



When Poly(A) Binding Proteins Meet Viral Infections, Including SARS-CoV-2

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ABSTRACT Viruses have evolved diverse strategies to hijack the cellular gene expression system for their replication. The poly(A) binding proteins (PABPs), a family of critical gene expression factors, are viruses' common targets. PABPs act not only as a translation factor but also as a key factor of mRNA metabolism. During viral infections, the activities of PABPs are manipulated by various viruses, subverting the host translation machinery or evading the cellular antiviral defense mechanism. Viruses harness PABPs by modifying their stability, complex formation with other translation initiation factors, or subcellular localization to promote viral mRNAs translation while shutting off or competing with host protein synthesis. For the past decade, many studies have demonstrated the PABPs' roles during viral infection. This review summarizes a comprehensive perspective of PABPs' roles during viral infection and how viruses evade host antiviral defense through the manipulations of PABPs.

KEYWORDS viral infection, host defense, poly(A)-binding protein (PABP)

Whether DNA or RNA viruses, no known virus encodes all apparatus required to synthesize viral proteins. Viruses compete with the host translational factory to translate their viral mRNAs. This situation inspires viruses to develop strategies to hijack the cellular gene expression system to promote their propagation in host cells. Viruses usually manipulate the translational apparatus by host cell shutoff, inhibiting host protein synthesis for viral replication. Few other viruses finish their propagation in host cells more quietly by shutting down only a small part of the host translational system or facilitating virus replication with ongoing host protein synthesis. Although viruses regulate cellular translation at different molecular levels, the important and early step to interfere with translation is to disrupt translation initiation machinery on polyadenylated mRNAs. The translation machinery contains eukaryotic initiation factors (eIFs), poly(A) binding proteins (PABPs), and other cellular factors (Fig. 1B). eIF4F is a protein complex that binds to the 5' cap of a mature mRNA. The eIF4F complex consists of eIF4E (a small cap-binding protein), eIF4A (a DEAD box RNA helicase), and the central factor eIF4G (a large scaffold protein) (1). eIF4G anchors the 43S pre-initiation complex (consisting of eIF3, eIF1, eIF1A, eIF2-GTP-tRNAiMet, eIF5, and the 40S subunit of the ribosome) to the 5'-end of the mRNA through the interaction with eIF3 (1). PABPs bind to the 3'-end poly(A) tail of mRNA and interact with the eIF4G protein on a 5' cap, thereby stabilizing the structure of mRNA by forming a head-to-tail loop and promoting the recruitment of ribosome subunits for translation initiations (1, 2). PABPs are general viral targets, and the modification of PABP activities allows viruses to

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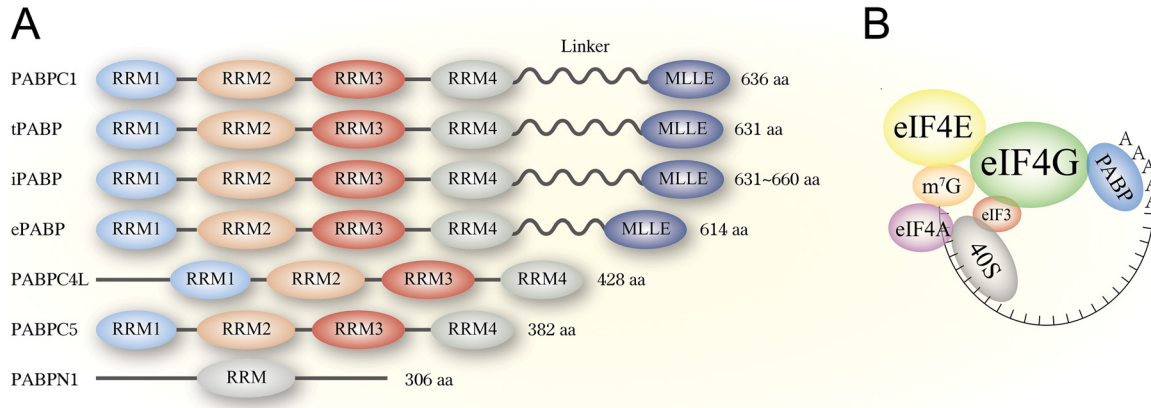


FIG 1 The structure of PABPs and translation initiation complex in uninfected cells. (A) The structure of different human PABPs. PABP comprises N-terminus RRM domains, C-terminus MLE domain, and a proline-rich linker sequence connect these two parts. PABPC5 and PABPN1 do not have MLE and the linker region. (B) The translation initiation complex in uninfected cells. PABPs bind to poly(A) tail eukaryotic cellular mRNA, and they guide 3'-end of mRNA to its 5' cap through interaction with eIF4G. eIF4G is a bridge between the PABP-poly(A) tail and 5' cap, forming a head-to-tail loop and recruiting ribosome 40S subunit for further translation initiations.

hinder the host translation initiations (3). To date, numerous studies have demonstrated that viruses target the translation initiation factor PABPs. Consequently, how viruses subvert PABPs during viral infections needs to be updated despite a review of PABP as a viral target being published more than a decade ago (3).

RNA-binding proteins (RBPs) regulate numerous post-transcriptional processes by binding to intended RNAs (4). A clear-identified and well-conserved group of RBPs is the PABPs subfamily. PABPs are a cluster of proteins that interact with polyadenylated mRNAs in eukaryotic cells. It was first discovered to be bound to the polyadenylated region of eukaryotic messenger RNAs (mRNAs) in the 1970s (5–7). In the early days, PABPs were mainly supposed to protect mRNA stability from deadenylation of the 3'-end poly(A) tail. In addition to its RNA-binding capabilities, PABPs are also critical mediators of gene expression at the level of RNA metabolism (8). Nevertheless, most studies claim the critical role of PABPs in enhancing the cellular translation initiation, which is PABPs binds poly(A) tail to 5' cap of mRNA to facilitate the efficiency of translation initiation or regulates the length of 3' poly(A) tail (PAT) for different translation purposes (8–10).

Moreover, PABPs act as enhancing factors of mRNA translation initiation and as translation factors themselves. They function as scaffold proteins, supporting protein-protein interactions with multiple translation factors, thus promoting translation initiation and regulating gene expression (11). To date, PABPs have been shown to take part in all the metabolic pathways of the mRNA, including mRNA polyadenylation, mRNA deadenylation, mRNA export, mRNA surveillance, mRNA translation and stability, mRNA decay, microRNA-associated regulation, and regulation of expression during development and so on (11–15). These metabolic pathways are good routines for the viruses to utilize in their infection strategies. Targeting PABPs by both DNA and RNA viruses again highlights the role of PABPs as central regulators of gene expression. This review updates an integrative account of the significance of PABP during viral infections.

