

Minding the message: tactics controlling RNA decay, modification, and translation in virus-infected cells

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With their categorical requirement for host ribosomes to translate mRNA, viruses provide a wealth of genetically tractable models to investigate how gene expression is remodeled post-transcriptionally by infection-triggered biological stress. By co-opting and subverting cellular pathways that control mRNA decay, modification, and translation, the global landscape of post-transcriptional processes is swiftly reshaped by virus-encoded factors. Concurrent host cell-intrinsic countermeasures likewise conscript post-transcriptional strategies to mobilize critical innate immune defenses. Here we review strategies and mechanisms that control mRNA decay, modification, and translation in animal virus-infected cells. Besides settling infection outcomes, post-transcriptional gene regulation in virus-infected cells epitomizes fundamental physiological stress responses in health and disease.

Responses to environmental and physiological stress demand swift, coordinated remodeling of the genome-wide expression landscape. Such abrupt adaptation provoked by stimuli that upset homeostasis is often controlled post-transcriptionally by mRNA decay and translation. As a powerful, genetically tractable model, virus infection provides a window to interrogate how mammalian cells react to biological stress and identify how virus gene products shape host cell responses by accentuating or subverting them. Indeed, virus-encoded effectors interact with cellular targets to regulate virus and host gene expression post-transcriptionally and determine infection outcomes. Virus mRNAs are absolutely reliant on host ribosomes and compete for them with cellular mRNAs. Similarly, differential mRNA accumulation regulated in part by RNA modification and decay is exploited by viruses to complete their reproductive cycle and by

host immune defenses to limit virus replication. Besides revealing fundamental mechanisms regulating gene expression and infection biology, viruses provide insight into human disease. Here, we review molecular interactions between select animal viruses and their hosts that regulate mRNA decay, modification, and translation, highlighting developments pertaining to genome-wide changes and stress responses.

Synopsis of virus genome structure and reproductive strategies

Viruses are obligate intracellular parasites unable to reproduce outside of host cells. Within eukaryotic hosts, viruses replicate in the cell cytoplasm or nucleus. Not all infections cause clinical disease, and outcomes vary depending on host, cell type, and immune status. Although acute infection results in virus reproduction and often host cell destruction, persistent infections exhibiting chronic or episodic virus production may endure over the host's lifetime. Viruses are classified by genome structure and replication strategies, each of which influences how viral mRNAs engage and impact cellular post-transcriptional regulatory pathways.

Composed of single- or double-stranded (ds) DNA or RNA, virus genome structures and sizes are diverse, ranging from ≤ 10 kb for small RNA or DNA viruses to >200 kb for the largest human DNA viruses. Still bigger megabase genomes exist for DNA viruses that infect *Acanthamoeba* (Schulz et al. 2017). RNA virus genomes are composed of single or multiple nucleic acid segments. Even large genomes maximize coding capacity by using proteases to generate multiple polypeptides from one single ORF, overlapping ORFs, and frameshifting (Atkins et al. 2016; Jan et al. 2016; Penn et al. 2020). Virus genome structure impacts mRNA biogenesis. Single-strand RNA viruses

[Keywords: RNA decay; RNA modification; animal viruses; infection stress; translational control]

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Article is online at <http://www.genesdev.org/cgi/doi/10.1101/gad.349276.121>.

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with genome polarity identical to that of mRNA [(+)-strand RNA viruses], with the exception of retrovirus virion RNA inside incoming virus particles, are translated upon infection, whereas those with opposite polarity [(−)-strand RNA viruses] or dsRNA genomes require a virus-encoded RNA-dependent RNA polymerase (RdRp) to produce mRNA. Following reverse transcription of their (+)-strand RNA genome and chromosomal integration, retrovirus mRNA biogenesis requires the host RNA polymerase II (RNAPII) and associated processing factors. While nuclear-replicating DNA viruses also rely on host mRNA biogenesis and processing factors, poxviruses such as vaccinia virus (VacV) replicate in the cytoplasm and encode viral functions for transcription, capping, and 3′ end processing.

While mRNA biogenesis and genome replication strategies vary, virus reproduction and protein synthesis are contingent on host ribosomes. Viruses may interfere with host protein synthesis by diverse mechanisms, ranging from near-global inhibition called host shutoff, which often involves destabilizing host mRNAs or inactivating translation factors, to triaging which host mRNAs are translated. Besides fostering virus mRNA translation, host shutoff restricts antiviral immune responses including interferon (IFN) production, which antagonizes virus reproduction and spread. Host antiviral effectors, many of which are induced by IFN, similarly target RNA stability and protein synthesis to suppress virus replication. Accordingly, post-transcriptional control of host cell-intrinsic immune defenses and virus reproduction is often achieved by regulating mRNA translation, modification, and decay.

Shaping the infected cell mRNA landscape

Evading, co-opting, or supplementing the host RNA decay machinery with viral factors remodels infected cell mRNA composition. Deadenylation-dependent decay is the canonical mechanism for bulk mRNA turnover whereby the stabilizing 3′-terminal poly(A) tail of most cellular mRNAs is degraded by deadenylase complexes CCR4–NOT and PAN2/3 (Heck and Wilusz 2018). Once shortened to preclude binding of cytoplasmic poly(A)-binding protein (PABP), an RNA-decapping complex is recruited, comprised of enzyme Dcp2, Dcp1, and decapping enhancer proteins (Fig. 1A). Upon protective m⁷G cap removal, the cellular 5′–3′ exonuclease Xrn1 degrades mRNAs bearing an exposed 5′ monophosphate (Fig. 1A). Alternatively, the RNA exosome complex can degrade deadenylated RNAs 3′–5′. Deadenylase recruitment by sequence-dependent binding of discrete RNA-binding proteins (RNA-BPs), such as the AU-rich element (ARE) BP tristetraprolin (TTP) or microRNAs, targets specific mRNAs for decay. Conversely, RNA-BPs that impede decay promoting factor binding stabilize specific mRNAs (Fukao and Fujiwara 2017).

