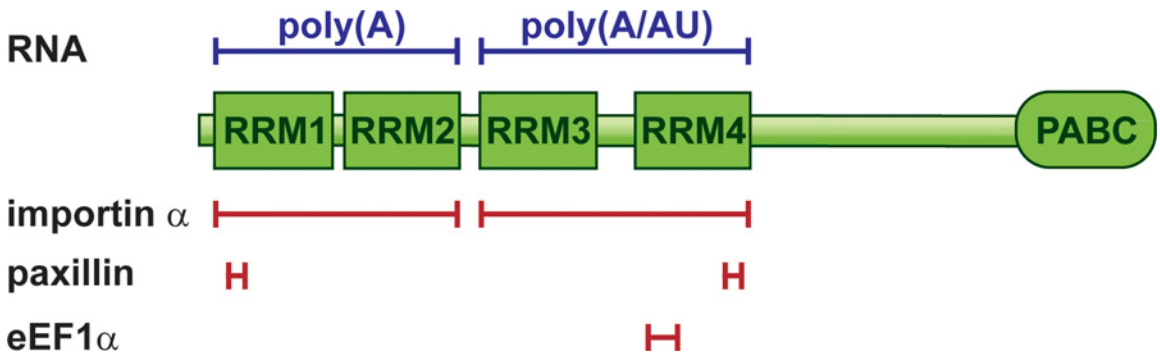
Figure 1 | PABP1 interactions implicated in localization

PABP1 has four non-identical RRMs, separated from a globular PABC domain by a linker region. RNA-binding capacity (blue lines) and current knowledge of discussed protein interactions (red brackets) are shown. PABP4, tPABP and ePABP share this domain organization and bind poly(A) RNA. PABP4 and ePABP are both known to bind AU-rich RNA. With the exception of PABP5, the high conservation of the RRMs strongly suggests that the depicted protein partners may be shared; however, the eEF1α-binding site is not well conserved in PABP4.



localization signals (NLS) and nuclear export signals (NES) associated with transport through nuclear pores [13]. Nevertheless, their import appears to be via the classical importin β karyopherin receptor pathway, due to importin α, an adaptor protein that binds importin β, interacting with multiple unmapped independent non-canonical NLSs present in the RRMs (RNA-recognition motifs) of PABP1 [11] (Figure 1). Crucially, these interactions are outcompeted by poly(A) RNA [11], suggesting that mRNA-bound PABP is not available for import (Figure 2A). Consistent with this, PABP accumulates in the nucleus when the cytoplasmic PABP–poly(A) ratio is increased by prolonged transcriptional inhibition or transient ribonuclease expression, both of which reduce cytoplasmic mRNA levels [10,11,14] or by PABP overexpression [7]. Other PABP interactions may also block importin α binding. Support for this comes from observations that cycloheximide-induced polysome stabilization prevents PABP nuclear localization [12], suggesting that release from translation complexes is also a pre-requisite for import (Figure 2A).

Consistent with the absence of an NES, PABP export is, with the exception of one study [8], insensitive to leptomycin B (LMB), an inhibitor of the chromosomal maintenance (CRM)1 export receptor [9,12,15]. It appears to occur via several alternative mechanisms (Figure 2B–D). One factor identified as being involved in PABP export is eukaryotic translation elongation factor (eEF)1α, which can bind a short sequence [$DXGX_2DX_2L$; transcription-dependent nuclear export motif (TD-NEM)] in PABP1 (Figure 1; Figure 2B). Deletion of this sequence, which can confer transcription-dependent, LMB-resistant nuclear localization to other proteins, results in nuclear accumulation of PABP1 [9]. eEF1α depletion retards PABP1 export [15] suggesting that it mediates the function of the TD-NEM sequence. However, the poor conservation of this sequence in PABP4 makes it unclear whether it also utilizes eEF1α. Although the mechanism by which eEF1α promotes PABP1 export remains obscure, since it is a translation factor, it is interesting to note that it is implicated in yeast tRNA export [16].