THE CLASSIFICATION OF PABPS

There are significant differences in PABPs family proteins among different species from yeast to humans. Different species have different numbers of PABP proteins. For example, dicot *Arabidopsis thaliana* contains eight PABPs (16, 17), *Xenopus laevis* contains three PABPs (18–20), and *Mus musculus* contains two PABPs (21, 22). In humans, seven PABPs have been discovered. In irrespective of species, PABPs can be classified according to their distribution in cells. PABPs include cytoplasmic PABPs, nuclear PABP,

embryonic PABP, and the X chromosome-encoded protein. Cytoplasmic PABPs (PABPC) includes PABPC1 (also called PABP1), tPABP (testis-specific PABP, also called PABPC2 or PABPC3), iPABP (inducible PABP, also called PABPC4 or PABP4), and PABPC4L; embryonic PABP is called ePABP or PABPC1L, and X chromosome-encoded protein is named PABPC5; and the nuclear PABP is named PABPN1 (11, 23, 24). Nevertheless, the most well-studied PABPs during viral infections are PABP1. Only PABP1 was reported in virus infections. This review focus on how PABP1 (refer to PABPs in the following text) is manipulated during viral infections.

THE STRUCTURE OF PABPS

Cytoplasmic PABPs bind specifically to the poly(A) tail of eukaryotic mRNAs via its RNA-recognition motifs (RRMs), which have a lower affinity for poly(U) and poly(G), and no detectable binding to poly(C) (25–28). The structures of PABPs are highly conserved, with its N-terminus containing four non-identical RRM, and its C-terminus consisting of a highly conserved carboxy-terminal helical domain named MLLE, previously known as PABC (Fig. 1A) (11, 29, 30). Proline-rich linker sequences connect the four RRM domains to the MLLE domain (31, 32). Despite that the RRM motifs are conserved for RNA recognition, their binding abilities to RNA and proteins appear to be specifically different (27, 28). For instance, RRM 1 and 2 exhibits highly poly(A) binding abilities to eIF4G and PABP-interacting protein 1 (Paip1), while RRM 3 and 4 provide lower binding affinity to poly(A) while binding to AU-rich RNA and mediate protein-protein interactions (25, 33, 34). Multiple genes encoding PABPs are found in metazoans and plant species.

Furthermore, not all PABPs encode four RRM domains. In plants like *A. thaliana*, only two of the eight PABP genes encode proteins containing four RRM domains (17). In plants, such as PABPs in *N. tabacum*, only one of the three expressed PABP genes have four RRM domains (17). In contrast to RRM's roles, the MLLE is not required for RNA recognition but is necessary for interaction with initiation factors through its binding site, such as the release factor eRF3, translation repressor Paip1/Paip2. A 15-residue sequence "PABP interaction motif," termed PAM2, is critical for this process. This oligomerization controls mRNA translation, deadenylation, and regulates PABPs binding ability to poly(A) tail and eIF4G (35–40).

VIRUSES USURP PABP FUNCTIONS FOR VIRAL INFECTIONS

Viruses have long been reported to shut off host protein synthesis, usually disrupting the translation initiation machinery. PABPs are general translation initiation factors targeted by viruses to promote viral propagation and/or thwart cell gene expression during infections. In eukaryotic cells, PABPs bind to the 3'-end poly (A) tail and indirectly bind to the 5'-end cap complex to promote efficient translation initiations (1). However, some viruses do not contain a canonical 5'-end cap and/or 3'-end poly(A) tail. Hence, viruses develop strategies to manipulate PABPs for viral replication and protein synthesis. Depending on distinct structures of viral mRNAs, different RNA viruses and DNA viruses favor different mechanisms to manipulate PABPs. In reported cases, viruses could commandeer PABPs to hinder the efficient host translation initiation through following ways, such as cleavage of PABPs by viral proteases, regulation of eIF4F-PABP translational complex, relocalization of cytoplasmic PABPs into the nucleus, interfering with PABPs containing stress granules (SGs), expressing viral translation factor analogs (3, 8, 41). The genomic structure of RNA viruses containing both canonical 5'-end cap and 3'-end poly(A) tail would prefer to use a cap-dependent translation initiation method to translate their mRNA while simultaneously shutting off the cellular and viral mRNA translation. In this situation, viruses would compensate their translation by distinct means to escape the whole translation shutoff. The more specific mechanism of how viruses escape their shutoff is summarized and discussed in each virus in this review. Coincidentally, DNA viruses transcripts are similar to host mRNAs, using a cap-dependent strategy. The genomic structure of RNA viruses lacking

a 5'-end cap usually bears an internal ribosomal entry site (IRES) in the 5' untranslated region (5'UTR). They utilize cap-independent translation to promote viral mRNA translation and inhibit the host protein synthesis by degrading PABPs or eIF4F complex. When RNA viruses have a genomic structure without a classic poly(A) tail, they usually express PABPs surrogates in enhancing viral mRNA translation initiation by binding to viral 3'-end tail and redistributing the cytoplasmic PABPs into the nucleus. Although there seems to be a rule to follow by deciphering the relationship between the viral mRNA structures and their strategies in usurping PABPs, the underlying mechanisms that each virus subverts PABPs are distinct. In this regard, more studies are warranted to draw a map about how viruses hinder the host PABPs.

Cap-dependent RNA viruses. (i) *Coronaviridae*. The coronavirus (CoV) contains a single-stranded, positive-sense RNA genome, which resembles the structure of most eukaryotic cellular mRNA. CoV genomic RNA contains a cap structure at the 5'-end, a poly(A) tail at the 3'-end, and untranslated regions (UTRs) (42). During CoV infections, knockdown of PABPs could attenuate virus propagations. For instance, transmissible gastroenteritis virus (TEGV) is a member of the *Coronaviridae* family, and it was reported that PABPs play significant roles in virus RNA synthesis, possibly by binding to the TEGV genome through its 3' end poly(A) tail (43). However, a new report showed that in bovine coronavirus (BCoV), it is the viral nucleocapsids (N) protein, not PABPs involving in RNA synthesis by binding to both 5'- and 3'-ends (44). Even though PABP is important for CoV replication (43, 45), it still unclear how PABPs influence virus RNA synthesis during the CoV life cycle.

Moreover, CoV competitively utilized PABPs as translation initiation factors with the host for viral mRNA translation. CoV could decrease the translation of host mRNA by its nucleocapsid (N) protein. For example, BCoV N protein competes with PABP to interact with poly(A) tail and eIF4E to decrease translation initiation efficiency of virus and host both *in vitro* and *in vivo* (46). This finding suggests that CoV can suppress host mRNA translation by competitively inhibiting the interaction between PABP and host mRNAs' poly(A) tails. Even this process could also harm viral mRNAs translation. However, N protein also binds to viral replicase proteins, which might be an important way to rescue the disturbance of viral mRNAs. Once viral replicase protein is synthesized, it associates with N protein and guides the N protein-associated viral mRNAs to the replication complex at the endoplasmic reticulum (ER) to promote viral mRNA synthesis (47). This process may compensate for viral mRNA quantity for later translation events.