Antiviral roles for mRNA decay and viral defensive lines

To evade the host RNA decay machinery, virus RNAs contain structures that impede degradation and sequenc-

es that recruit stabilizing RNA-BPs (Fig. 1A). Viruses also manipulate stabilizing and destabilizing host factor availability. Most viral RNAs possess a 5′ m⁷G cap and poly(A) tail akin to cellular mRNAs or features that protect them from exonucleases. m⁷G caps are added to RNAPII transcribed viral mRNAs by the cellular capping machinery in the nucleus (most DNA viruses and retroviruses), adjoined by viral capping enzymes (poxviridae and many RNA viruses), or acquired by excising a short 5′-terminal fragment from host mRNAs (“cap snatching”) that in turn primes virus RdRp-directed transcription (orthomyxoviridae [e.g., influenza], arenaviridae, and bunyaviridae [e.g., Lassa fever virus]). Alternatively, a viral protein (VPg) covalently attached to (+)-sense virus genomes (caliciviridae and picornaviridae) can protect the RNA 5′ end (Decroly and Canard 2017). Unusually, two copies of liver-specific cellular microRNA miR-122 bind to a 5′ sequence in the (+)-sense hepatitis C virus (HCV) RNA genome, blocking Xrn1-mediated decay and promoting translation (Henke et al. 2008; Li et al. 2013). HCV replication further requires DEAD-box RNA helicase eIF4A2, which interacts with the virus replicon in a miR122-dependent manner and is critical for gene regulation by microRNAs (Ahmed et al. 2018; Wilczynska et al. 2019).

Distinct tactics preserve poly(A) 3′ tails, which are added by the nuclear host machinery (most DNA viruses), by viral poly(A) polymerases (poxviridae), or by transcription of a poly(U) template (e.g., paramyxoviridae, rhabdoviridae, and orthomyxoviridae). Viral poly(A) tail stability may be enhanced by non-A nucleotide incorporation to slow deadenylation, so-called “mixed tailing,” promoted by virus-encoded sequences (Fig. 1A; Hyrina et al. 2019; Kim et al. 2020). Following recognition of stem-loops in hepatitis B virus (HBV) RNAs and human cytomegalovirus (HCMV) noncoding (nc) RNAs by the cellular RNA-BP ZCCHC14, recruitment of TENT4 noncanonical poly(A) polymerases allows non-A nucleotide incorporation (often Gs) into viral poly(A) tails (Kim et al. 2020). HCMV also up-regulates cytoplasmic polyadenylation machinery, extending virus and cellular mRNA poly(A) tails (Batra et al. 2016). While flaviviridae, bunyaviridae, and arenaviridae encode a 3′-terminal stem-loop to block exonucleases, an RNA 3′-terminal sequence bound by rotavirus protein NSP3 (Fig. 1A) stimulates translation and likely protects from exosome action (Brinton et al. 1986; Meyer and Southern 1993; Deo et al. 2002; Geerts-Dimitriadou et al. 2012; Gratia et al. 2015).

To disrupt RNA decay, viruses obstruct host factor function using structured RNA and/or by perturbing their localization (Fig. 1A). Proteases encoded by porcine reproductive and respiratory syndrome virus (PRRSV), poliovirus (PV), and coronavirus (CoV) cleave decapping activator Dcp1a (Dougherty et al. 2011; Tao et al. 2018; Zhu et al. 2020). PV also induces degradation of deadenylase PAN3 and exonuclease Xrn1 and disrupts processing bodies (P-bodies), cytoplasmic sites enriched for RNA decay proteins (Dougherty et al. 2011). During rotavirus infection, Nsp1 degrades PAN3, both Xrn1 and Dcp1a are relocalized from the cytoplasm to nucleus (Bhowmick

