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RNA Biology
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/krnb20

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Published online: 01 Mar 2011.

To cite this article: Zhenghe Li & Peter D. Nagy (2011) Diverse roles of host RNA binding proteins in RNA virus replication, RNA Biology, 8:2, 305-315, DOI: 10.4161/rna.8.2.15391

To link to this article: http://dx.doi.org/10.4161/rna.8.2.15391

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REVIEW

RNA Biology 8:2, 305-315; March/April 2011; © 2011 Landes Bioscience

Diverse roles of host RNA-binding proteins in RNA virus replication

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Key words: Plus-strand RNA virus; replication; virus-host interaction; host factor; RNA-binding proteins; RNA-dependent RNA polymerase; viral replicase complex

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Plus-strand (+)RNA viruses co-opt host RNA-binding proteins (RBPs) to perform many functions during viral replication. A few host RBPs have been identified that affect the recruitment of viral (+)RNAs for replication. Other subverted host RBPs help the assembly of the membrane-bound replicase complexes, regulate the activity of the replicase and control minus- or plus-strand RNA synthesis. Host RBPs also affect the stability of viral RNAs, which have to escape cellular RNA degradation pathways. While many host RBPs seem to have specialized functions, others participate in multiple events during infection. Several conserved RBPs, such as eEF1A, hnRNP proteins and the Lsm 1–7 complex, are co-opted by evolutionarily diverse (+)RNA viruses, underscoring some common themes in virus-host interactions. On the other hand, viruses also hijack unique RBPs, suggesting that (+)RNA viruses could utilize different RBPs to perform similar functions. Moreover, different (+)RNA viruses have adapted distinctive strategies for co-opting unique RBPs. Altogether, a deeper understanding of the functions of the host RBPs subverted for viral replication will help development of novel antiviral strategies and give new insights into host RNA biology.

Introduction

There are several hundreds of different RNA viruses that cause wide spread diseases in plants and animals. Due to the RNA nature of their genomes, these viruses have to utilize many RNA-binding proteins of both viral and host origin, for their replication. Since replication of viral genomic RNA takes place in the cytosol of the infected cells, viruses must be capable of recognizing and amplifying only their own genomes while discriminating against the numerous cellular RNAs present in cells. Overall, the efficiency and specificity of viral RNA genome amplification is quite remarkable since the host itself lacks pre-existing RNA replication machinery and RNA viruses have very limited-coding capacity. Therefore, it is predictable that RNA viruses would co-opt host RNA-binding proteins (RBPs) to facilitate their replication or evade host RNA degradation pathways.

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Submitted: 11/23/10; Revised: 02/28/11; Accepted: 03/07/11
DOI: 10.4161/rna.8.2.15391

The genome of each positive-strand (+)RNA virus codes for an RNA-dependent RNA polymerase (RdRp) that, often together with a few other replication ancillary proteins, provides the core enzymatic activity to amplify the viral RNA genome using the original viral (+)RNA as template. Despite the diverse genome expression strategies, (+)RNA viruses employ a common approach for replication. After entry into host cells, the genome of (+)RNA virus is released from the virion and serves as mRNA exploiting the host translation machinery. Once sufficient amounts of viral RdRp protein and other ancillary replication proteins are synthesized, the viral (+)RNA is rescued from translation into genome replication. Replication produces negative-strand (-)RNA, which, in turn, serves as template for the synthesis of new (+)RNA progeny. In the case of several groups of (+)RNA viruses, replication also leads to the generation of subgenomic (sg) mRNAs. Replication of (+)RNA viruses is an asymmetric process, resulting in a 10- to 100-fold excess of the positive- over negative-strand RNAs. An intriguing feature of virus replication is that the newly made viral (+)RNAs participate in several competing processes, such as new rounds of translation, replication or encapsidation.[1,2] For plant (+)RNA viruses, the new (+)RNA progeny also participate in cell-to-cell movement. It is likely that RBPs play critical roles in determining the localization and selected function of viral (+)RNAs during any given period of infection.

Similar to cellular mRNAs, viral (+)RNAs also contain both protein-coding and untranslated (UTR) regions. Interestingly, the UTRs are usually highly structured and predicted to be involved in long-range interactions, often involving 5' UTR-3' UTR interactions, resulting in genome "circularization". Also, the genomic RNAs of several (+)RNA viruses harbor conserved secondary and tertiary structural elements within their coding regions. Altogether, there are specific RNA structures, called cis-acting elements, within the genomic (+)RNA, which provide diverse functions. These elements include promoters that regulate the site of initiation, polarity and timing of RNA synthesis;[3] enhancers and silencers that control the efficiency of RNA synthesis;[4-8] stabilizing elements that protect viral RNA from degradation;[9] replicase assembly elements that serve as platforms for the assembly process;[10,11] and recognition elements that confer binding specificity to the viral replication machinery.[12-18] Thus, replication of viral RNA is a highly regulated, efficient process that is specified by structural features of

the viral RNA and the dynamic interaction of viral RNA with RBPs leads to the formation of functional ribonucleoprotein (RNP) complexes.

Since the host mRNAs and other cellular RNAs are always associated with RBPs, often forming stable and functional RNP complexes, it is likely that viral (+)RNAs are also bound by viral or host RBPs and not present as "naked" (+)RNAs in infected cells. Many of the host RBPs are conserved, abundant and play essential roles in many aspects of host RNA biogenesis ranging from RNA processing, splicing, posttranscriptional modifications, RNA transport, subcellular localization and translation to RNA decay.[19] The RBPs have diverse functions, including RNA polymerases, RNA chaperones, helicases, specific RNA-binding factors, scaffold proteins or RNA modifying enzymes. Altogether, identification of those host RBPs that affect (+)RNA virus infections is a major area in current virology research as described in the following chapters.

Recent evidence suggests that cellular RBPs likely play essential and regulatory roles in many steps of (+)RNA virus genome amplification.[20-23] The ability of viral RNAs to co-opt host RBPs could determine the efficiency of replication, the permissiveness of certain cell types, the host range of a given virus, the pathology of viral infection and virus evolution. Identification of co-opted host RBPs and elucidation of their functions in viral replication may provide new ways to control viral diseases and advance our understanding of cell biology. This review provides an overview on the currently defined roles of cellular RBPs during (+)RNA virus replication, whereas RBPs involved in other steps of the infection process will not be discussed here.