A recent study demonstrated that CoV could manipulate PABPs in a different strategy. SARS-unique domain (SUD) is a non-conserved part of non-structural protein 3 (NSP3) shared by SARS-CoV-2 and SARS-CoV (48–50). Brunn et al. showed that SUD promoted PABP-interacting protein 1 (Paip1) and PABPs interactions by binding to 40S/80S ribosome, and Paip1 interacts with the RRM domains of PABPs to stimulate translation, thus increasing both viral and host mRNAs translation efficiency (36, 40, 51–53). However, viruses hinder host translation by specifically degrading host mRNAs and blocking them from binding to the 40S ribosome by viral protein NSP1 (54–56). Consequently, only viral but not host translation is enhanced by SARS-CoV-2 and SARS-CoV SUD (51).

In conclusion, the CoVs either evade cellular shutoff by compensating viral mRNA levels or blocking host mRNA translation by viral protein after stimulating a high activity of the translation system.

(ii) *Arteriviridae*. Porcine reproductive and respiratory syndrome virus (PRRSV) is a single-stranded positive-sense RNA virus containing a 5'-end cap, 3'-end poly(A) tail, and UTRs. Depending on the similar viral mRNA structures, PRRSV and CoV may use similar strategies to manipulate PABPs. However, this hypothesis is not verified as limited studies reported manipulating PABPs in PRRSV. Jiang et al. found that PRRSV N protein was responsible for redistributing cytoplasmic PABPs into the infected nuclei through the interaction with the C-terminal half of PABPs (57). Moreover, knockdown of PABPs significantly influences viral RNA synthesis and virus titers, suggesting that the mRNA translation or replication of PRRSV is closely related to PABPs (57). The

underlying mechanisms of how PRRSV N protein or other viral proteins manipulate PABPs need further investigation.

(iii) *Togaviridae*. The Rubella virus (RV) belongs to the *Rubivirus* genus of the *Togaviridae* family. Its genomic structure is a positive-strand, capped, and polyadenylated RNA. Like other viruses with similar RNA structures, such as PRRSV, RV would redistribute cytoplasmic PABPs into the nucleus (58). This phenomenon is also observed in rotavirus and herpes simplex virus (HSV), which have classic 5'-end cap mRNA. Notably, RV capsid protein binds to the C-terminal region of PABPs and co-localizes it to the perinuclear region of the cell *in vitro* and *in vivo* (58). PABPs levels increased in RV infected cells, but its activity in translation may be blocked, causing the inhibition of translation; however, this situation was alleviated by excess PABPs (58).

Nevertheless, it is still unclear whether the interactions between RV capsid protein and PABPs are associated with viral mRNA translation by restricting PABPs in the nucleus or hijacking PABPs to inhibit cellular protein synthesis. Furthermore, it was suggested that by sequestration of PABPs, the viral capsids could increase the efficiency of viral RNA packaging into capsids instead of viral RNA translation (58). If so, more nucleocapsid formation-related identifications need to be performed to verify this hypothesis (59).

(iv) *Orthomyxoviridae*. Influenza A contains a single-stranded, negative-sense RNA genome. Its genome is both capped and polyadenylated with 5'-UTR. Influenza A encodes a non-structural protein 1 (NS1) that binds to the 5'-UTR region of viral mRNA and functions in viral replication and protein synthesis (60, 61). NS1 also interacts with PABPs and eIF4G on its different binding domains (59). It does not evict PABPs from the eIF4G as relative amounts of eIF4G, and PABPs proteins are co-purified with NS1. NSP1 specifically accelerates PABPs and eIF4G to form a complex with it, and this complex is beneficial for viral translation initiation (62). This mechanism of manipulating PABPs is very different from other positive-sense RNA viruses.

(v) *Rhabdoviridae*. Some viruses induce SGs formation in infected cells, such as the rabies virus (RABV), the typical species of the *Lyssavirus* genus within the *Rhabdoviridae* family (63). The viral genome is a single-stranded, negative-sense RNA consisting of a 5'-end cap and 3'-end poly(A) tail (64). No report shows how RABV manipulates PABPs in a cap-dependent way. However, RABV might exploit PABPs to disrupt the formation of SGs. PABP-specific SGs are among the major distinguishable RNA particles in host cells (41, 65). It is an important component of host antiviral defense. Viral infection exerts pressure on the host cells to induce the formation of SGs (41). However, viruses must face the adverse environment from host immunity and take various strategies to block the formation of SGs and promote its infection and proliferation effectively. RABV mRNAs synthesize in cytoplasmic viral factories, known as Negri bodies (NBs), closely related to SGs (63). This close correlation of viral mRNAs accumulating around SGs reveals material communications between them and may inhibit the antiviral function of SGs (63). Nevertheless, it is unclear how the virus targets PABPs in RABV induced SGs, and the relationship between PABP-specific SGs and viral infections needs further explorations generally.

Cap-independent RNA viruses. (i) *Picornaviridae*. The genera *Enterovirus*, *Rhinovirus*, *Hepatovirus*, *Parechovirus*, *Cardiovirus*, and *Aphthovirus* belong to the *Picornaviridae* family. Picornavirus contains an uncapped and polyadenylated positive-strand RNA genome with UTRs. Lacking the 5'-end cap, they employ an IRES located in the 5'-UTR instead to initiate the translation of viral mRNAs (66). As a 5'-end cap is required in host cellular translation initiation, in this regard, IRES serves as a 5'-end cap-like element in picornavirus mRNA translation initiation. Picornavirus exhibits alternative translation control strategies based on the IRES structure of the viral genome.

RNA viruses of this family have been extensively responsible for PABPs and eIF4G cleavage by the viral proteases, facilitating viral translation by inhibiting cellular mRNA translation (Fig. 2). 3C is a viral cysteine protease that cleaves the proline-rich linker of the PABPs and eIF4G structure (67). The 3C proteases of coxsackievirus (CV), poliovirus (PV), encephalomyocarditis virus (EMCV), and duck hepatitis A virus (DHAV) target