In addition to impeding nuclear import, the role of mRNA in determining PABP nucleocytoplasmic distribution may extend to export (Figure 2C; Figure 3A). PABPs bind mRNAs in the nucleus alongside PABPN1 [17], suggesting they may be exported on mRNAs. Supporting this, indirect inhibition of mRNA export, either by a viral splicing-inhibitor protein or by chemical transcription inhibitors, results in PABP nuclear localization [10,18,19]. Critically, targeting mRNA export directly by knockdown of the mRNA-export adaptor Tip-associated protein (TAP) also results in PABP nuclear accumulation [10] (Figure 3B). Since transcription is essential for ongoing mRNA export [20], this mRNA export-dependent PABP export shares some mechanistic features with TD-NEM-mediated export, but it is unclear to what extent these pathways coincide. eEF1α functions at the cytoplasmic side of the nuclear envelope [15], so could potentially play a late-stage role in mRNA export-dependent PABP export.

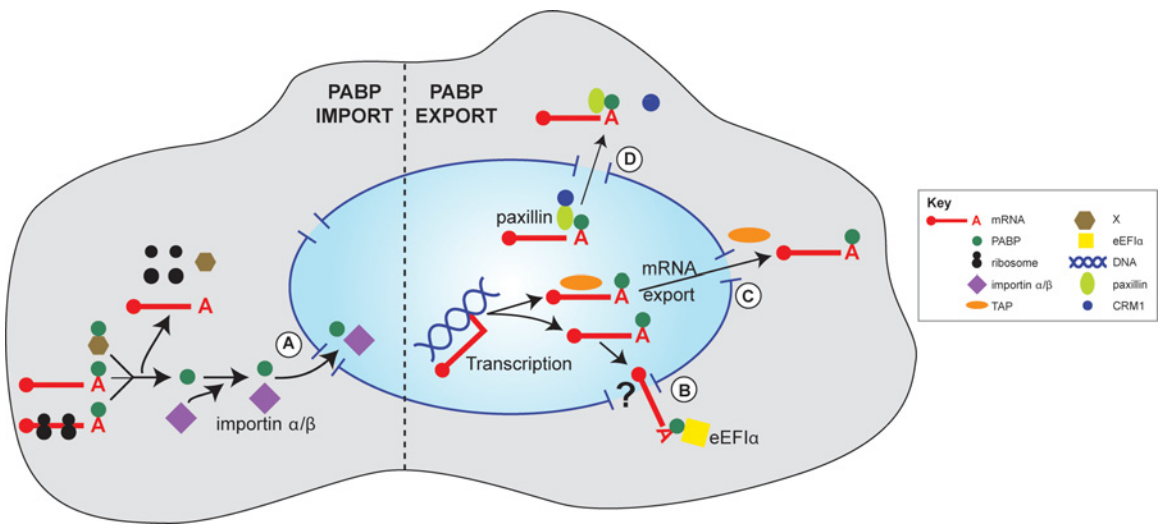
According to one study, PABP export is LMB-sensitive [8] and may therefore be CRM1-dependent under certain circumstances. Mutagenesis and knockdown experiments indicate that this occurs via an interaction of PABP with the NES-containing focal adhesion–adaptor protein, paxillin (Figure 1; Figure 2D). This interaction was observed in NIH3T3 fibroblasts [8,21] but not in other cell lines [12,19,22], suggesting that it does not represent a general PABP-export pathway, consistent with PABP export generally being LMB-resistant.

Perturbations of the steady state

Some types of cellular stress and viral infections induce PABP nuclear accumulation (Figure 3B) by mechanisms that enhance import, inhibit export or both. Following UV irradiation, poly(A) mRNA accumulates in the nucleus with similar kinetics to PABP1 and PABP4, consistent