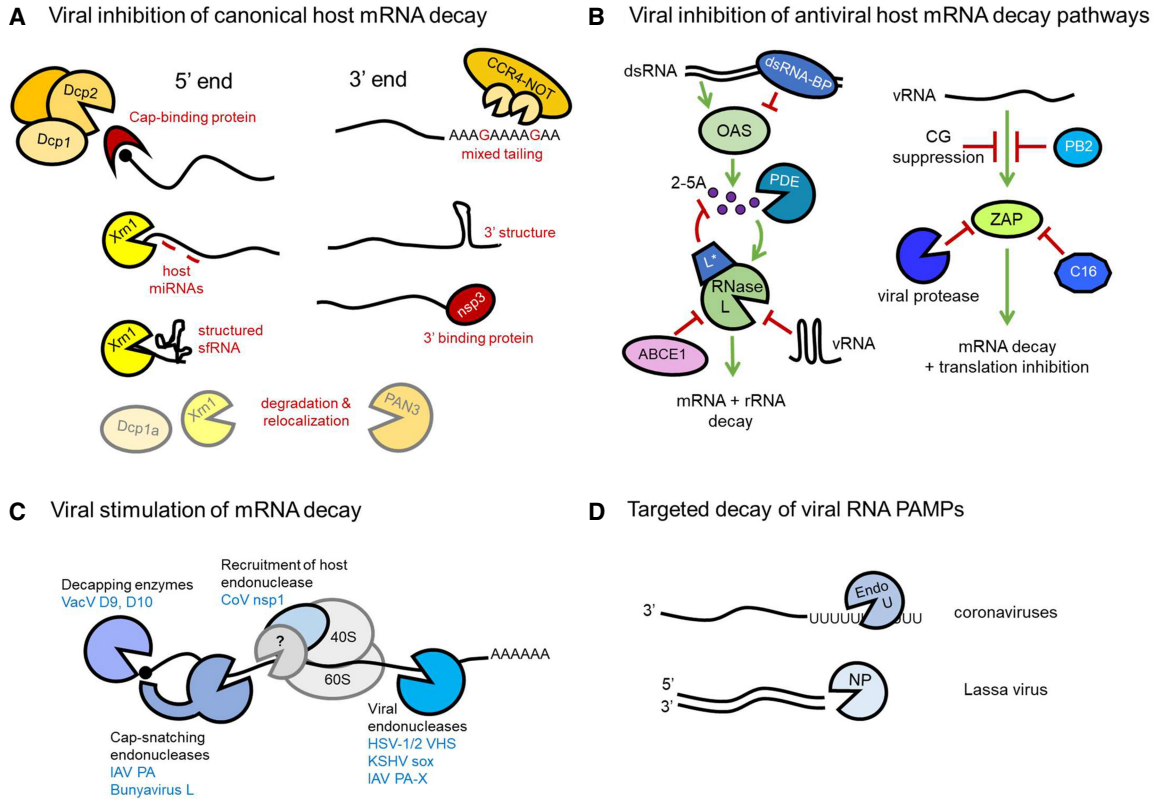


Figure 1. Viral strategies to oppose and promote mRNA decay. (A) Inhibition of cellular proteins that effect 5'–3' mRNA decay can be achieved by protection from decapping by cap binding proteins (VPg) and obstruction of the exonuclease Xrn1 by miRNAs and RNA structure (sfRNA). 3' end decay is similarly opposed by recruitment of viral proteins and formation of RNA structure, and “mixed tailing” can also inhibit poly(A) tail deadenylation by CCR4–NOT. Both 5' and 3' targeting cellular mRNA decay proteins may be degraded or relocalized during infection. (B) Viruses inhibit OAS/RNase L and ZAP antiviral cellular RNA decay pathways using diverse strategies. Recognition of dsRNA by OAS is blocked by viral dsRNA-BPs. Viral phosphodiesterases (PDEs) degrade second messenger 2-5A. RNase L activation can also be blocked by viral proteins, up-regulated cellular negative regulator ABCE1, or viral RNA structures. ZAP recognition of virus (vRNA) is evaded by CG suppression, viral ZAP-binding proteins, and ZAP cleavage by virus proteases. (C) Viral proteins stimulate mRNA decay via multiple modalities. They can contain direct enzymatic activity such as mRNA decapping and endonucleolytic cleavage, which may be cap-proximal. In contrast, coronavirus nsp1 binds the 40S ribosome and, although no direct nucleolytic activity has been identified, effects mRNA cleavage in infected cells, leading to speculation that it recruits a host decay enzyme. (D) Viral RNA PAMPs are directly controlled by viral dsRNA-specific exonucleases or U-specific endonucleases that, by limiting the potential for 5' (–)-strand poly(U) sequences to complex with A-rich sequences, prevent dsRNA formation.

et al. 2015), and additional host decay proteins are relocalized to cytoplasmic inclusions (Dhillon and Rao 2018; Dhillon et al. 2018). Similarly, adenovirus (Ad) relocalizes decay proteins including Xrn1 to cytoplasmic aggresomes (Greer et al. 2011). Degrading or sequestering these host mRNA decay effectors is expected to slow viral and cellular RNA turnover in infected cells, but has not been fully examined. In a different approach, a structured 3' UTR in flavivirus (+)-sense RNA genomes limits complete 5'–3' digestion by Xrn1 (Pijlman et al. 2008). Short, noncoding subgenomic flavivirus RNAs (sfRNAs) accumulate as a result (Silva et al. 2010; Chapman et al. 2014a,b), functionally sequestering XRN1, as demonstrated by global host mRNA stabilization in HCV-infected cells (Moon et al. 2015). While expected to extend flavivirus RNA genome longevity, how host mRNA dysregulation contributes to infection pathogenesis remains unknown.

Host mRNA quality control pathways that ensure transcripts bearing mutations or processing errors and spurious transcripts are destroyed also dispose of viral RNAs. RNA viruses with sequentially arranged ORFs are subject to nonsense-mediated decay (NMD), which targets transcripts that have a long distance between a stop codon and the poly(A) tail, and can restrict virus replication (Popp et al. 2020; May and Simon 2021). With long 3' UTR-containing RNAs vulnerable to NMD, retroviral RNA elements in Moloney murine leukemia virus (MMLV) and Rous sarcoma virus prevent NMD machinery detection and cleavage, respectively (Weil and Beemon 2006; Hogg and Goff 2010). The cellular helicase UPF1, which is required for NMD target recognition (Rao et al. 2019), is down-regulated by human immunodeficiency virus 1 (HIV-1) and inhibited by human T-lymphotropic virus type 1 (HTLV-1) protein tax (Mocquet et al. 2012; Nakano et al. 2013). Zika virus (ZIKV), Semliki forest virus

(SFV), and CoV capsid proteins also interact with UPF1 and can antagonize NMD (Fontaine et al. 2018; Wada et al. 2018; Gordon et al. 2020; Contu et al. 2021).

Multiple antiviral host RNA decay pathways are encoded by IFN-stimulated genes (ISGs). Oligo adenylate synthetases (OASs) 1, 2, and 3 bind and are activated by dsRNA, a pathogen-associated molecular pattern (PAMP) generated by RNA virus replication or from complementary transcripts of opposing DNA virus genome strands. Activated OAS produces 2'-5' oligo adenylate (2-5A), which stimulates latent RNase L (Fig. 1B), an endoribonuclease that broadly attacks mRNA and rRNA to inhibit translation and promote apoptosis. Viral countermeasures (Fig. 1B) include shielding dsRNA from OAS detection by deploying dsRNA-BPs such as herpes simplex virus 1 (HSV-1) Us11 (Sánchez and Mohr 2007), HCMV TRS1 and IRS1 (Marshall et al. 2009), VacV E3L (Chang et al. 1992), influenza virus A (IAV) NS1 (Min and Krug 2006), and reovirus $\sigma 3$ (Imani and Jacobs 1988). Downstream from OAS activation, CoV and rotavirus phosphodiesterases cleave 2-5A to prevent RNase L activation (Zhao et al. 2012; Zhang et al. 2013; Thornbrough et al. 2016; Goldstein et al. 2017), while Theiler's murine encephalomyelitis virus L* protein inhibits RNase L activation by blocking 2-5A binding (Sorgeloos et al. 2013; Drappier et al. 2018), and PV RNA elements competitively inhibit RNase L (Han et al. 2007; Townsend et al. 2008). In contrast, EMCV and HIV up-regulate ABCE1 (Martinand et al. 1998, 1999), a host RNase L BP that prevents activation by 2-5A (Bisbal et al. 1995), turning an endogenous RNase L regulator against the host.