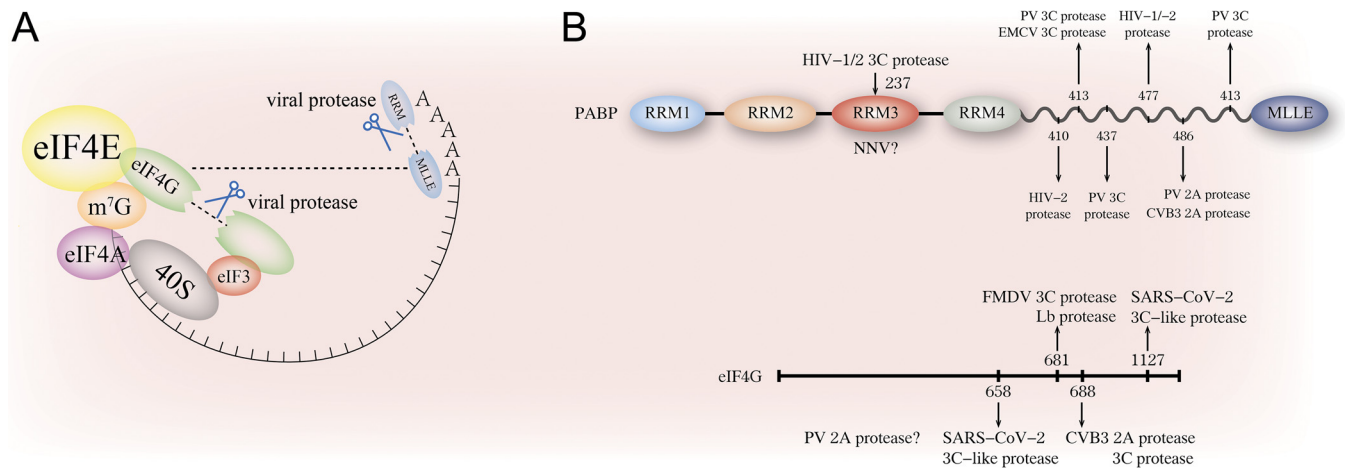


FIG 2 Cleavage of PABPs or eIF4G by viral proteases. (A) Cleavage of PABPs and eIF4G on the translation initiation complex by viral proteases. Viral 2A, 3C, and other viral proteases will cut PABPs from their RRM domains or proline-rich linker sequences when host cells are infected. This cleavage will lose the interaction between PABPs and eIF4G, leading to inhibition of cellular translation. Besides, viral protease (2A/3C/Lb proteases) will cleave eIF4G, separating its N-terminus from C-terminus, thus destabilizing PABPs interactions with poly(A) or disrupting eIF4G interaction with other translation initiation factors. (B) Schematic of the cleavage sites on PABPs and eIF4G by different viral proteases. The cleavage site of PV protease on eIF4G and NNV protease on PABPs is not reported yet. Thus, “?” mark is used to indicate the unreported cleavage site.

PABPs to destabilize PABP-poly(A) association (68–71). These 3C proteases separate the N-terminus of PABPs from its C-terminus by cleaving its flexible linker. Even the recognition sites vary (Fig. 2B). PV 3C cleaves PABPs at Q537/G538, Q437/G438, and Q413/T414, while the cleavage sites on PABPs by EMCV and DHAV 3C are WTAQ437/G438 and Q367/G368, respectively (70, 72, 73). PABPs are also degraded by PV and coxsackievirus B3 (CVB3) 2A proteases between amino acids 486 and 487. Even this cleavage is not as efficient as 3C protease does (67, 70). Moreover, PV 2A protease would cut eIF4G, which evicts the N-terminus of eIF4G from the C-terminus, destabilizes the PABP-eIF4G interaction, and causes impaired cellular translation initiation (74).

Picornaviruses escape from their shutoff through a cap-independent initiation way. PV mRNA is translated using an IRES instead of a 5'-end cap, which does not require intact eIF4G (74–76). Intriguingly, the truncated eIF4G works more efficiently on the viral IRES-driven than the host cap-driven translation (77). PABPs might promote PV mRNA translation without eIF4G as it interacts with other eIFs. Although 3C protease mediates the proteolysis of PABPs, leading to the inhibition of host translation, there are still some uncleaved PABPs. These uncleaved PABPs promote PV mRNAs translation (75, 78), and picornavirus could evade the complete shutoff by utilizing the uncleaved PABPs.

Concerning the cleavage of eIF4G, it is mediated by viral 2A, 3C protease, or other viral proteases. For example, foot-and-mouth disease virus (FMDV) 3C protease and leader (Lb) protease induce the cleavage of eIF4G at C-terminus residue 681/682 (79, 80). CVB3 2A proteases degrade eIF4G at 688/689, and 3C also cleaves eIF4G even with no evidence showing the cleavage site (81). SARS-CoV-2 3C-like protease, also called the main (M) protease or non-structural G protein 5 (NSP5), induces the cleavage of eIF4G at two sites LQ658/GI659 and LQ1127/QA1128, even the role of host cell shutoff behind this cleavage is not elucidated (82).

FMDV Lb protease also cleaves G3BP1 and G3BP2, the scaffold protein in the stress granules (SGs), to disturb the formation of SGs (83). G3BP1 interacts directly with the viral IRES region and negatively regulates viral translation. FMDV 3C protease cleaves G3BP1 at amino acid residue 284/285 to release the IRES site and destroy the G3BP1 role to activate innate immunity (84). Another picornavirus CVB3 3C protease cleave G3BP1 at amino acid residue 325/326, inhibiting SG formation and promoting CVB3 replication (85). In addition, Feline calicivirus (FCV) NS6 protease was reported to cleave G3BP1 to inhibit SG formation (86).

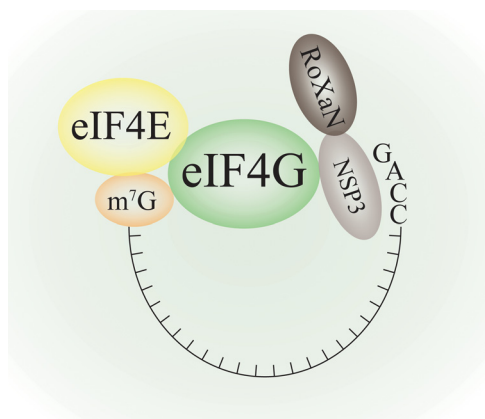


FIG 3 Displacement of PABPs by viral structure protein. In RV infected cells, viral protein NSP3 surrogate PABPs by binding to viral 3'-end tail (GACC tail instead of AAAA tail in RV mRNAs). NSP3 and RoXaN are two RV proteins that bind to eIF4G to promote viral mRNAs translation.

(ii) *Caliciviridae*. The family of *Caliciviridae* consists of *Vesivirus*, *Lagovirus*, *Norovirus*, *Sapovirus*, and *Nebovirus* genera. The genome structure is highly conserved with a positive-sense, single-stranded RNA. However, Calicivirus RNA contains a 3'-end poly(A) tail and short UTRs without a canonical 5'-end cap (87). Calicivirus genome is different but closely related with picornaviruses. Calicivirus does not contain IRES elements. Instead, the 5'-end covalently links with a small virus-encoded protein (VPg), which would interact with the classic translation initiation factors for translation (88). FCV and norovirus (NV) express 3C-like protease because it shares similarity to picornavirus 3C protease in the active site region. Viral 3C-like protease also inhibits cellular translation by the cleavage of PABPs. FCV and norovirus cleave PABPs within the proline-rich linker as well (89).