Figure 2 | RNA is a major determinant of PABP nucleocytoplasmic localization

(**A**) Association of PABPs with translation complexes (represented by ribosomes) and/or mRNA prevents its availability for import. Complexes with other proteins (X; e.g. PABP-interacting protein (Paip)2) may also maintain its cytoplasmic steady state. Once released, PABP can be bound by the importin α/β complex which mediates the classical nuclear import pathway. It is possible that imported PABP may normally rapidly bind to newly synthesized poly(A) tails. (**B–D**) PABP export from the nucleus. (**B**) Cytoplasmic eEF1α facilitates PABP export by an unknown mechanism (represented by '?'). PABP exported by this pathway may be bound to mRNAs since it is dependent on ongoing transcription. (**C**) PABP exits the nucleus bound to mRNAs via the mRNA-export pathway which is mediated by a complex containing TAP. (**D**) PABP (perhaps mRNA-associated) exits the nucleus bound to paxillin via the classic CRM1 export pathway. This is likely to represent a minor pathway. Blue: nucleus with pores depicted as breaks in the surrounding blue line; grey: cytoplasm.



with a block in mRNA-export-dependent PABP export [10,12]. Hydrogen peroxide treatment, but not all inducers of oxidative stress (see 'Stress granules' section), can also redistribute PABP to the nucleus [19].

Nuclear accumulation of PABP occurs during infection with members of several virus families [23] and can in many cases be explained by alterations in the import/export mechanisms described above. For instance, PABP1 nuclear relocalization occurs during infection with bunyaviruses that inhibit cellular transcription [24–27], but not with those that do not [27]. This is consistent with impeded mRNA-export dependent or TD-NEM-mediated PABP export.

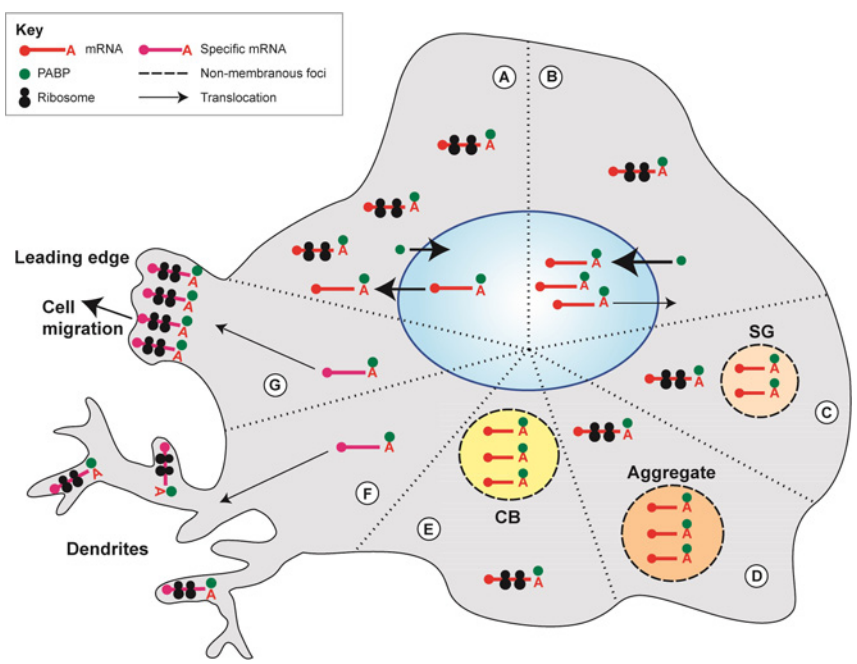
PABP nuclear import can also be enhanced by targeting mRNA distribution. A number of γ-herpesviruses which promote PABP nuclear accumulation during lytic infection [11,14,28,29] express cytoplasmic ribonucleases. These cause widespread mRNA turnover, inhibiting host-cell gene expression and rendering PABP accessible for importin α-mediated nuclear import [11]. Both altered PABP import and export may be targeted during lytic infection with herpes simplex virus 1 (HSV-1) [19] via cytoplasmic mRNA degradation [30] and impaired host-cell transcription and mRNA export [31]. Finally, rotavirus expresses a non-structural protein, (NSP)3, which evicts PABP from translation complexes [32]. However, to promote PABP nuclear relocalization, NSP3 must also interact with a cellular RNA-binding protein of unknown function [33], suggesting that making PABP available for import may be a multistep process or that release from translation complexes is, at least in some cases, insufficient to explain its relocalization.