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Identification of Host RBPs Affecting (+)RNA Virus Replication

Traditionally, host RBPs interacting with the viral RNA were identified using co-purification or pull-down experiments with immobilized viral RNAs, followed by protein determination with mass spectrometry or other methods.[24-28] Several host RBPs have been shown to co-localize with the viral replicase complex (RC), suggesting that they are integral components of viral RCs.[29-36] Recently, high throughput approaches have been developed to identify viral RNA-binding host proteins using yeast protein microarrays carrying thousands of purified recombinant host proteins, as demonstrated for *Brome mosaic virus* (BMV) and *Tomato bushy stunt virus* (TBSV).[37,38] The various screens with the BMV and TBSV RNAs reveal that as many as ~50 host proteins could interact with viral RNAs during infection.

Host RBPs have also been identified in the purified viral replicases. For example, proteomic analysis of the affinity purified tombusvirus RC from yeast led to the identification of several host proteins, including RBPs, such as Tdh2/3 (a yeast homologue of mammalian glyceraldehyde-3-phosphate dehydrogenase, GAPDH) and eukaryotic translation elongation factor 1A (eEF1A).[34] Similarly, the purified replicase complexes from *Tobacco mosaic virus* (TMV) and *Turnip mosaic virus* also contain eEF1A.[39,40]

Another popular approach to identify host genes affecting (+)RNA virus replication is systematic genome-wide approaches using yeast single-gene deletion (YKO) and the essential gene (yTHC) libraries or RNAi screens in Drosophila or mammalian cell cultures.[41-47] These screens have led to the identification of many host RBPs as well. For example, the screens covering ~95% of all yeast genes, have led to the identification of ~130 genes affecting TBSV replication, of which 25 genes are known RBPs.[46,47] To date only a few of these RBPs, such as Nsr1 (nucleolin), Bud21, Npl3 and Xrn1 5'-3' exoribonuclease have been shown to bind to the TBSV RNA.[38,48] Nevertheless, the identified RBPs will be useful in formulating hypotheses that can be tested to determine the specific functions of these host RBPs during (+)RNA virus infections. Overall, the currently characterized host RBPs constitute only a small fraction of those identified in the genome-wide screens, suggesting that many more important RBPs are awaiting to be further characterized to gain deeper insights into the roles of host RBPs in (+)RNA virus replication.

Host RBPs Affect the Process of Viral (+)RNA Recognition and Recruitment for Replication

Replication of (+)RNA viruses can be divided to several sequential steps.[49] Events during the early steps affect the subsequent steps, allowing (+)RNA viruses to regulate the replication process. Replication starts with selective recognition of the cognate (+)RNA genome. The template selection is tightly connected with recruitment of the (+)RNA template and viral replication proteins to the sites of replication, which are specific subcellular membranes in infected cells. Template selection for replication likely involves the switch of the genomic (+)RNA from translation to replication, since the same (+)RNA is used for both processes. Recruitment is followed by the assembly of viral RC, which contains the (+)RNA template, viral replication proteins, subverted host proteins and host membranes. The fully assembled and activated viral RC then will synthesize the complementary (-)RNA, which subsequently serves as a template for the synthesis of new (+)RNA progeny. The newly made (+)RNAs are then released from replication. This cascade of events demonstrates the sophisticated organization of efficiency of (+)RNA virus replication.

RBPs facilitate viral (+)RNA template selection. Viral (+)RNA replication is a selective process since viruses are known to replicate only the cognate or very closely related (+)RNA genomes, but discriminate against heterologous viruses and the abundant cellular RNAs. The current models predict the selectivity of (+)RNA replication is due to specific template selection by dedicated viral replication proteins and less frequently by the viral-coded RdRp proteins, such as protein A for Flock house virus.[50] Accordingly, the partially or fully purified RdRp preparations from virus infected cells often display limited template specificity.[21] The promiscuity of viral RdRp in vitro is in contrast with high selectivity of viral replication in vivo. How viral replicase discriminates its cognate template from numerous cellular RNAs in the infected cells remains an enigma for many viruses. The emerging evidence suggests that viral replication proteins can bind selectively to specific cis-acting elements,

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called viral recognition elements, in the viral (+)RNA genomes. Indeed, mutations of these RNA elements severely impair virus replication as shown for several (+)RNA viruses.[12,13,15-18,51,52] For instance, the auxiliary replication protein p33 of TBSV forms a homodimer or a heterodimer with p92^{pol} RdRp and specifically recognizes a C•C mismatch present within a stem-loop structure located in an internal replication element (RE) within the RdRp coding sequence in the (+)RNA genome. The binding of p33 to RE is absolutely required for selective recruitment of the TBSV (+)RNA into replication.[16,53,54] However, it is highly possible that host RBPs could also contribute to the recruitment of TBSV (+)RNA. Accordingly, eEF1A has been found to bind specifically to the stem-loop 3 (SL3) in the 3' UTR of TBSV,[38] which stimulates the recruitment of (+)RNA template to cellular membranes. Chemical inhibitors of eEF1A, which block eEF1A-RNA binding, inhibits membrane association of TBSV (+)RNA and represses viral RNA synthesis in vitro.[55] For BMV, the helicase-like replication protein 1a mediates the recruitment of genomic RNAs to replication. The recruitment also requires the binding of host deadenylation complex Lsm1-7 to the tRNA-like structure (TLSs) within the 3'-UTR of BMV RNAs.[56,57]

Another degree of replication specificity may be conferred by cis-preferential replication mechanism of viral genome. Studies with several viruses indicate that genome translation and replication are coupled.[58-64] Those genomic RNAs, which undergo translation and produce functional replication proteins, will be preferentially subjected to replication due to binding of the newly made viral replication proteins in cis to the same genomic (+) RNA used for translation. In addition to the viral replication proteins, host factors could also contribute to cis-preferential replication. For example, in the case of poliovirus (PV), it has been suggested that the host poly(rC)-binding protein (PCBP), also known as heterogeneous nuclear ribonuclear protein E (hnRNP E), plays a pivotal role in template selection.[65] PCBP interacts with two RNA structures within the 5'-UTR of PV genome that are important for both translation and replication. The binding of PCBP to stem-loop IV of internal ribosomal entry site (IRES) is essential for cap-independent translation of PV genome (**Fig. 1A**).[65-68] PCBP also interacts with an upstream cloverleaf structure and forms RNP with polymerase precursor 3CD protein to promote initiation of (-)RNA synthesis (**Fig. 1C**).[13,68-70]

The dependence of translation of BMV genomic (+)RNAs, but not sgRNA, on Lsm1-7 complex might also facilitate the selection of legitimate RNA templates for replication versus illegitimate (heterologous or defective) RNAs prior to the 1a-mediated recruitment of viral RNAs into replication.[71] Similarly, Hepatitis C virus (HCV) also utilizes Lsm1-7 complex and polypyrimidine tract-binding protein (PTB) for both translation and replication,[29,72] indicating these cellular factors could be involved in template selection for several (+)RNA viruses.