Zinc finger antiviral protein (ZAP) is an ISG-encoded RNA-BP with a preference for GC-rich sequences and thus functions to detect "nonself" RNA (Takata et al. 2017). ZAP activity has been ascribed to translational inhibition and RNA decay in RNA virus infections, the latter linked to RNA exosome recruitment (Guo et al. 2007) and the host endonuclease KHNYN (Ficarelli et al. 2019). CG dinucleotide suppression in HIV-1 and HCMV genomes, mimicking mammalian DNA genomes, is a tactic to resist ZAP (Fig. 1B; Takata et al. 2017; Lin et al. 2020; Gonzalez-Perez et al. 2021). Whereas IAV protein PB2 inhibits RNA binding by ZAP (Tang et al. 2017), ZAP is cleaved by PRRSV and enterovirus A71 (EV-A71) proteases (Xie et al. 2018; Zhao et al. 2020) and sequestered by VacV protein C16 (Peng et al. 2020). ZAP is expressed as long (L) and short (S) isoforms, both of which contain RNA recognition motifs but differ in intracellular localization and RNA targeting (Schwerk et al. 2019; Kmiec et al. 2021). ZAP-S also binds to the SARS-CoV-2 programmed ribosomal frameshifting (PRF) RNA element to inhibit PRF, which is essential for RdRp and nonstructural protein production (Zimmer et al. 2021).

Last, ISG20 possesses 3'-5' exoribonuclease activity in vitro (Nguyen et al. 2001) and suppresses RNA virus replication (Espert et al. 2003; Zhou et al. 2011). Antiviral action in vivo, however, relies more on ISG20 inhibiting viral mRNA translation and modulating ISG expression than RNA decay (Weiss et al. 2018; Wu et al. 2019).

Proviral roles for mRNA decay—viruses on the offensive

To ensure translational dominance, some virus mRNAs rely on their sheer abundance compared with host mRNAs, rather than specific *cis*-elements or *trans* factors, to competitively acquire ribosomes (Bercovich-Kinori et al. 2016; Finkel et al. 2021). By encoding endoribonucleases that accelerate RNA decay (Fig. 1C), Kaposi's sarcoma-associated herpesvirus (KSHV) and HSV reduce infected cell mRNA abundance (Glaunsinger and Ganem 2004; Pheasant et al. 2018; Friedel et al. 2021). Broad targeting of host and viral mRNAs is observed, the latter facilitating sharp temporal transitions in virus gene expression (Pasička et al. 2008). The HSV-1 virion host shutoff endonuclease (*vhs*) is targeted to mRNAs by associating with translation initiation factors eIF4H and eIF4A (Doepker et al. 2004; Feng et al. 2005; Page and Read 2010), although spliced mRNAs are transiently protected from *vhs* cleavage until exon junction complex removal by the first round of translation (Sadek and Read 2016). A loose target consensus sequence was found for the KSHV endoribonuclease *sox* as well as a RNA element that protects select host immune mRNAs from decay (Gaglia et al. 2015; Muller and Glaunsinger 2017). Besides its shrewd use by segmented, (–)-sense RNA viruses to acquire 5' ends, cap snatching results in decapitated host transcript decay (Fig. 1C). The endoribonuclease is provided by virus RdRp components (IAV PA protein and bunyavirus large "L" protein). During IAV PA translation, a ribosomal frameshift generates a second endoribonuclease, PA-X (Fig. 1C), to further enforce host shutoff (Jagger et al. 2012; Bavagnoli et al. 2015; Chaimayo et al. 2018). PA-X interacts with host mRNA processing factors and preferentially targets spliced mRNAs (Gaucherand et al. 2019).

VacV uses a distinct tactic by encoding two mRNA decapping enzymes (D9 and D10) (Fig. 1C) produced at different times during infection, each of which contains a nudix hydrolase motif similar to that found in cellular Dcp2 (Parrish and Moss 2007; Parrish et al. 2007). While Dcp2 is active within a complex of decapping-enhancing proteins needed for mRNA targeting, D9 and D10 require no additional proteins for activity and contribute to global host shutoff (Parrish and Moss 2007; Parrish et al. 2007). Viral transcripts are not immune to D9 and D10 (Liu et al. 2015), and whether these enzymes show any target selectivity remains unknown.

Although discovered as host shutoff effectors that promote virus mRNA ribosome access, viral mRNA decay enzymes unexpectedly control immunogenic viral dsRNA accumulation. In addition to limiting protein synthesis (via OAS/RNase L), dsRNA stimulates IFN production and antiviral ISG expression (Liu and Gack 2020). Attenuated replication and hyperactivation of host defenses associated with dsRNA accumulation occur during infection with virus mutants deficient for VacV decapping enzymes (Liu et al. 2015), IAV PA-X (Jagger et al. 2012; Hayashi et al. 2015; Rigby et al. 2019), and HSV-1 *vhs* (Strelow and Leib 1995; Pasička et al. 2008; Burgess and Mohr 2018; Dauber et al. 2019). Instead of destabilizing RNA globally, other viruses focus their RNA decay

enzymes on virus RNAs detected as PAMPs (Fig. 1D). CoVs deploy a ribonuclease endoU that degrades (–)-sense viral RNA bearing 5'-U tracts copied from (+)-strand poly (A) tails (Kindler et al. 2017; Hackbart et al. 2020), while Lassa fever virus (LASV) NP has 3'-5' exoribonuclease activity that degrades dsRNA (Qi et al. 2010; Hastie et al. 2011; Mateer et al. 2020). Viruses lacking these proteins accumulate dsRNA and replicate poorly.

Viruses also disrupt targeted decay pathways. The generally destabilizing AU-rich element (ARE)-BP AUF1 is sequestered by a ncRNA (EBER1) produced by Epstein-Barr virus (EBV), a herpesvirus subfamily member, and this is proposed to extend virus RNA half-life (Lee et al. 2012). AUF1 is degraded by picornaviruses, and while it directly binds picornaviral RNA, its capacity to inhibit infection has been linked to mRNA translation and stability (Rozovics et al. 2012; Cathcart et al. 2013; Wong et al. 2013). Conversely, RNA virus genomes recruit stabilizing ARE-BP HuR (also known as ELAVL1) (Sokoloski et al. 2010; Nadar et al. 2011; Shwetha et al. 2015).