Nuclear roles of cytoplasmic PABPs

Very little is known about why cytoplasmic PABPs transit through the nucleus. PABP1 binds to polyadenylated pre-mRNAs and NMD substrates in the nucleus [17], suggesting association with mRNAs at an early stage, perhaps to prime them for NMD-mediated quality control or efficient translation and stabilization following export. It has been suggested, by analogy to yeast PAB-1 [34,35], that mammalian PABPs may facilitate mRNA export [7,8] but, to our knowledge, no supporting evidence has been presented. Rather, knockdown of PABP1 and/or PABP4 does not influence nucleocytoplasmic mRNA distribution [10] and forced nuclear localization of PABP1 results in an mRNA-export block (Figure 3B), perhaps as a result of accompanying mRNA hyperadenylation. Hyperadenylation may mark mRNAs as aberrant [22], although this remains to be shown. Lastly, it is possible that nuclear transit may simply reduce cytoplasmic PABP levels or, by analogy with transcription factor storage in the cytoplasm, facilitate its storage. Consistent with this, PABP knockdown does not affect recovery following UV irradiation [10] or HSV-1 replication [19], suggesting that high levels of PABP in the nucleus *per se* are not required for these processes.

Figure 3 | Model for mRNA as a driver of PABP localization

(**A**) At steady state, PABP is predominantly cytoplasmic but shuttles to and from the nucleus (arrows, see Figure 2 for details). mRNA binding appears to be a major determinant of PABP distribution, through dual roles in PABP nuclear export and cytoplasmic retention. (**B**) Perturbations in mRNA sub-cellular localization or abundance, which enhance PABP import or impede export (indicated by relative arrow size), result in PABP nuclear accumulation. For instance, blocking mRNA export directly retains PABP in the nucleus but also leads to reduced cytoplasmic mRNA concentrations over time, increasing import. Similarly, high PABP concentrations within the nucleus, following increased import, can lead to mRNA hyperadenylation blocking mRNA export and increasing PABP retention. (**C–G**) Although PABPs are predominantly diffusely cytoplasmic, they can also be observed in foci, punctuate granules or at specific sites where they may be enriched by mRNA localization. (**C**) In stressed cells PABP can be found in SGs. (**D**) In diseased cells PABP can be found in RNA-containing aggregates. (**E**) In spermatids, tPABP is enriched in RNA-rich chromatoid bodies. (**F**) In neurons, PABP1 is present at sites distant from the cell body (e.g. dendrites, shown) where it is often observed in punta/granules. (**G**) PABP is observed at the leading edge of motile cells, a region thought to be the site of localized translation. It may be transported there on localized mRNAs and be involved in regulating their translation. Higher PABP concentrations are represented by more mRNA-bound PABPs and non-translated versus translated mRNAs are distinguished by the presence of ribosomes. Blue: nucleus; grey: cytoplasm.



Cytoplasmic foci

RNA-binding proteins are not always evenly distributed throughout the cytoplasm but can be assembled into dynamic non-membranous foci, such as stress granules (SGs) and processing bodies (P bodies or PBs) which are considered to be sites of mRNA storage and decay, respectively [36,37]. Moreover, they are sometimes present in granules associated with mRNA transport or enriched at sites of localized translation [38]. These foci and sites are enriched in mRNAs as well as PABPs with the exception of PBs, consistent with the deadenylation of mRNAs destined for decay in these foci [36].

Stress granules

The cellular stress response is characterized by translational silencing of most mRNAs. This is often accompanied by formation of SGs, which act as sites of mRNA storage [36,39] and contain eukaryotic translation initiation factors (eIFs) and small, but not large, ribosomal subunits [40]. PABP1 (and, where studied, PABP4 [10]) has been observed in SGs during heat shock-, arsenite-, osmotic shock- and UV irradiation-induced stress [10,39,41,42] (Figure 3C). Although PABP1 is considered to be a *bona fide* SG component and SG marker, PABPs are not required for SG formation because, in contrast with manipulating 'core' SG components [e.g. T-cell internal antigen (TIA)-1, TIA-1-related protein (TIAR) or Ras–GTPase-activating protein SH3-domain-binding protein (G3BP); 39,43], knockdown or overexpression of PABP1 and/or PABP4 does not affect SG formation or mRNA localization to SGs [10]. This suggests that PABPs may passively localize to SGs as a consequence of mRNA accumulation at these foci and raises the question of what function, if any, PABPs may perform in SGs. It can be envisaged that they may stabilize mRNAs during storage and/or participate in rapid translational re-activation after SG disassembly. Alternatively, sequestration in SGs may reduce the amount of PABP available for translation.