Intriguingly, not only eukaryotic (+)RNA viruses, but bacteriophage Qβ also takes advantage of host RBPs for its (+)RNA template recruitment. The binding of the Qβ replicase to the viral (+)RNA is mediated via the interactions of ribosomal protein S1 with two internally located recognition elements (S site and M site) within the Qβ genome.[73,74]

Host RBPs inhibiting recruitment of viral (+)RNA templates for replication. (+)RNA viruses are able to hijack cellular RBPs for their genome translation and replication, but the host cell may also utilize an arsenal of RBPs to interfere with viral processes. For example, antiviral effect could be manifested by a host protein via specific binding to the viral (+)RNA followed by RNA degradation or redirecting/sequestering the viral (+)RNA to particular cellular compartments (away from the regular replication sites), preventing the viral (+)RNA from executing its normal functions. This strategy could be especially potent at the early stages of virus infection, when only single or a few copies of viral (+)RNAs are present in the infected cells, possibly leading to a basic resistance mechanism against viruses. Such scenario has been shown for the host nucleolin protein and TBSV. Nucleolin is a nucleolus-localized protein, but it also shuttles between the cytoplasm and the nucleus. It specifically binds to a stem-loop region within the 3'-UTR of TBSV genomic RNA and inhibits TBSV replication when it is present at the beginning, but not at the late stage of virus infection.[48] Deletion of nucleolin binding sites from TBSV genome renders the replication of mutant RNA independent of the presence of nucleolin. Based on in vitro assay using cell-free extract from yeast model host, nucleolin has been found to inhibit TBSV replication likely by interfering with the recruitment of the viral (+)RNA for replication.[48] Similarly, Arabidopsis NTR1 protein with three hnRNP K-homology (KH) RNA-binding domains has been shown to specifically bind to both 5'- and 3'-UTR of *Tomato mosaic virus* (ToMV) genome and to inhibit ToMV multiplication. BTR1 inhibits the translation of a reporter mRNA harboring a ToMV BTR1-binding site, suggesting that it may inhibit ToMV replication at the early stage of infection that might include (+)RNA recruitment.[75]

The Roles of Host RBPs during the Switch from Translation to Replication

Upon infection of cells by (+)RNA viruses, the viral genomic (+) RNA serves as template for both translation and genome replication, albeit the two essential processes are in conflict with each other as they utilize the same (+)RNA template but proceed in opposite directions. Indeed, when ribosome-bound bacteriophage Qβ RNA is used as template for replication, the Qβ replicase is not able to complete the (-)RNA synthesis efficiently.[2] Similarly, translating ribosome also inhibits PV RNA synthesis.[76] Treatment of cell-free translation and replication-compatible lysate with puromycin after translation, which induces dissociation of translating ribosome from mRNA, stimulates genome replication. On the other hand, additional translation inhibitors such as cycloheximide, which "freeze" the ribosome on mRNA, have inhibitory effect on viral RNA synthesis highlighting the necessity of clearance of ribosome from viral (+)RNA prior to replication.[1] Therefore, (+)RNA viruses need to temporally coordinate these two processes to allow sufficient production of viral proteins before switching to replication. Such translation-replication balance has also been shown to be important for efficient amplification of Qβ in an in vitro reconstituted system.[77] In addition, viral genomic (+)RNAs need to avoid degradation by

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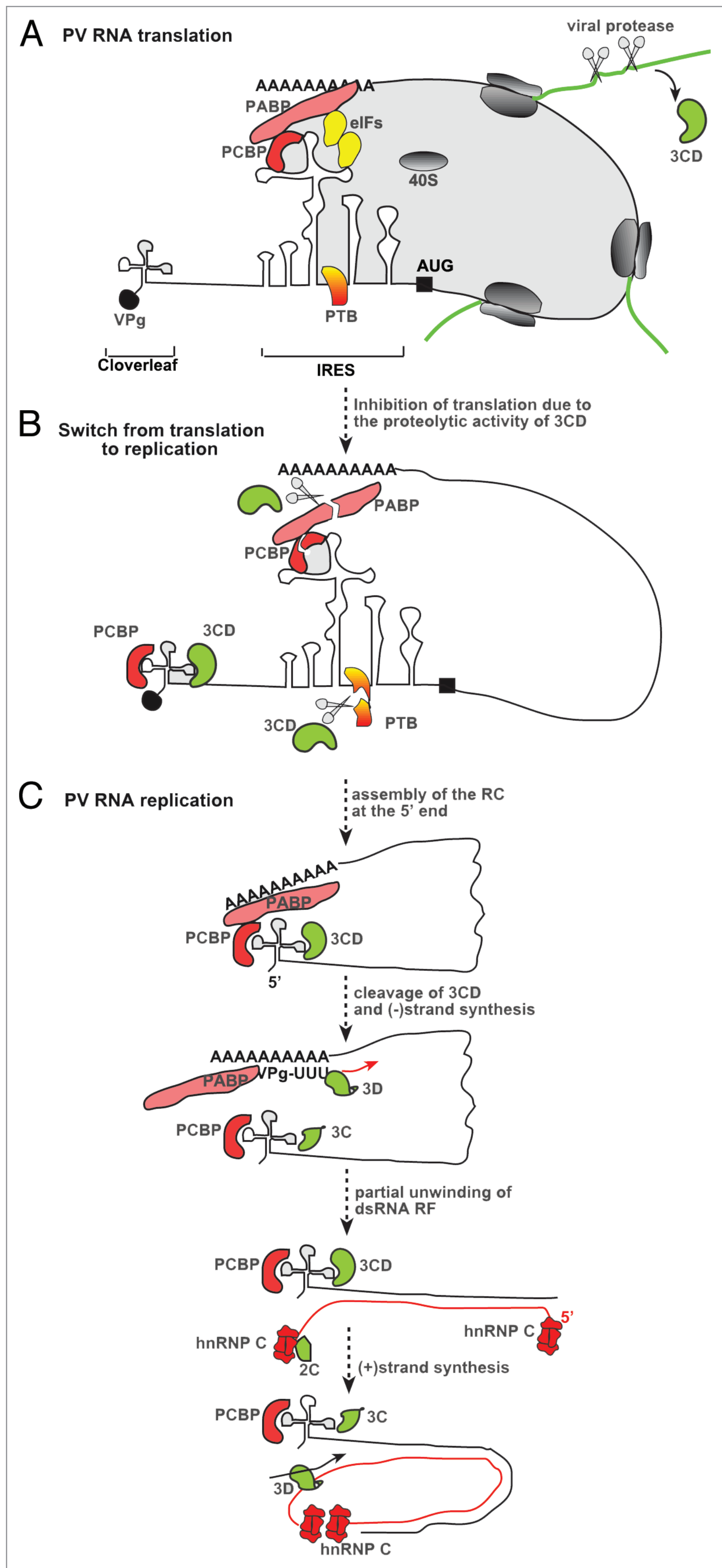