Host decay enzymes can be co-opted to play proviral roles too. Xrn1 is required by VacV to degrade decapped mRNA and suppress accumulation of dsRNA from complementary viral transcripts (Burgess and Mohr 2015; Liu and Moss 2016). A similar role for Xrn1 is likely in Sindbis virus (SINV) and IAV-infected cells as enhanced IFN induction and impaired virus replication are observed in Xrn1 knockout cells (Garcia-Moreno et al. 2019; Liu et al. 2021). The SKI complex, an RNA helicase cofactor of the cytosolic exosome, stimulates CoV and IAV replication (Weston et al. 2020), possibly via interactions with virus dsRNA BPs (IAV NS1 and MERS ORF4a) that suppress IFN signaling (Niemeyer et al. 2013; Ayllon and García-Sastre 2015). Although endonucleolytic activity has not been found in vitro, CoV Nsp1 reportedly promotes host mRNA decay (Fig. 1C), suggesting an unidentified host endoribonuclease may be needed (Kamitani et al. 2009; Nakagawa and Makino 2021). Finally, viruses repurpose host decay factors. RNA (+) strand viruses including HCV conscript the Lsm1–7 complex, which usually stimulates mRNA decapping, to promote virus mRNA translation and RNA replication (Díez et al. 2000; Scheller et al. 2009; Jungfleisch et al. 2015).

Although infection changes host and viral RNA decay dynamics, the secondary impact on RNA-BP availability and activity is poorly understood. Broad RNA destabilization reduces the abundance of RNAs targeted by RNA-BPs, while virus RNA (vRNA) accumulation qualitatively alters the pool of RNA-bound versus available RNA-BPs. RNA decay triggered by viral endonucleases perturbs transcription and nuclear RNA processing, the latter resulting in part from nuclear accumulation of normally cytoplasmic PABP (Kumar and Glaunsinger 2010; Abernathy et al. 2015). HuR sequestration by SINV destabilizes host HuR-regulated mRNAs (Barnhart et al. 2013), and appropriation of RNA-BPs that regulate ISG mRNA translation by dengue virus (DENV) limits the IFN response (Bidet et al. 2014). New RNA–protein interactome approaches highlight the impact of RNA-BPs sequestered by vRNA during RNA virus infection, including SARS-CoV-2, yielding new

avenues for investigation (Flynn et al. 2021; Kamel et al. 2021; Lee et al. 2021; Schmidt et al. 2021; Iselin et al. 2022).

Targeting decay and translation by RNA modification

N⁶-adenosine methylation (m⁶A) can alter gene expression post-transcriptionally and is the most widespread internal mRNA base modification in eukaryotes (Zaccara et al. 2019; He and He 2021). The m⁶A epitranscriptomic landscape is shaped by rival activities of a methyltransferase writer core complex (METTL3 catalytic subunit, METTL14, and WTAP) that installs m⁶A on nascent mRNA cotranscriptionally and “eraser” demethylases FTO and ALKBH5, which remove m⁶A marks in vitro (Jia et al. 2011; Zheng et al. 2013; Liu et al. 2014; Ke et al. 2017; Rosa-Mercado et al. 2017). Deposition of m⁶A by METTL3/14 occurs largely at consensus DRACH (D = A,G,T; R = A,G; and H = A,C,U) motifs, only a fraction of which are modified (He and He 2021). While detected throughout transcripts, m⁶A is enriched within terminal exons near stop codons and poly(A) signals (He and He 2021). Recognition of m⁶A-modified sites by “reader” RNA-BPs, including YTH domain-containing proteins in the cytoplasm (YTHDF1, YTHDF2, and YTHDF3) or nucleus (YTHDC1), differentially recruits effector proteins that impact RNA nuclear processing and export and mRNA stability and translation (Zaccara et al. 2019; He and He 2021). YTHDF1,2,3 bind to the same RNAs and act redundantly to regulate RNA decay (Lasman et al. 2020; Zaccara and Jaffrey 2020).

Virus mRNAs are m⁶A-modified (Williams et al. 2019), and the major ways by which host m⁶A modification and recognition components post-transcriptionally regulate virus gene expression and replication are summarized in Table 1. Replication of many RNA viruses (HIV, IAV, human metapneumovirus [HMPV], respiratory syncytial virus [RSV], PV, EV71, and CoVs) was stimulated by METTL3/14 and reduced by m⁶A demethylases. In some but not all cases, specific m⁶A sites and readers have been identified that are required for protein expression, replication, and pathogenesis (Kennedy et al. 2016; Tirumuru et al. 2016; Lichinchi et al. 2016a; Courtney et al. 2017; Hao et al. 2019; Xue et al. 2019; Han et al. 2020; Yao et al. 2020). The nuclear reader YTHDC1 regulates HIV alternate splicing, while m⁶A recognition by cytoplasmic YTHDF2, which promotes decay of m⁶A-containing host mRNAs, stabilized virus transcripts. Thus, sequence context of YTHDF2 m⁶A recognition influences transcript fate (Tsai et al. 2021). Remarkably, m⁶A was detected in RNA genomes of viruses that replicate exclusively in the cytoplasm (RSV, HMPV, PV, EV71, ZIKV; HCV, DENV, West Nile virus [WNV], and yellow fever virus [YFV]), including seasonal and pandemic CoVs, whose reproduction was suppressed by depletion of METTL3 or YTHDF1,3 cytoplasmic m⁶A readers (Burgess et al. 2021; Li et al. 2021). METTL3 catalytic activity was further required for efficient CoV RNA synthesis, protein accumulation, and replication (Burgess et al. 2021). Further work is needed to identify the specific m⁶A modification

Table 1. Key ways in which host m⁶A modification components influence virus replication