(iii) *Retroviridae*. Human immunodeficiency virus (HIV) is *Lentivirus* belonging to the *Retroviridae* family. Retrovirus genomic RNAs contain 5'-end cap, 3'-end poly(A) tail, and UTRs regions, resembling host cellular transcripts. HIV mRNA utilizes cap-dependent translation initiation. However, HIV mRNA also contains the IRES region, which uses IRES-dependent translation initiation (90). Retroviruses like HIV, simian immunodeficiency virus (SIV), or Moloney murine leukemia virus (MMLV) contain the IRES region (91–93), which may let the virus take advantage of cap-independent translation, even without intact eIF4G. Like picornavirus or calicivirus, which do not contain a classic 5'-end cap but an IRES part, HIV-1 and HIV-2 encode proteases to degrade eIF4G and PABPs (94). HIV-1 and HIV-2 proteases cleave PABPs at amino acid residue 237/238 and 477/478, while HIV-2 additionally cleaves at 410/411 (95). The reason may be based on the IRES region located in the 5'-UTR. Although these viral IRESs contain diverse sequences, many have similar secondary structures and facilitate translation through similar mechanisms (96).

Overall, these studies demonstrated that cytotytic RNA viruses, including the *Picornaviridae*, *Caliciviridae*, and *Retroviridae*, downregulate host metabolism mostly by drastically degrading cellular translation factors, such as PABPs and eIF4G, while viral translation continues via a cap-independent mechanism, which ensures that the translational machinery stays available only to viral mRNAs.

Non-polyadenylated RNA viruses. (i) *Reoviridae*. Rotavirus is a double-stranded RNA virus belonging to the *Reoviridae* family. The rotavirus mRNAs are capped but not polyadenylated. The rotavirus mRNA structure is quite different from the host mRNA, and the rotavirus uses distinct translation logic from the cap-dependent translation initiation. It is well known that the PABP-eIF4G complex is efficient for the translation initiation of cellular polyadenylated mRNAs, and rotavirus dispatched a viral non-structural protein NSP3 to compete with PABPs from binding to eIF4G (Fig. 3) (97). Consequently, rotavirus utilizes NSP3 to mediate the shutdown of host protein synthesis

by suppressing the translation of cellular mRNAs. Poncet et al. found out that in infected cells, NSP3 is genetically linked to GACC-tailed mRNA, not poly(A)-tailed mRNA, competing with host for efficient translation initiation (98, 99). Notably, the 3'-end of rotavirus mRNA contains a conserved binding site (GACC motif) for NSP3 (99). The homodimerized NSP3 recognizes the specific motif and interacts with eIF4G to enhance viral mRNA translation, thus escaping from the host shutoff (100).

Rotavirus NSP3 usurps PABPs by working as a surrogate of PABPs to evict them from the translation initiation complex and redistributing the cytoplasmic PABPs into the nucleus. This redirect of PABPs requires the interaction of NSP3 with eIF4G and RoXaN (rotavirus X protein associated with NSP3) (101, 102). Another research showed that the nuclear localization of PABPs by NSP3 upon rotavirus infection simultaneously happens with the altered splicing of the stress-related transcription factor XBP1, and the eIF4G-binding domain of NSP3 is required for this process (103). XBP1 is a cellular factor involved in innate immunity and stress response (104). During infections, it could be possible that NSP3 evicts PABPs from eIF4G change the conformation of PABPs or eIF4G, thus exposing the nuclear import signal of cytoplasmic PABPs (103), and PABPs are relocated into the nucleus to interact with XBP1 pre-RNA, causing retention of transcripts. Alter splicing of XBP1 could be a specific host response to rotavirus infection or virus cause nuclear localization of PABPs. Despite that NSP3 displaces PABPs' roles in host protein translation initiation, the function or mechanism of rotavirus NSP3 needs to be elucidated for further understanding.

(ii) Nodaviridae. Nervous necrosis virus (NNV) is classified as the *Betanodavirus* genus of the *Nodaviridae* family. NNV has a positive, single-stranded RNA containing a 5'-end cap but lacks a 3'-end poly(A) tail. It is a pathogen causing viral nervous necrosis disease in marine fish, larvae, and juveniles (105). Chang et al. reported that NNV infections induced host shutoff by degrading host cytoplasmic PABP and translocating it into the nucleus (106). The NNV sequestered PABPs in the infected nucleus via interaction with its coat protein (106). This interaction requires the N-terminal shell domain of NNV coat protein and proline-rich linker region of PABPs (106). This mechanism of host shutoff is also seen with RV (58). Moreover, PABPs were degraded up to the RRM3 domain at a later infection stage through the ubiquitin-proteasome system, distinct from viruses like picornaviruses, calicivirus, or other viruses retrovirus, which carry proteolytic enzymes to degrade PABPs. It is a relatively new mechanism found in manipulating PABPs during viral infection.

Plant RNA viruses. The studies between plant viruses and PABPs are limited. Despite some of the PABPs structures in plant cells may be distinct from human or animal cells, it was targeted by plant viruses to affect efficient translation initiation. In some plant RNA viruses, their viral mRNAs lack both 5'-end cap and/or 3'-end poly(A) tail. Its mRNAs have cap-independent translation enhancer elements (CITEs) located in the 3' UTR, mediating their translation. For instance, in red clover necrotic mosaic virus (RCNMV), A-rich sequence (ARS) and 3'-end CITEs are substitutes for the 3'-end poly(A) tail and the 5'-end cap of eukaryotic mRNAs for translation initiation (107). PABPs bind to ARS in the viral 3' UTR to facilitate translation of uncapped nonpolyadenylated viral mRNAs (107). Some plant viruses use IRES for translation initiation, like the picornavirus or calicivirus. However, unlike many IRES elements, the crucifer-infecting tobamovirus (CrTMV) contains a polypurine tract rather than a pyrimidine-rich tract for PABPs binding activities (108). For example, PABPs interact with the polypurine tract of CrTMV IRES in the presence of poly(A) tail to enhance IRES activity (108). In tobacco etch virus (TEV), PABPs play important roles in the kinetics and stability of eIF4F binding to IRES, thus facilitating viral mRNAs translation initiations (109). VPg of turnip mosaic virus (TuMV) plays an important role in the cap-independent initiation of viral protein synthesis by interacting with PABPs and eIF4B to eIF4F, which resembles what happens in calicivirus (110, 111).

DNA viruses. RNA viruses manipulate PABPs in diverse manners as the structures of viral mRNAs are diverse. DNA viruses have double-stranded DNA, and their viral

transcripts are both capped and polyadenylated; therefore, they are more likely to employ the canonical cap-dependent translation initiation way for their replications.