Figure 1. A model of the roles of host RBPs in PV replication. (A) The roles of host RBPs in PV translation. The binding of host RBPs to stem-loop IV of internal ribosomal entry site (IRES, shown as stem-loop structures) is essential for cap-independent translation of PV genome. (B) The roles of host RBPs in a switch by the PV RNA from translation to replication. The dual roles of PCBP2 in PV translation and replication place PCBP2 in an ideal position to mediate the switch from translation to replication. The viral 3CD likely serves as a "sensor" to measure viral protein translation, while PCBP2 acts as a "molecular switch". The involvement of PCBP2 in PV replication is facilitated by the proteolytic cleavage of PCBP2 by the viral protease 3C/3CD during the mid-to-late phase of infection. (C) The roles of host RBPs in PV RNA replication. PCBP interacts with the 5' cloverleaf structure and forms RNP with polymerase precursor 3CD protein to promote initiation of (-)RNA synthesis. The replication initiation complex formed at 5'-UTR, which contains the viral $3D^{pol}$ RdRp (either activated via a cleavage of the 3CD precursor to yield the matured $3D^{pol}$ or via direct recruitment of $3D^{pol}$), is brought to 3'-end by genome circularization via interaction of PCBP with PABP bound to the poly(A)-sequence in the 3'-UTR. hnRNP C has been proposed to maintain the single-stranded form of the 3'-end of PV (-) RNA via its RNA chaperone activity, and then, recruit viral 3CD replication protein to form an initiation complex for (+)RNA synthesis. Since hnRNP C interacts with both termini of PV (-)RNA, hnRNP oligomerization could bring the 5'- and 3'-end sequences into proximity, thus facilitating initiation of (+)RNA synthesis. The detailed functions of the RBPs and viral factors are described in the text.

mRNA decay pathways after translation in order to be recruited to subsequent replication.

Increasing evidence shows that some viral replication proteins facilitate repression of translation and switch to viral RNA synthesis.[2,78-81] Host RBPs also play important roles in regulation of this event through their interactions with various cis-elements in the viral (+)RNA. Indeed, interaction of PV 3CD protein with stem-loop D of the cloverleaf structure at the 5' end of PV (+)RNA greatly increases the binding affinity of PCBP2 to stem-loop B, resulting in repositioning of PCBP2 from the translation element (IRES) to the replication element (i.e., the cloverleaf structure).[65] These events lead to inhibition of translation and promotion of RNA synthesis[65,76] (**Fig. 1B**). The dual roles of PCBP2 in PV translation and replication place PCBP2 in an ideal position to mediate the switch from translation to replication. It appears that viral 3CD serves as a "sensor" to measure viral protein translation, while PCBP2 acts as a "molecular switch". The involvement of PCBP2 in PV replication is facilitated by the proteolytic cleavage of PCBP2 by the viral protease 3C/3CD during the mid-to-late phase of infection.[82] While the full-length PCBP2 with three RNA-binding (KH) domains binds selectively to the stem-loop IV of IRES,[83] the proteolytic cleavage within a linker sequence between KH2 and KH3 renders the

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truncated PCBP2 protein (which lacks the KH3 domain) unable to bind to IRES. This leads to inhibition of PV translation.[82] Interestingly, the truncated form of PCBP2 still maintains the activity to rescue PV (+)RNA replication in a PCBP2-depleted extract. This led the authors to propose an elegant model for translation-replication switch based on viral protease-mediated cleavage of PCBP2 (**Fig. 1B**).

Apart from PCBP2, other cellular factors, such as polypyrimidine tract-binding protein (PTB), poly(A)-binding protein (PABP) and lupus autoantigen (La), are also required for efficient PV IRES-dependent translation.[84] It is conceivable that proteolytic cleavage of these factors may also contribute to inhibition of PV translation and the switch to (+)RNA replication.[85,86] Overall, it appears that the combination of mechanisms may act in concert to trigger the switch from translation to PV RNA replication (**Fig. 1B**).

Studies with BMV and yeast model host revealed that the mRNA decapping activation complex Lsm1-7 and Pat1, Dhh1 might participate in facilitating the switch from translation of the BMV RNAs to viral replication. The purified Lsm1-7 complex binds to the tRNA-like structure (TLS) within the 3' UTR and intergenic region (IR) of BMV RNA3.[87] Lsm 1–7-dependent RNA3 translation and replication require TLS and substitution of TLS with poly(A) tail was found to circumvent the requirement of Lsm1-7 in translation of BMV RNA3 and its recruitment into replication. Efficient Lsm1-7-mediated translation also required specific RNA structures in the IR, whose deletion resulted in strong inhibition of RNA3 translation, while increased the recruitment of RNA3 into replication.[87] The interaction of BMV RNA3 with Lsm1-7 might lead to clearance of translation initiation factors as described for cellular mRNAs with shortened poly(A) tail.[88,89] Then, the formed mRNP complex is recruited to processing body (P-body),[88,89] where the P-body components might facilitate replicase assembly by concentrating viral RNAs and replication protein in discrete compartment without the competition of translating polyribosome. Remarkably, the human homolog of yeast Lsm1-7 and Pat1, Dhh1 complex is also important for HCV translation and RNA accumulation.[72,90] The reconstituted Lsm1-7 heptameric ring-shape complex specifically binds to HCV 5'- and 3'-UTR which contains important cis-element for translation and replication.[72]

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For bovine viral diarrhea virus (BVDV),[91] and HCV,[92] host RPBs NF90/NFAR have been shown to circularize the genome through interactions with both 5'- and 3'-UTRs and the interaction appears to inhibit translation but promote RNA replication.[93] It seems that the circular conformation of the viral genome is different during translation and replication. Thus, the switch from translation to replication could be mediated by viral replication proteins and host RPBs via architectural remodeling of the viral genomic RNA.