Cellular process	Role of m ⁶ A machinery	Virus
mRNA splicing	m ⁶ A recognition by nuclear reader YTHDC1 regulates alternative virus mRNA splicing	HIV, Ad
	Regulates host mRNA splicing	DENV, WNV, ZIKV, HCV
mRNA decay	Reader YTHDF2 stabilizes virus transcripts and promotes host mRNA decay	HIV
	Reader Tudor SND1 stabilizes virus ORF50 mRNA	KSHV
	Reader YTHDF1 stimulates lytic mRNA decay and promotes latent gene expression	EBV
	Site-specific m ⁶ A modification of IFNB1 by METTL3/14 mRNA promotes RNA decay	HCMV, Ad, IAV, VSV
	YTHDF2 recruits ISG20 to m ⁶ A-containing virus mRNA and stimulates decay	HBV
Gene expression	METTL3/14 stimulates virus gene expression and replication	RNA viruses: HIV, IAV, HMPV, RSV, PV, EV71, CoVs DNA viruses: SV40, Ad, KSHV
	Virus protein expression restricted by METTL3/14 and stimulated by FTO or ALKBH5	HCV, ZIKV
	Site-specific modification of virus mRNA and readers required for protein expression, replication, and pathogenesis	IAV, HIV, EV71, RSV, SV40
	METTL3/14 and YTHDF1 reader recognition of m ⁶ A stimulates translation of some ISG-encoding mRNAs	VSV
	YTHDF1,2,3 cleavage by virus protease restricts ISG expression	EV71

sites in virus RNAs and host RNAs that might influence CoV replication. In contrast, METTL3/14 restricted HCV protein expression and virus reproduction without changing RNA replication, whereas FTO stimulated HCV protein expression (Gokhale et al. 2016; Gonzales-van Horn and Sarnow 2017). ZIKV reproduction was also repressed by METTL3/14 and stimulated by FTO and ALKBH5 (Lichinchi et al. 2016b). How nuclear host m⁶A modification components accumulate in the cytoplasm and how they recognize virus RNA remain outstanding questions. One exciting possibility involves association with METTL3 with a virus RdRp (Hao et al. 2019).

Interfering with METTL3 also reduced gene expression of nuclear-replicating DNA viruses SV40, Ad, HBV, and herpesviruses, which produce m⁶A-containing mRNAs (Lavi and Shatkin 1975; Moss et al. 1977; Hesser et al. 2018; Imam et al. 2018; Tsai et al. 2018). Reader YTHDF2 is needed for SV40 replication and m⁶A acceptor site ablation reduced virus reproduction (Tsai et al. 2018). By binding to YTHDF2, ISG20 is recruited to m⁶A-containing HBV transcripts and stimulates their decay (Imam et al. 2020). Nuclear m⁶A-interacting factors concentrated at sites of nascent Ad RNA synthesis and METTL3 loss reduced late gene expression by deregulating viral RNA processing and reducing splicing efficiency (Price et al. 2020). How specific virus m⁶A acceptor sites impact the spectrum of discrete alternatively spliced isoforms remains unanswered. The m⁶A pathway becomes progressively less important for HSV-1 gene expression over time, as the virus ICP27 protein redistributes nuclear methyltransferase components into the cytoplasm, reducing RNA modification on host and virus mRNAs (Srinivas et al. 2021). This

could represent another way HSV-1 limits host RNA processing, as most late virus RNAs do not contain introns. EBV transcriptome m⁶A modification stimulated viral latent gene expression in part by mRNA stabilization and repression of lytic genes via YTHDF1-stimulated RNA decay (Lang et al. 2019; Xia et al. 2021). While most lytic KSHV transcripts were m⁶A-modified (Tan et al. 2018), the host m⁶A machinery was shown to have a complex proviral and antiviral impact on viral gene expression depending on cell type (Hesser et al. 2018). By binding to a m⁶A-modified hairpin within the KSHV ORF50 mRNA, which encodes a potent virus regulatory protein (Baquero-Perez et al. 2019), the host Tudor SND1 protein stabilizes ORF50 mRNA and is essential for KSHV early gene expression.

Host antiviral immune defenses, including IFNB1 transcript accumulation and ISG expression (Table 1), are regulated by m⁶A (Shulman and Stern-Ginossar 2020; McFadden and Horner 2021). METTL3/14 depletion stimulated IFNB1 accumulation and inhibited DNA (HCMV and Ad) and RNA (VSV and IAV) virus reproduction, whereas ALKBH5 depletion restricted IFNB1 accumulation and stimulated HCMV reproduction (Rubio et al. 2018; Winkler et al. 2019). Cellular m⁶A modification components also regulate IFNB1 mRNA accumulation in uninfected cells exposed to dsDNA (Rubio et al. 2018). This established that responses to nonmicrobial dsDNA in uninfected cells, which shape host immunity and contribute to autoimmune disease, are regulated by enzymes controlling m⁶A epitranscriptomic changes. Indeed, IFNB1 mRNA is m⁶A-modified at specific sites, which regulates IFNB1 mRNA decay in HCMV-infected cells and

IFNB1 mRNA biogenesis and decay in uninfected, dsDNA-treated cells (Rubio et al. 2018; Winkler et al. 2019). The m⁶A reader YTHDF3, together with eIF4G2 and PABPC1, stimulates FOXO3 mRNA translation, the product of which negatively regulates ISG transcription and stimulated VSV replication (Zhang et al. 2019). Many ISG mRNAs are m⁶A-modified, and this reportedly stimulates translation of a subset (McFadden et al. 2021). Indeed, YTHDF1,2,3 are cleaved by EV71 2a protease, and this has been proposed to antagonize ISG expression in infected cells (Kastan et al. 2021). Reduced m⁶A on mRNA encoding α -ketoglutarate dehydrogenase promoted RNA decay, limiting metabolite (itaconate) accumulation required for VSV replication (Liu et al. 2019b). Virus-induced alterations to host transcript m⁶A content influences their splicing or translation and regulates infection by *Flaviviridae* members DENV, WNV, ZIKV, and HCV (Gokhale et al. 2020).