Other stress- or pathology-induced cytoplasmic PABP-containing granules that share some properties with SGs have been observed. For instance, following hypoxia, large RNA granules containing PABP1 and poly(A) mRNA, but lacking TIAR and small ribosomal subunit proteins [44], are observed during translational arrest in specific hippocampal neurons. There is no evidence that PABP promotes assembly or disassembly of these granules suggesting that, like in SGs, it may accumulate via its association with localized mRNA but this remains to be experimentally verified.

Furthermore, many neurodegenerative diseases are characterized by neuronal cytoplasmic inclusions containing aggregated and often mutated proteins, such as the PABP-interacting protein transactive response DNA-binding protein (TDP)-43 or fused in sarcoma (FUS) in amyotrophic lateral sclerosis (ALS) and FUS in sub-types of frontotemporal lobar degeneration (FTLD) [45]. Post-mortem analysis of ALS and FTLD patients showed PABP1 up-regulation and strong co-localization of PABP1 with the aggregates [46,47], rather than its nuclear relocalization (Figure 3D). Interestingly, inhibiting FUS nuclear import in cultured cells results in cytoplasmic inclusions [46] positive for SG markers, including PABP. These 'SG-like inclusions' may represent precursors of the larger aggregates seen in ALS and FTLD patients as SGs have been observed to enlarge upon prolonged stress [48] and their size is sensitive to alterations in TDP-43 or G3BP (a TDP-43 target) levels [49]. Intriguingly, a correlation between PABP levels and disease phenotype was observed with a *Drosophila* ALS model [50], suggesting that PABP can influence toxic aggregate formation despite its lack of effect on SG formation. However, this remains to be directly demonstrated.

PABPs can be relocalized to multiple sites upon stress

In a few cases, a particular type of stress can drive PABP relocalization to multiple, distinct sites. This can occur sequentially, as observed after UV irradiation, where both PABP1 and PABP4 briefly localize to SGs and subsequently to the nucleus [10]. The reason for this is unclear but it is possible that their nuclear relocalization may have a role in destruction of the transcriptome.

Interestingly, distinct PABP localizations can also be observed simultaneously in rubella virus (RUBV)-infected cells, which either maintain normal PABP distribution, relocalize PABP to the nucleus [51] and/or to a subset of 'non-classical SG-like foci' (containing G3BP but not TIA-1). Perinuclear PABP relocalization has also been reported upon RUBV infection [52]. Why and how this occurs during RUBV infection is unclear but nuclear and perinuclear PABP relocalization may result from increased PABP levels [7,52] and interactions with the RUBV capsid protein [52] respectively.

tPABP is present in chromatoid bodies

Germ cells undergo periods of extensive transcription quiescence and harbour specialized non stress-associated cytoplasmic RNP granules (germ granules), thought to serve as hubs of post-transcriptional regulation. In post-meiotic round spermatids a single structure known as a chromatoid body (CB), in which tPABP is one of the most abundant proteins, develops [53–55] (Figure 3E). Although CBs appear essential for fertility in mice [53,56], the function(s) of CB-associated tPABP remain(s) elusive but the restriction of its expression to a subset of male germ cells and striking localization, which is not shared by PABP1, are intriguing.

Mitochondrial localization of PABP5

PABP5, which contains only the RRM regions in common with PABP1 (Figure 1), appears to be predominantly present in the cytoplasm [57]. However, alternative translation initiation at a downstream AUG reveals a cryptic mitochondrial targeting sequence and yields a truncated PABP5 isoform of currently unknown function that is enriched in mitochondria [57].