RBPs and Viral RNA Synthesis

Regulation of the assembly of the viral RC. It is becoming evident that the assembly of functional viral RCs is a highly regulated process, which involves complex interactions among viral (+)RNA, the viral replication proteins and co-opted host proteins and lipids. The viral genomic (+)RNA can serve as a platform for the assembly of the viral RC. For example, purified preparations of TBSV p33/p92^{pol}, BMV 1a/2a^{pol} and *Alfalfa mosaic virus* (AlMV) P1/P2 are nonfunctional in vitro when purified from yeast or plant cells in which these replication proteins are expressed in the absence of cognate viral RNAs.[94-97] In contrast, when the above viral proteins are co-expressed with the cognate (+)RNAs, then the obtained viral replicases become active and are able to utilize added RNA templates in vitro. To explain the replicase "activation" phenomenon, it has been suggested that the complexes of these replication proteins must be assembled via the help of the viral RNAs that likely serve as "assembly platforms". Detailed works defined that only short regions within the viral (+) RNAs are required for the assembly/activation of the BMV and TBSV RdRps.[10,11] Although the mechanism of viral RdRp activation by (+)RNA template has not yet been determined, it is possible that the presence of viral (+)RNA may trigger conformation changes in the viral RdRps. Alternatively, viral RNA could be essential for recruitment of cellular RBPs to form functional viral RC. Indeed, the roles of host RBPs in replicase assembly and function has been documented for Qβ bacteriophage (**Fig. 2A**). In addition to virus-encoded polymerase β-subunit, functional Qβ replicase holoenzyme also contains three host translation factors: ribosomal protein S1 and elongation factors Tu (EF-Tu) and EF-Ts. β-subunit is the catalytic core of the replicase and the interaction of β-subunit with EF-Tu and EF-Ts is essential to maintain its polymerization activity (**Fig. 2A**).[98] The replicase binding to the (+)RNA template is mediated by S1, which recognizes two internal sites (M and S site), while EF-Tu is involved in binding to the (-)RNA template.[74] Crystal structure of β subunit in complex with EF-Tu and EF-Ts shows that the co-opted translation elongation factors have chaperone-like function to maintain the folding of the active β-subunit. EF-Tu:Ts may also regulate RNA folding and contribute to separation of RNA duplex formed between the template and nascent strands.[99,100] An additional Qβ host factor, known as Hfq, is recruited by binding to 3'-end of Qβ genome and is required for (-)RNA synthesis[101] (**Fig. 2A**).

Notably, several host proteins have been shown to interact with both viral proteins and the viral RNA. For example, hnRNP A1 interacts with HCV NS5b and both ends of the genomic (+) RNA,[102] while hnRNP C binds to PV (+)RNA and 3CD replication protein.[103,104] Also, eEF1A binds to viral replication proteins and viral (+)RNAs of several viruses, such as West Nile virus (WNV),[105,106] TBSV[54,55] and TMV.[107,108] Proteome-wide screens also revealed significant overlap of cellular factors that bind to TBSV (+)RNA and replication proteins.[54,109] These data suggest that viruses may utilize multiple molecular functions of subverted host factors to regulate RNA synthesis in the tightly organized viral replication compartments.

Regulation of negative-strand RNA synthesis by host RPBs. During viral RNA replication, (-)RNA synthesis initiates from the 3'-terminal promoter sequence present in the viral (+)RNA.[110] Unexpectedly, many viral RdRps bind to 5' or internal sites in the (+)RNA genome, suggesting that additional factors could facilitate the re-positioning of the RdRp over the 3' terminal promoter