Poxviridae. *Poxvirus* genera is a large, complex, enveloped virus belonging to the *Poxviridae* family. Unlike herpesviruses, which take advantage of the host DNA and RNA polymerases, poxvirus could replicate in the cytosol as it encodes itself DNA and RNA polymerases. Poxvirus replicates in the cytoplasmic compartments known as DNA factories, containing viral mRNA, RNA-binding proteins, ribosomal proteins, virally transcription factors, and cellular translation initiation factors eIF4E and eIF4G (112). Poxvirus and herpesvirus mRNAs are translated via the classic cellular cap-dependent route. Vaccinia virus (VV), a model of the poxvirus, utilized its viral factors to inactivate the eIF4E binding protein (4E-BP) (113). 4E-BP is a translational repressor that sequesters eIF4E from its association with eIF4G, a core bridge between PABPs and eIF4F complex (114). VV negatively regulate eIF4F to suppress cellular cap-dependent mechanism to translate their mRNAs by destroying 4E-BP (113). Moreover, in VV infected cells, eIF4E, eIF4G, and PABPs are redistributed to the distinct viral replication compartments in the cytoplasm (113). VV hijacks of the host translation apparatus to DNA factories enhance the efficiency of viral replication and thwart cellular protein synthesis.

Herpesviridae. *Herpesviridae* family comprises three subfamilies, including the *Alphaherpesvirinae*, *Betaherpesvirinae*, and *Gammaherpesvirinae*. Alphaherpesvirus and betaherpesvirus are represented by herpes simplex virus 1 (HSV-1) and human cytomegalovirus (HCMV), respectively, whereas Kaposi's sarcoma-associated herpesvirus (KSHV) and Epstein-Barr virus (EBV) are two models of a gammaherpesvirus. HSV-1 and KSHV induce host shutoff gene expression while HCMV does not. Besides this, they develop both similar and distinct mechanisms to ensure efficient viral mRNAs translation initiation.

Alphaherpesvirus. PABPs could shuttle between the cytoplasm and the nucleus under the assist of many viruses even without a typical nuclear export or import signal. For instance, PABPs are associated with HSV-1 ICP27 protein. HSV-1 immediately early gene-encoded protein ICP27 is a nucleo-cytoplasmic shuttling protein involved in transcriptional and posttranscriptional regulation of viral and cellular gene expression (115). Gromeier and colleagues investigated the significance of ICP27-PABP interaction. They reported that in HSV-1 ICP27 alone expressed HeLa cells, PABPs were largely relocated into the nucleus without affecting the expression levels and integrity of PABPs or their associating translation initiation factors (116). Moreover, the interaction of ICP27 and UL47 decreased PABPs interactions to their physiological binding partner eIF4G and Paip2 (116). It is unknown whether the dissociation of eIF4G or Paip2 from PABPs could also result from PABPs redistribution to the nucleus, causing fewer cytoplasmic PABPs ready for efficient translational initiation.

Another group investigated the ICP27-null mutant and discovered that ICP27 does not influence the relocation of PABPs into the nucleus, suggesting that other HSV-1 encoded viral factors may influence PABPs relocation (117). It is argued that redistribution of PABPs into the nucleus was *vhs* dependent (118). Again, more work needs to be done on understanding how HSV-1 manipulates PABPs during infection. Although both ICP27 and UL47 are RNA-binding proteins, abundant nuclear PABPs seem more convenient for interacting with viral mRNA poly(A) tails in the nucleus and facilitating viral mRNAs export from the nuclei. These findings suggest that HSV-1 targets PABPs by changing its subcellular localization and disrupting its binding to the translational initiation complex. Gray and colleagues found that HSV-1 ICP27 also form a complex with PABPs and eIF4G to promote small ribosomal subunit recruitment for viral mRNAs translation purposes independently (119), suggesting PABP-eIF4G interaction is not only targeted for mRNA repression but also activation. Besides, similar to VV, HSV-1 infection also enhances eIF4F assembly by phosphorylation and proteasome-mediated degradation of the 4E-BP, thus negatively regulating eIF4F complex formation (120), which is similar to what happens in VV infected cells. Consequently, viruses may also target PABPs to affect viral or cellular mRNA processing and transport in

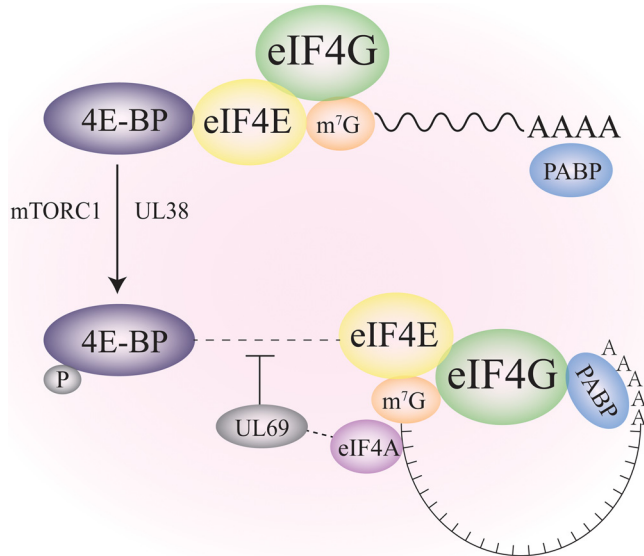


FIG 4 Negative regulation of PABPs by HCMV proteins. 4E-BP, a translation inhibitor binding to eIF4E, regulates cellular translation initiation. HCMV excludes 4E-BP from the translation initiation complex to promote viral mRNA translation. HCMV UL38 disassociates 4E-BP from eIF4E by enhancing its phosphorylation through the mTORC1 signal, thus relieving the inhibition of translation initiations. UL38 also increases PABPs levels in the cytoplasm, assisting viral mRNA translations. HCMV UL69 excludes 4E-BP from cap-binding complex and PABPs by indirectly interacting with eIF4A.

addition to mRNA translation initiation. More viral and cellular factors related to this process await investigations to propose a clear and intact model to decipher how ICP27 or other associated proteins commandeer PABPs or other translation initiation factors during HSV-1 infections.

HSV-2 is another alphaherpesvirus that might utilize PABPs during infections. However, the interaction between PABPs and HSV-2 encoding factors is not clear. Viral protein *vhs* is required to disrupt SGs, but the abundance of PABPs is not changed in SGs of infected cells (121). Whether PABPs or their binding partner were affected by *vhs* or other viral factors is not clear, and future investigations are needed to explore if *vhs* interact with PABPs to disrupt SGs integrity.