PABP and localized translation

Localization of specific mRNAs to discrete cellular regions permits site-specific protein synthesis and depends on motifs within their 3′-UTRs, often called 'zip codes' [58,59]. Localized translation underlies multiple aspects of neuronal biology, including dendrite branching, synapse formation and plasticity [60] and is crucial for processes such as learning and memory [60].

Knockout studies of PABP-interacting proteins in mice suggest that PABPs are important for linking neuronal activity to mRNA translation [61] and several lines of evidence suggest that they may be involved in localized mRNA translation (Figure 3F). Firstly, PABP is present in neuronal regions distant from the cell body, e.g. dendrites, axonal filopodia and terminal growth cones [62,63] and co-localizes in punta/granules with RNA-binding proteins, such as the well-characterized HuD [64], implicated in activity-dependent localized translation, as well as with putative regulatory factors, e.g. Makorin RING zinc finger protein (MKNR)1 [65], with which it interacts. Furthermore, PABP interacts with dendritically localized regulatory RNAs, e.g. brain cytoplasmic (BC)1 and BC200 RNA [62,66]. Although the contribution of PABP to the regulation of localized mRNAs is not fully understood, several functions can be envisaged; it may maintain mRNA stability or may be targeted to achieve repression (e.g. during transport) and/or facilitate activity-dependent translation [64–68]. Finally, as PABP binds the dendritic-localizer sequence of vasopressin mRNA [69], it is formally possible that it may contribute to mRNA transport.

In migrating cells, mRNAs and components of the translational machinery, including PABP1, localize to the leading edge of lamellipodia [8,70], suggesting motility may involve localized translation (Figure 3G). The interaction of PABP1 with paxillin, a component of focal complexes at lamellipodia, provides a potential explanation for PABP1 localization [21]. Disruption of the paxillin–PABP1 interaction, which results

in nuclear retention of PABP1, reduces cell spreading and migration [21] but the extent to which this reflects mis-regulation of localized mRNAs remains unclear.

Perspectives

PABPs confer the role of the poly(A) tail in regulating mRNA translation and stability, but it appears that it is the mRNA that determines PABP nucleocytoplasmic distribution by mediating its nuclear export and impeding its import. Although data suggest one import pathway and up to three possible export pathways for PABP, further work is needed to understand the interplay of these export pathways. For example, to what extent are the TD-NEM and mRNA-dependent pathways linked; under what circumstances might the CRM-1-dependent paxillin pathway be utilized; and, if multiple pathways are functional, is their relative use regulated or does redundancy ensure residual PABP export under conditions where bulk PABP export is impeded? Our knowledge of the regulation of PABP import is also unlikely to be complete as PABP protein partners may, like mRNA, also compete with importin α, thereby contributing to PABP cytoplasmic retention. Moreover, the relationship between PABP and mRNA localization is less clear for cytoplasmic foci and the sites of localized translation, with the exception of classical SGs. Finally, it remains to be determined whether the post-translational modification status of PABP [71] contributes to either its nucleocytoplasmic or intracytoplasmic distribution, for instance by causing release from RNA and/or other complexes.

Whereas the mechanisms that govern PABP localization are becoming clearer, its functional consequences remain obscure, although roles in mRNA export and SG formation appear ruled out. For instance, why does tPABP reside in CBs; and why do PABPs show dynamic regulated accumulation at different locations? Perhaps the ability to localize to different compartments is linked to the need for different programs of post-transcriptional regulation during cell differentiation, stress or viral infection when PABP presence at, or exclusion from, particular sub-cellular locations may be required. More controversially, perhaps the relocalization of PABPs *per se* is not the target of regulation but is merely a reflection of mRNA localization and turnover. One exception to this 'Devil's advocate's' viewpoint is probably their function at sites of localized translation, although it remains to be determined to what extent they are fulfilling canonical compared with non-canonical roles at these sites. These and other unresolved issues discussed within this review serve to highlight that our knowledge of PABP biology remains surprisingly basic.

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