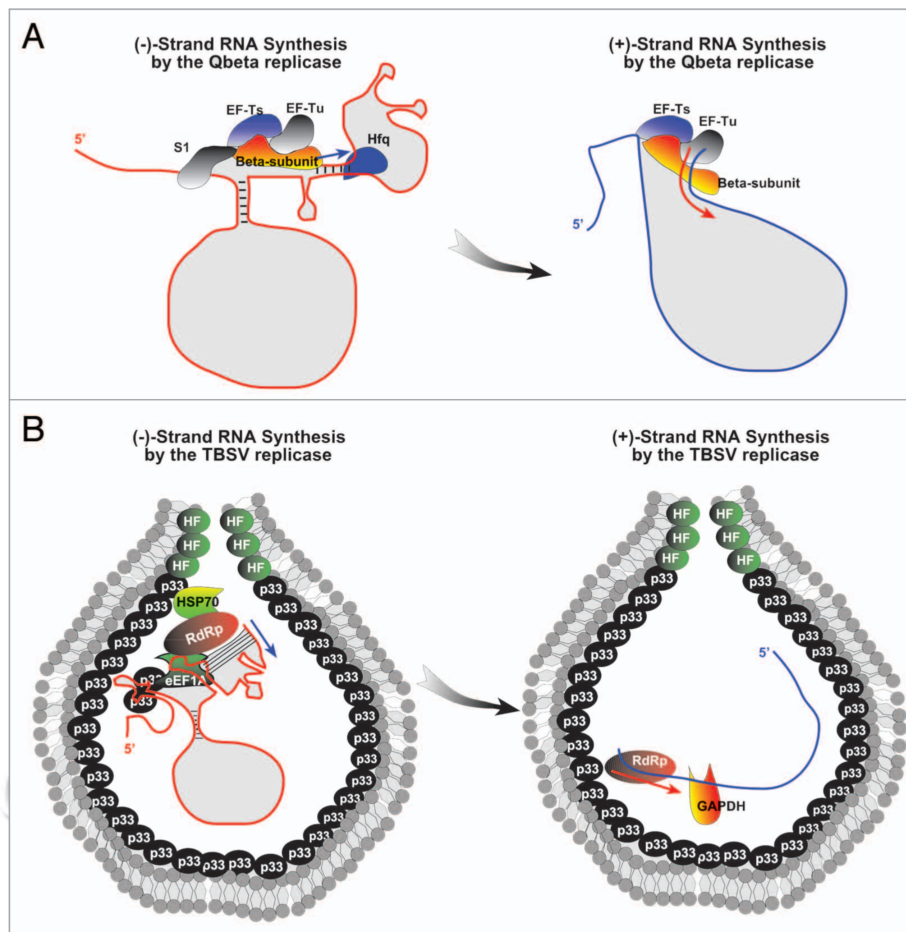

Figure 2. Comparison of the co-opted host factors for Qbeta bacteriophage and TBSV replication. (A) The long-range interactions between regions in the Qbeta (+)RNA genome are depicted by multiple lines. The detailed functions of the RBPs and viral factors are described in the text. (B) The long-range base-pairing in the TBSV (+)RNA genome brings recruitment element bound by p33 into the vicinity of the 3'-UTR, which also has base-pairing between the silencer element and the 3' end as depicted by multiple lines. The shown RBPs facilitate TBSV RNA synthesis as described in the text.

sequence prior to initiation.[15,16,73,111] Accordingly, increasing amounts of evidence suggest that long-distance interactions within the (+)RNA genome mediated either by protein-RNA or RNA-RNA interactions could bring the 5' terminal or internal cis-elements into proximity of the 3'-terminal sequences in the genomic RNA. For example, Qβ replicase is thought to bind to an internal recognition site (M site), which is about 1,450 nt away from the 3'-end of the genome.[111] A long-range RNA-RNA base-pairing that forms between the loop of the 3' terminal hairpin and a 1,200 nt upstream sequences serves to bring the Qβ replicase in close proximity to the 3'-terminus prior to initiation.[112,113] Similarly, in the case of TBSV, a long-distance base-pairing between internal replication protein binding site and 3'-UTR is essential for (-)RNA synthesis and replicase assembly.[114] Genome cyclization of Dengue virus (DENV) is mediated via long-distance RNA-RNA interaction of complementary sequences in the 5'- and 3'-UTR, including the cyclization sequences (CS) and upstream AUG region (UAR), which is required for genome replication.[115-117] Also, a kissing-loop interaction between a sequence within the HCV NS5b coding region and the 3'-UTR is essential for HCV replication and is proposed to facilitate the coordination of the viral polymerase to the very 3'-end of the viral genome.[118] The above-mentioned long-distance RNA-RNA interaction has been observed in the absence of protein, however, it is possible that host RBPs may facilitate or stabilize these RNA structures.

The cloverleaf structure in the 5'-UTR of PV (+)RNA serves as a platform for formation of the essential RNP complex consisting of PV 3CD replication protein and the co-opted PCBP (**Fig. 1C**).[119] Then, the replication initiation complex formed at 5'-UTR, which contains the viral $3D^{pol}$ RdRp (activated via a cleavage of the 3CD precursor to yield the matured $3D^{pol}$) is brought to 3'-end by genome circularization via interaction of PCBP with PABP bound to the poly(A)-sequence in the 3'-UTR (**Fig. 1C**).[120] In the case of mouse hepatitis coronavirus (MHV), communication between the viral UTRs is facilitated by interactions between the PTB protein bound to 5'-UTR and hnRNP A1, which is bound to 3'-UTR of the viral genome. Mutations that impair binding of host factors to the UTRs inhibit replication and transcription of a MHV RNA, confirming the significance of host RPBs in coronavirus replication.[121]

eEF1A is one of the most common RBPs that has been identified in association with 3'-UTR of a wide variety of (+)

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RNA viruses.[54,105-107,122] Mutation analysis of eEF1A-binding sites within the 3'-UTR of WNV revealed correlation between eEF1A binding and (-)RNA synthesis. eEF1A also interacts with WNV NS5 protein and is co-localized with the WNV RC in the infected cells, suggesting that it facilitates the interaction between the viral replicase and the 3'-UTR of the viral gRNA.[105] Similarly, eEF1A has been shown to interact with TBSV replication proteins and 3'-UTR of viral RNA and is an integral component of the viral RC (**Fig. 2B**).[54] A set of mutants of eEF1A was found to enhance TBSV RNA replication in yeast and increase (-)RNA synthesis in a cell-free TBSV replicase assay. Moreover, eEF1A was shown to stimulate initiation of (-)RNA synthesis in vitro by a closely related recombinant viral RdRp, suggesting a direct role of eEF1A in (+)RNA virus replication.[55] This function of eEF1A could be facilitated by binding of eEF1A to a regulatory RNA element, termed replication silencer, which base-pairs with the extreme 3'-terminus of the viral RNA and downregulates (-)RNA synthesis in vitro.[123] The binding of eEF1A to p92^{pol},[38] might facilitate the proper positioning of the viral RdRp over the 3'-promoter to enhance the initiation events (**Fig. 2B**).[55] Similar to TBSV replication silencer-promoter base-pairing, the 3'-terminal sequence of Qβ (+)RNA also forms a pseudoknot structure with an adjacent sequence that buries the promoter. Opening up this structured sequence prior to initiation of RNA synthesis is likely due to the Hfq host factor, an Sm-like protein, which forms hexameric complexes and harbors RNA chaperone activity. Hfq is required for efficient synthesis of Qβ (-)RNA both in vivo and in vitro.[98] However, Qβ RNAs carrying mutations at the 3'-terminus, which disrupt the pseudoknot formation, are able to replicate independent of Hfq, suggesting that the RNA chaperone function of Hfq is to "unmask" the 3'-end and facilitate the access of the replicase to the 3'-terminus of the genome during replication[101] (**Fig. 2A**). Another similarity between tombusvirus and Qβ RNA replication is the interaction of eEF1A with tombusviruses replication proteins p33 and p92 RdRp, which leads to stabilization of p33 and stimulation of tombusvirus replicase activity,[54,55] reminiscent of the functions described for EF-Tu:Ts in Qβ RC[99,100] (**Fig. 2A and B**).