Betaherpesvirus. In HSV-1, HCMV, and KSHV-infected cells, viral mRNAs compete with host mRNAs for translation by stimulating the assembly of cellular translation initiation factors eIF4F (122, 123). However, only HCMV increases host eIF4F components (eIF4E, eIF4G, and eIF4A) and cytoplasmic PABPs levels, and this process requires the inactivation of cellular translational repressor 4E-BP (124). HSV-1 and KSHV exclude PABPs from the eIF4F complex by restricting them in the nucleus (116, 125). By contrast, HCMV manipulates PABPs in a cytoplasmic-dependent manner. PABPs in HCMV infected cells aggregate in the cytoplasm and are sensitive to rapamycin complex 1 (mTORC1)-mediated inhibition of 4E-BP phosphorylation (Fig. 4) (124). HCMV UL38 preserves the role of mTORC1 activity to inactivate 4E-BP. mTORC1 kinase mediates the inactivation of 4E-BP, the inactivated 4E-BP resulted in the release of eIF4E, leading to more efficient eIF4E-eIF4G interaction for more efficient translation initiation (122, 126, 127). Finally, the accumulated PABPs in the cytoplasm are ready to bind to eIF4F and promote efficient translation of viral mRNAs. Moreover, UL38 is an HCMV encoded target of mTORC1 activator, which translationally increases PABPs synthesis by regulating terminal oligopyrimidine (TOP) elements found on PABP mRNA 5' UTR (127). The HCMV-induced PABPs accumulation promotes eIF4F assembly, thus increasing host translation initiation factors to foster viral protein synthesis and stimulate virus replication (127). Another HCMV UL69 protein also antagonizes the active state of 4E-BP by a different mechanism. UL69 interacts directly with eIF4A, excluding 4E-BP from the cap-binding complex and PABPs (128). In the meantime, the host is trying to restrict HCMV

by increasing Paip2 levels (129). Paip2 is a gene expression repressor that is tightly regulated with PABPs. Despite the cellular Paip2 functioning as an innate defense to impede virus propagation, HCMV could sufficiently increase PABP levels to overcome its repression caused by Paip2 (129). VV, HSV-1, and HCMV can inactivate 4E-BP to promote the initiation of viral mRNA, even exploiting different mechanisms. Thus, depending on these discoveries, it is still worth studying how other HSV-1 and HCMV proteins manipulate PABPs and propose a working model of different herpesviruses, which might be good antiviral targets for the future.

Gammaherpesvirus. Redistribution of PABPs into the nucleus is, at least in part, a typical method utilized by viruses to induce host shutoff. In KSHV, viral protein K10/10.1 may target PABPs for their redistribution into the infected nuclei, which would mediate host translation defects. However, the importance and mechanism of this interaction are not elucidated due to the unknown function of the K10/10.1 protein in KSHV (130). Additionally, KSHV ORF37 encodes a protein named SOX which strongly induces a host shutoff (131, 132). KSHV SOX was shown to possess both endonuclease and exonuclease activity and facilitates host shutoff by promoting cytoplasmic mRNA degradation, nuclear mRNA hyperadenylation, and their nuclear retention (133–137), causing retaining of host mRNAs in infected nuclei and mediating mRNA export defects (125, 137); The nuclear import signals of PABPs are masked when bind to RNA in the cytoplasm, and SOX is sufficient to mediate nuclear relocalization of PABPs by degrading mRNAs on PABPs, resulting in RNA-free PABPs imported into the nucleus (138).

Moreover, during KSHV lytic infections, an intronless viral long noncoding (lnc) RNA called polyadenylated nuclear (PAN) RNA is transcribed at high levels (139). SOX upregulates the accumulation of PAN RNA in the nucleus further to restrict PABPs in the nucleus (139). These measures taken by SOX are consistent with the host shutoff effect. In addition to that, PAN RNA might promote viral gene expression at the late stage of infections as knockdown of PAN RNA is associated with the reduced amount of virus released into cell culture media (139).

ORF57 induces the translocation of PABPs from the cytoplasm to the nucleus, similar to SOX protein (140). Moreover, KSHV ORF57 is responsible for the stability of viral PAN RNA structures (140, 141). PABPs inhibit PAN RNA accumulation by destabilizing its structure in the absence of ORF57. However, the N-terminus of ORF57 interacts with the RRM of PABPs, colocalizing PABPs with nuclear PAN RNA and alleviating the negative effect of PABPs on PAN (140). As the relocating nuclear PABPs interrupt mRNA nuclear export and cause subsequent hyperventilation, one of the functions of ORF57 is probably to prevent viral RNA from hyperadenylation in the nucleus.

KSHV expressed another protein, ORF10, which directly targeted the nuclear export pathway by interacting with Rae1 (142), a highly conserved eukaryotic cellular export factor to inhibit nuclear mRNA exit. Export of mRNA-ribonucleoprotein (mRNP) complex requires the transit of them through the nucleopore complex (NPC), and Rae1 was involved in mRNA export by interacting with Nup98 at NPC, disrupting Rae1 and Nup98 complex working in nuclear mRNA export (133, 142). EBV and murine gamma-HV 68 (MHV68) encode homologs of KSHV SOX: BGLF5 and muSOX, respectively (143). KSHV SOX roles are mimicked by these two homologs suggesting the universal roles of KSHV SOX and the possible representative mechanism model in gammaherpesviruses (Fig. 5).

Epstein-Barr virus (EBV) encodes an RNA-binding protein EB2 to facilitate translation initiation of viral mRNA through association with PABP-eIF4F (144). EB2 protein is encoded to promote the recruitment of viral mRNAs in the cytoplasm. Most of the viral genes of herpesvirus are intronless, and herpesvirus requires a specific mechanism of mRNA export and translation for efficient expression of their non-intron mRNAs. EBV EB2 can shuttle between the nucleus and the cytoplasm and enhance the nuclear export of intronless viral mRNAs (145). Gruffat et al. provided a model showing how EB2 of EBV facilitates the efficient translation of viral mRNAs (144). They reported that EB2 (Fig. 5) first binds to mRNA's cap-binding complex (CBC) in the nucleus. After the formation of mature mRNAs, mRNPs are transported into the cytoplasm by CBC (144). The mature

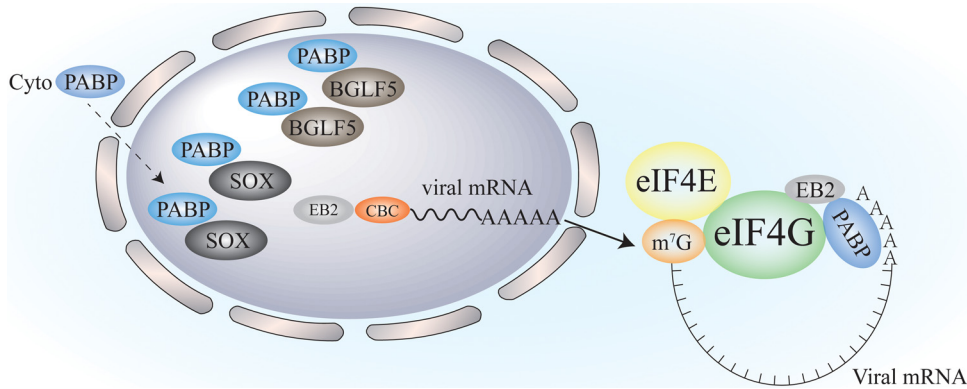


FIG 5 Redistribution of cytoplasmic PABPs into the infected nucleus. In herpesviruses infected cells, viral proteins such as ICP27 and UL47 in HSV-1, SOX in KSHV, and BGLF5 in EBV are required to redistribute of PABPs into the nucleus. This process inhibits cellular translation by decreasing cytoplasmic PABPs. In addition, EBV EB2 protein promotes viral mRNA export from the nucleus and associate with PABP-eIF4F to promote translation initiation of viral mRNAs.