Cytosine methylation and acetylation at C5 (m⁵C) and N4 positions (ac⁴C) regulate retrovirus reproduction (Squires et al. 2012; Li et al. 2017; Arango et al. 2018). MLV genomic RNA modification by m⁶A and m⁵C stimulate virus replication (Courtney et al. 2017; Eckwahl et al. 2020). HIV-1 transcripts contain m⁵C, and interfering with m⁵C nuclear methyltransferase NSUN2 dysregulated HIV-1 mRNA alternative splicing, correlated with reduced virus mRNA ribosome recruitment, and inhibited virus replication (Courtney et al. 2019). Similarly, ac⁴C enhanced mRNA translation and stability (Arango et al. 2018) and was detected on genomic HIV-1 virion RNA (McIntyre et al. 2018). Disrupting ac⁴C HIV mRNA acceptor sites without altering coding content reduced virus gene expression, and reducing expression of N-acetyltransferase 10 (NAT10), which installs ac⁴C, inhibited HIV-1 replication by increasing RNA decay (Tsai et al. 2020). The extent to which other RNA modifications (McIntyre et al. 2018; Wiener and Schwartz 2021) impact virus reproduction is an exciting research direction, potentially exposing new ways gene expression is shaped post-transcriptionally by physiological stress.

Appropriating host ribosomes in virus-infected cells

Mechanisms and regulation of 40S ribosome loading on virus mRNAs

All viral mRNAs must capture cellular ribosomes. This begins with 40S recruitment, a necessary, regulated translation initiation step. It is coordinated in eukaryotes by initiation factors (eIFs) that assemble a specialized ribonucleoprotein complex on the mRNA 5' end to engage 40S loaded with methionine-charged initiator tRNA (met-tRNA_i). Recognition of m⁷G-capped virus mRNAs typically relies on the host cap-binding protein eIF4E, which together with the large scaffold eIF4G1 and the RNA helicase eIF4A forms a heterotrimeric complex called eIF4F (Pelletier and Sonenberg 2019). Association of eIF3-bound 40S with eIF4F via binding to eIF4G1 enables 40S loading onto m⁷G-capped mRNA. Diverse virus strategies preserve cellular eIF4F accessibility and activity and subvert

host defenses that curtail eIF4F activity (Fig. 2). To stimulate virus capped mRNA translation, repressive host eIF4E-binding protein family members including 4E-BP1 are inactivated. By interacting with eIF4E, 4E-BP1 stoichiometrically restricts eIF4E binding to eIF4G1. Accordingly, 4E-BP1 represses cap-dependent translation by limiting eIF4E binding to eIF4G and preventing (1) eIF4F assembly and (2) 40S loading onto capped mRNAs (Pelletier and Sonenberg 2019). Phosphorylation of 4E-BP1 by the Ser/Thr kinase mTORC1 liberates eIF4E from the 4E-BP1 repressor and allows tuning of cap-dependent translation to physiological cues that regulate mTORC1 (Fig. 2). The latter can be subverted to constitutively stimulate anabolic programs such as protein synthesis and restrict catabolic outcomes such as autophagy during acute infection and lytic virus growth (Rubio and Mohr 2019). Alternatively, it can be harnessed to balance whether an infection remains latent or lytic reproduction ensues, as interfering with 4E-BP1 inactivation by mTORC1 stimulates latent HSV-1 genomes in neurons to reactivate and commence their reproductive lytic cycle (Kobayashi et al. 2012b; Hu et al. 2019). As transient mTOR inhibition in axons stimulates reactivation (Kobayashi et al. 2012b), differential mRNA translation localized within axons is possibly required. Identifying these mRNAs will further our mechanistic understanding of how HSV sustains and transitions out of latency in neurons.

Many DNA and RNA virus effectors co-opt host PI3-kinase–Akt–mTORC1 signaling in part to antagonize 4E-BP1 and stimulate translation of capped virus mRNAs (Fig. 2). Herpesviruses, adenoviruses, poxviruses, paramyxoviruses, and orthomyxoviruses (IAV) constitutively stimulate mTORC1 during their lytic reproductive cycle (O'Shea et al. 2005; Werden et al. 2007; Moorman et al. 2008; Walsh et al. 2008; Arias et al. 2009; Chuluunbaatar et al. 2010; Hale et al. 2010; Kuss-Duerkop et al. 2017; Zhan et al. 2020). By mimicking the cellular kinase Akt, the HSV-1 Ser/Thr kinase Us3 inactivates the host tuberous sclerosis complex (TSC) via directly phosphorylating TSC2 on Akt target sites (Chuluunbaatar et al. 2010). Us3 further disrupts host AMPK-dependent responses to energy insufficiency by preventing TSC2-dependent mTORC1 inhibition by AMPK (Vink et al. 2017). Additionally, Us3 uncouples mTORC1 activation from amino acid sufficiency signals (Vink et al. 2018). Both of these functions enable sustained mTORC1 activation and virus replication during physiological stress. Inactivation of 4E-BP1 is accompanied by virus-induced eIF4F assembly, which proceeds via distinct mechanisms. The HSV-1 ICP6 protein N terminus interacts with the eIF4G N terminus, enhances eIF4E binding to eIF4G, and stimulates virus mRNA translation (Walsh and Mohr 2006). While cytoplasmic PABP availability in HSV-1-infected cells is reduced by its nuclear accumulation, the viral ICP27 RNA-binding protein stimulates 40S recruitment in a PABP- and eIF4G-dependent manner. By recruiting PABP, which in turn interacts with eIF4G, ICP27 stimulates translation of capped mRNAs, imitating a mechanism used by cellular RNA-BP Dazl (deleted in azoospermia-like) (Smith et al. 2017). In contrast, eIF and PABP