Regulation of plus-strand RNA synthesis by RBPs. Similar to (-)RNA synthesis, initiation of (+)RNA synthesis is likely facilitated by co-opted host RBPs. Brunner and co-workers identified the cellular hnRNP C, which binds specifically to the 3'-end of the PV (-)RNA (**Fig. 1C**).[103,124] hnRNP C, which is redistributed to the cytoplasm from nucleus upon PV infection, also interacts with the PV 3CD precursor protein. It has been suggested that hnRNP C functions to maintain the single-stranded form of the 3'-end of PV (-)RNA via its RNA chaperone activity and then, recruit viral 3CD replication protein to form an initiation complex for (+)RNA synthesis.[103] Accordingly, depletion of hnRNP C from a PV replication-competent Hela extract inhibited (+) RNA synthesis, which could be rescued by addition of wt recombinant hnRNP C protein, but not by a truncated form deficient in binding to 3CD. Since hnRNP C interacts with both termini of PV (-)RNA, hnRNP oligomerization could bring the 5'- and 3'-end sequences into proximity, thus facilitating initiation of (+) RNA synthesis (**Fig. 1C**).[104]

For WNV, the 3'-terminal 96 nt of (-)RNA containing a conserved stem-loop structure is proposed to function as promoter for (+)RNA synthesis.[125] Interestingly, the stress granule proteins, termed the T-cell intracellular antigen-1 (TIA-1) and the TIA-1-related protein (TIAR) bind specifically to the 3'-SL of WNV (-)RNA.[126] Mutations in 3'-SL, which reduce TIA1/TIAR binding, greatly decreases genomic RNA amplification, suggesting that specific binding of TIA1/TIAR facilitates efficient (+)RNA synthesis.[127]

In addition to the host RBPs, which bind to (-)RNA, those RBPs that bind to the 5'-terminus of (+)RNA might also affect (+) RNA synthesis. For example, the 5'-terminal cloverleaf structure present in PV (+)RNA is also required for initiation of (+)RNA synthesis, in addition to its established role as a promoter for (-) RNA synthesis.[68-70] By duplication of the 5'-terminal cloverleaf structure, which allows the separation of its potential functions in initiation of RNA synthesis of both polarities, Dorothee and Andino have shown that, it is the cloverleaf structure formed in the (+)RNA, not the corresponding one in the (-)RNA, that is required for initiation of new (+)RNA synthesis. The binding of PCBP and 3CD to cloverleaf of (+)RNA is also required for (+)RNA synthesis. These findings led the authors to propose a trans-initiation model for PV (+)RNA synthesis, in which the PCBP and 3CD first bind to cloverleaf in (+)RNA to form an RNP complex that functions to keep the 3'-end of (-)RNA single stranded (by preventing the base-pairing of the 5'-end of the (+)RNA with the complementary minus-strand sequence) and facilitate the delivery of 3D polymerase to the (-)RNA template in trans (**Fig. 1C**).[128]

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Regulation of asymmetrical RNA synthesis by host RPBs. A characteristic feature of (+)RNA viruses is the asymmetric nature of viral RNA synthesis, which leads to 10:1 to 100:1 ratio of (+) versus (-)RNA progeny. The asymmetric replication could be attributed to differences in intrinsic promoter strength, as well as the presence of various regulatory RNA elements that function to enhance or repress RNA synthesis. Host RBP factors are also likely involved in regulating this process by interacting with viral replication proteins and cis-acting RNA elements. Indeed, the ratio of Qβ (+) versus (-)RNA is determined by the concentration of the co-opted hfq in vitro. In the presence of abundant amount of Hfq protein, equal quantities of (+) and (-)RNA is synthesized, while limiting amount of Hfq protein results in excess of (+) versus (-)RNA.[98]

The mechanism of asymmetric replication for eukaryotic (+) RNA viruses might be different from that of Qβ bacteriophage, since replication of eukaryotic RNA viruses is associated with virus-induced membrane invaginations that are derived from subcellular membrane surfaces in the infected host cells. Since the (+)RNA progeny must be released from the membrane-bound replicase to the cytoplasm, while (-)RNA remains inside the replication compartment,[129] this step could also serve to regulate (+) versus (-)RNA levels. The mechanism underlying the asymmetric replication and release of (+)RNA progeny is largely unknown. An abundant metabolic enzyme GAPDH, which is recruited into the tombusvirus RC,[34] has been shown to regulate asymmetrical TBSV RNA synthesis (**Fig. 2B**).[35] Interestingly, depletion of

GAPDH preferentially inhibits the accumulation of (+)RNA, resulting in a 1:1 ratio of RNA progeny of both polarities in yeast and in a natural plant host. It has been shown that GAPDH selectively binds to an AU pentamer sequence (AUUUA) present in the vicinity of the 3'-terminus of TBSV (-)RNA. Deletion of the AUUUA sequence also led to the production of (+) versus (-)RNA RNAs in a 1:1 ratio, even in the presence of wild-type levels of GAPDH. Based on these data, it has been proposed that GAPDH binds to and retains TBSV (-)RNA for multiple rounds of (+)RNA synthesis inside of the spherules containing the membrane-bound tombusviral RC (**Fig. 2B**). The (+)RNA progeny, which are not bound by GAPDH, then become released from the RC into the cytosol.[35] It is also possible that GAPDH could play a direct role in (+)RNA synthesis, similar to that proposed for hnRNP C during PV replication.

Regulation of subgenomic RNA synthesis by host RPBs. Many (+)RNA viruses with multiple open reading frames (ORFs) in the genomic (+)RNA express the 3' proximal ORFs through the production of sgRNAs.[130] The synthesis of sgRNAs is coordinated by cis- or trans-acting transcription elements.[130-132] The viral replicase, possibly together with host factors, is involved in recognition of subgenomic promoter(s), followed by initiation and termination of transcription. For example, sgRNA transcription in coronaviruses requires the interaction between 5'-terminal leader sequence and an intergenic (IG) sequence immediately upstream of the initiating AUG of each ORF.[133] In an attempt to identify host RBPs regulating MHV sgRNA transcription, Li et al. has found that one of the host proteins, hnRNP A1, specifically binds to the leader and IG sequences in MHV (-) RNA.[134] Interestingly, the binding affinity of IG to hnRNP A1 correlates with the efficiency of MHV sgRNA transcription.[134,135] Overexpression of wt hnRNP A1 has been shown to stimulate MHV RNA synthesis, while expression of dominant-negative mutant of hnRNP A1 inhibited replication.[136] In vitro experiments indicate that the interaction of hnRNP A1 with the leader and IG sequences is essential for sgRNA transcription.[137] Furthermore, hnRNP A1 also interacts with MHV N protein,[138] suggesting that hnRNP A1 could recruit the viral N protein to MHV transcription sites. Another host protein implicated in regulating MHV sgRNA transcription is PTB (hnRNP I). PTB specifically interacts with positive-strand leader sequence, as well as with the 5'-UTR in (-)RNA. Deletion of PTB-binding sites in MHV defective interfering RNA significantly inhibits sgRNA transcription, with less effect on (-)RNA synthesis.[139,140]