viral mRNAs then interacted with the N-terminus of eIF4G and PABPs to facilitate translation initiation in the cytoplasm (144). HSV-1 ICP27, HCMV UL69, and KSHV ORF57 are homologs of EBV EB2. They play important roles in viral mRNA translation, and their mechanisms are different and not fully explored. For example, KSHV ORF57 proteins recruited a cellular factor PYM to promote viral mRNAs translation, and the interaction between ORF57 and PYM links the 40S subunit of ribosomes and initiation factors (146). ICP27 of HSV-1 and UL69 from HCMV were both claimed to target PABPs and eIF4A/eIF4G to facilitate translation initiation as described above (119, 128, 147, 148). The *Herpesviridae* could relocate PABPs into the nucleus. However, it looks like only gamma-herpesvirus would accelerate host mRNA decay to promote this process. The mechanism models of how the *Herpesviridae* target PABPs await further clarifications.

Summary and future perspectives. The host mRNA translation apparatus has long been recognized as a base to attack during viral infections. PABPs are the number one targets as they play significant roles in translation initiation. Manipulating PABPs would impede host translation efficiency and hijack them to work for viral mRNA synthesis simultaneously. In general, there are a few ways to control PABPs activities.

Firstly, PABPs are cleaved by viral proteases. *Enterovirus* (PV and CV), *Hepatitis virus* (HAV and HCV), *Calicivirus* (FCV and NV), *Lentiviruses* (HIV-1 and HIV-2) encoding proteases mediate proteolysis of PABPs and/or the eIF4G, which directly decrease the translation initiation efficiency. In addition, in PV and CV, PABPs were observed to facilitate viral RNA replication directly via an unknown mechanism. Secondly, PABPs are displaced from the translation initiation complex. For example, rotavirus NSP3 displaces PABPs in the interaction with eIF4G and evicts PABPs to mediate host shutoff. Thirdly, a virus may target PABPs for their presence in virus-induced host SGs via an unclear mechanism. More work is needed to understand how the virus regulates PABPs in SGs. Last but not least, PABPs are redistributed from the cytoplasm into the nucleus to shut off host translation initiation. Different viruses could use different strategies to achieve the same aim. For example, rotavirus and herpesvirus use different mechanisms to restrict PABPs in the nucleus.

Although similar measures are taken to target PABPs, the underlying mechanisms are disparate, and virus replication would be promoted differently (see Table 1). Most investigations on PABPs focus on it as an initiation factor, but it has additional roles in RNA metabolism, such as RNA splicing, RNA decay, and others. Whether these additional ways are served as targets for viral manipulations remains future investigations. Besides, are there more viral and cellular factors involved? More specifically, an overview map of how viruses target PABPs needs to be elucidated. In the meantime, the cytoplasmic PABPs are the most studied at present. Other members of the PABPs family are less explored during viral infections. The specific functions of other PABP family

TABLE 1 Manipulation of PABPs by viruses

Genome	Virus family	Virus	Mechanism
dsDNA	<i>Herpesviridae</i>	HSV-1	Relocalization of PABPs into the nucleus and disrupt PABPs binding to eIF4G and Paip2 by ICP27 and UL47 interaction; promote viral mRNAs translation by ICP27-PABP-eIF4G complex
		HCMV	Increase cytoplasmic PABPs levels and induce their accumulation to promote eIF4F assembly; UL38 and UL69 exclude 4E-BP from the cap-binding complex and PABPs to promote viral mRNAs translation initiation
		KSHV	Induces host shutoff and relocalization of PABPs into the nucleus by SOX; ORF57 and PYM interaction link 40S subunit to facilitate viral mRNAs translation; ORF57 prevent viral RNA from hyperadenylation by interacting with PABPs to stabilize viral PAN RNA
		EBV	BGLF5 redistribute PABPs into the nucleus; EB2 associate with PABP-eIF4F to promote translation initiation of viral mRNAs
(+)ssRNA	<i>Picornaviridae</i>	PV	Cleavage of eIF4G and PABPs by protease 2A and 3C
		CV	Cleavage of PABPs by protease 3C and may increase PABPs levels by manipulating vimentin rearrangements
	<i>Caliciviridae</i>	EMCV	Cleavage of PABPs between Q437 and G438 sites by protease 3C
		FCV	Cleavage of PABPs by 3C-like protease
		NV	Cleavage of PABPs by 3C-like protease
	<i>Togaviridae</i>	RV	Redistribute PABPs into the nucleus
	<i>Flaviviridae</i>	DENV	Recruit PABPs to viral 3'-UTR to activate its translation
		HCV	Cleavage of PABPs by protease 3C
		HAV	Cleavage of PABPs by protease 3C
		DHAV	Cleavage of PABPs between Q367 and G368 sites by protease 3C
	<i>Ateriviridae</i>	PRRSV	N protein recruits PABPs accumulate at perinuclear sites of viral synthesis and sequesters it to inhibit cellular protein synthesis
(-)ssRNA	<i>Coronaviridae</i>	TEGV	PABPs bind to viral genome poly(A) tail to increase virus propagation
		BCoV	Inhibit interaction efficiency between poly(A) and eIF4F by N protein
	<i>Rhabdoviridae</i>	RABV	May modify PABP containing SGs to promote viral replication
dsRNA	<i>Reoviridae</i>	Rotavirus	NSP3 is a surrogate of PABPs that link RV mRNA to eIF4G for efficient translation initiation; redistributing PABPs into the nucleus needs NSP3/RoXaN interaction

members are still vague and need to be further clarified during viral infection. According to the current research results, the roles of PABPs were investigated in cell lines and may vary from case to case. Organoids are recommended to mimic viral infections in actual circumstances to improve the consistency of the virology study and warranty fidelity.

PABPs have roles in RNA metabolism, including cellular mRNA decay, mRNA deadenylation, mRNA export, mRNA surveillance. PABPs may regulate viral mRNAs identified by the innate immune system through pattern recognition receptors (PRRs) (149). How PABPs mediate, viral mRNAs metabolism is unrevealed. It reminds us that viruses may target PABPs to metabolize viral RNAs to escape PRRs arrest, suggesting PABPs' possible roles in innate immunity, an undiscovered and promising area during viral infections.

Although the importance of PABPs during viral infections has been concerned in the last decades, their function in infected cells is not fully addressed in many aspects. With the progress of cell research technology, different views on the roles of PABPs during viral infection and the whole organism may appear. Here, we have outlined and discussed the current knowledge of the PABPs during viral infection and provided information for future study of PABPs.

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