Another host RPB implicated in viral sgRNA synthesis is hnRNP-K, a predominantly nuclear poly(C)-binding protein. Hardy and colleagues have found that hnRNP-K co-immunoprecipitates with the Sindbis virus (SINV) nsP1, nsP2 and nsP3 proteins. Moreover, hnRNP-K is redirected to viral RC in infected cells. hnRNP K is also co-precipitated with the SINV sgRNA, but not with the gRNA, suggesting that it could participate in sgRNA transcription.[141]

The production of noncoding sgRNAs with regulatory roles also requires host RBPs, namely Xrn1 5'-3' exoribonuclease, as shown for Yellow fever virus and other flaviviruses.[142,143] Interestingly, the host Xrn1 also affects tombusviral RNA recombination and RNA stability.[144]

Host RBPs and Stability of Viral RNA

Viruses must interact with cellular factors or pathways to maintain the integrity of viral RNAs and to suppress RNA degradation pathways. Relevant for this review is the role of host RBPs in stabilizing the viral RNAs. For example, HuR, which is a regulator of cellular mRNA stability, binds specifically to the U-rich element (URE) in the 3' UTR of SINV and Venezuelan equine encephalitis virus (VEEV). The binding of the SINV RNA to HuR redirects the otherwise nuclear-localized HuR to cytoplasm upon SINV infection.[9] Downregulation of HuR expression leads to accelerated decay of SINV mRNA and reduced virus production, indicating that HuR inhibits deadenylation-mediated degradation of SINV RNA through its binding to URE.[145] Similarly, the 3' UTR of the MHV coronavirus binds to the mitochondrial aconitase, a metabolic enzyme involved in citric acid cycle, which likely increases the stability and hence increases translation of viral proteins.[146]

Other viruses whose genomes lack either 5'-cap or 3'-poly(A), or both, may recruit host RBPs through various RNA elements to stabilize their genomes. The genome of PV contains a 5' cloverleaf structure, which binds to PCBP that stabilizes PV (+)RNA in HeLa S10 extract. A mutant PCBP protein, which cannot bind to the cloverleaf structure, causes an accelerated degradation of PV (+)RNA. The interaction of PCBP with the PV (+)RNA likely blocks the Xrn1 5'-to-3' exonuclease-mediated RNA decay, since in vitro capped PV (+)RNA could bypass the requirement of PCBP in stability assays.[147]

The 3'-UTR of HCV contains a number of stem-loop structures and a large U-rich tract, which interact with the La autoantigen to prevent HCV degradation in HeLa S100 extract.[148] HuR is also showed to bind to the U-rich tract in the 3'-UTR of HCV[149] and knock-down of HuR expression by siRNA has been shown to inhibit HCV IRES-mediated translation and replicon RNA replication.[150] However, the relevance of HuR in relation to HCV (+)RNA stability is not yet clear. Proteomics analysis have led to the identification of more than 70 human proteins associated with the HCV 3'-UTR and several of the identified host RPBs, such as hnRNP C and D, HuR, FBP, FBP2, YB-1 and NF90, have been implicated in controlling cellular mRNA stability.[151] It will be interesting to find out if these host RPBs indeed participate in protection of the labile HCV (+)RNA from degradation.

The tRNA-like structure (TLS) in the 3' end of turnip yellow mosaic virus (TYMV) becomes aminoacylated and interacts with host tRNA-binding proteins, such as eEF1A, which protects the viral RNA from RNase A digestion in vitro.[152] Overall, how efficiently viruses can circumvent the viral RNA degradation may determine the outcome of infections. The above mentioned examples highlight the notion that the stability of viral RNA play an important role in successful infection and different viruses may evolve different mechanisms to protect their genomes, which likely involves subverted host RBPs.

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Conclusion and Future Perspectives

Over the past 10 years, a great deal of knowledge has been accumulated on the host RBPs co-opted for viral (+)RNA replication. It is becoming evident that multiple steps in (+)RNA virus replication require coordination of (+)RNA elements viral factors and host-encoded RBPs. Indeed, recent genome- and proteome-wide screens have identified several hundred host factors affecting (+)RNA replication and 10–20% of these factors are RBPs.[37,38,45,96,109] However, the functions of most of these RBPs in virus replication have yet to be determined.

The remarkable magnitude and diversity of host RBPs subverted for (+)RNA virus replication highlights that RBPs are major players determining virus-cell interactions. Several conserved RBPs, such as eEF1A, hnRNP proteins and Lsm 1–7 complex, have been identified in association with evolutionarily diverse (+)RNA viruses, underlying some common themes in virus-host interactions. However, there are unique RBPs identified as well, suggesting that either (+)RNA viruses could utilize different RBPs to perform similar functions or different (+)RNA viruses adapted unique strategies by co-opting specialized RBPs.

Due to the interdependent and sequential nature of many processes during (+)RNA virus infection, for instance, translation, replicase assembly, negative- and positive-strand RNA synthesis, pinpointing the exact step in which host RPBs are involved remains challenging. Therefore, the use of tractable model replication systems, such as TBSV, BMV and FHV in yeast, together with the fast-maturing RNAi technology, as well as structural and cell biology approaches, should facilitate rapid advance in our understanding of the roles of RPBs in (+)RNA virus replication. Knowledge of the functions of the subverted host RBPs in virus replication may not only lead to the development of novel antiviral strategies, but also facilitate our understanding of host RNA biology.

Acknowledgements

The authors thank Drs. Daniel Barajas, Tyng-Shyan Huang, Kunj Pathak and Judit Pogany for valuable comments. This work was supported by the National Science Foundation (IOB-0517218) and NIH-NIAID to P.D.N.

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