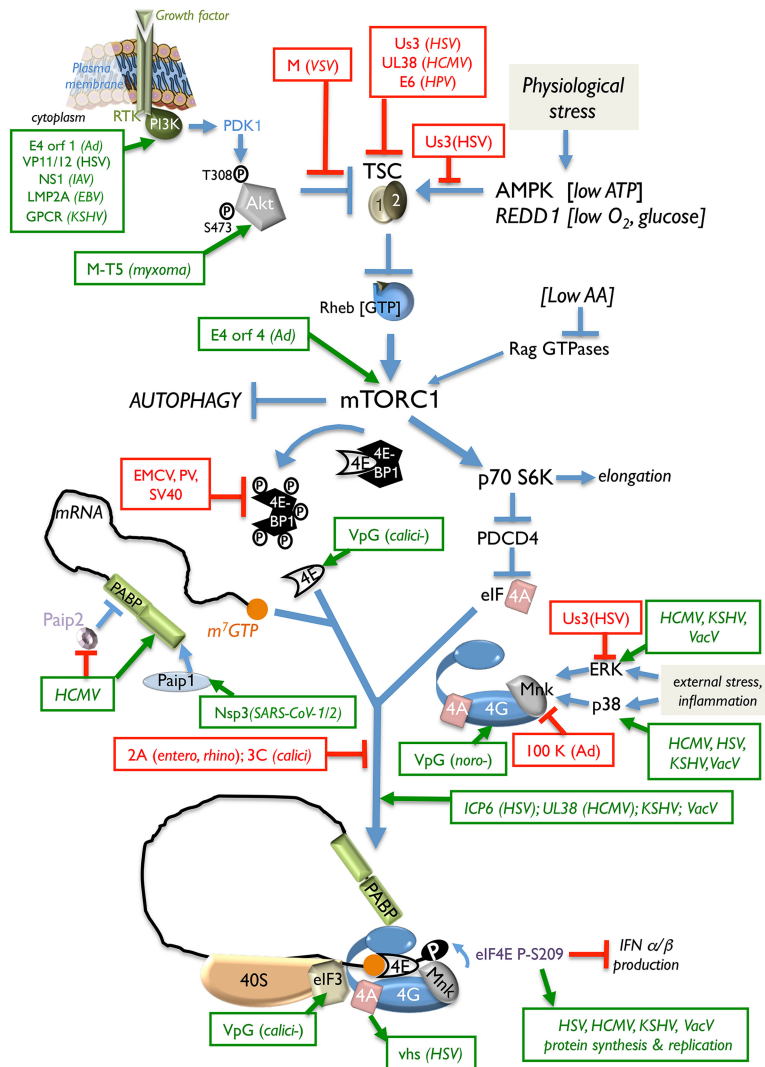


Figure 2. Controlling cap-dependent 40S ribosome loading in virus-infected cells. Sampling extracellular and intracellular cues (growth factor, nutrients, O₂, and energy) allows 40S ribosome loading onto capped mRNAs to be responsive to changing environmental and physiological conditions, including virus infection. Receptor tyrosine kinase (RTK) signaling through PI3-kinase (PI3-K) and PDK1 stimulates Akt phosphorylation (T308 and S473). Once activated, Akt represses the tuberous sclerosis complex (TSC1/2), which results in Rheb-GTP accumulation and mTORC1 activation. Physiological stress (energy, O₂, or nutrient insufficiency) prevents mTORC1 activation. The translational repressor 4E-BP1 regulates the availability of the cap-binding protein eIF4E. Hyperphosphorylation and inactivation of 4E-BP1 releases eIF4E, which interacts with eIF4G and the DEAD-box helicase eIF4A to assemble the multisubunit eIF4F complex on m⁷G-capped mRNA. Regulated eIF4F assembly controls eIF3-bound 40S loading onto capped mRNA. Virus-encoded effectors that stimulate (green) or repress (red) the indicated host factors to control 40S loading and translation initiation are shown. (SV40) Simian virus 40, (calici-) calicivirus, (noro-) norovirus, (entero) enterovirus, (rhino) rhinovirus.

abundance increases upon infection with HCMV, a related herpesvirus from a distinct subfamily. Unlike HSV-1 infection, host protein synthesis proceeds, and the genome-wide translational landscape is remodeled by HCMV. Differentially translated cellular mRNAs have been identified that stimulate virus growth or host defenses (McKinney et al. 2014; Tirosh et al. 2015). RNA structure remodeling among regulated host genes in part confers HCMV infection responsiveness (Mizrahi et al. 2018) along with mTORC1 activation by the viral UL38 protein, which stimulates cap-dependent translation of mRNAs containing a terminal oligopyrimidine (TOP) sequence element including PABP (McKinney et al. 2012, 2014). Reduced eIF4F assembly and virus growth were observed by interfering with HCMV-induced PABP1 accumulation (McKinney et al. 2012). By raising PABP abundance, HCMV overcomes an unexpected host antiviral response that increases PABP-interacting protein 2 (Paip2) levels, which inhibits PABP binding to eIF4G and poly(A) RNA (McKinney et al. 2013). PABP is also targeted in SARS-CoV-1/2 replicon transfected cells by nsp3, which interacts with PABP-interacting protein-1 (Paip1) and 40S/80S ribosomes to enhance

virus but not host protein synthesis (Lei et al. 2021). In lieu of controlling eIF abundance, DNA viruses that replicate in the cytoplasm (VacV and ASFV) sequester eIF4E, eIF4G, and PABP within and around discrete replication compartments (RCs) to increase their effective local concentration (Katsafanas and Moss 2007; Walsh et al. 2008; Castelló et al. 2009; Zaborowska et al. 2012). Cells infected with mammalian orthoreovirus, a dsRNA virus, also accumulate eIFs in cytoplasmic RCs (Desmet et al. 2014). How these factors concentrate within specific cytoplasmic regions is unknown and might inform mechanisms underlying local mRNA translation.

The host eIF4G-associated Ser/Thr kinase Mnk-1, which is activated by ERK and p38, influences infected cell protein synthesis by phosphorylating eIF4E. Binding of eIF4E to eIF4G delivers Mnk-1 to its substrate eIF4E, stimulating eIF4E S209 phosphorylation (Fig. 2). Situated near the eIF4E cap-binding pocket, S209 phosphorylation weakened cap binding affinity, (Scheper et al. 2002; Zuberek et al. 2004; Slepnev et al. 2006), possibly accelerating cap release during initiation. The mechanism underlying how eIF4E phosphorylation regulates translation

of a subset of mRNAs involved in proliferation, circadian rhythms, stress response, inflammation, and memory formation remains elusive (Furic et al. 2010; Herdy et al. 2012; Cao et al. 2015; Bramham et al. 2016; Proud 2019). Many viruses (large DNA viruses, CoV, and flavi, noro, and paramyxo viruses) promote eIF4E phosphorylation by stimulating ERK and/or p38, which activates Mnk1 (Mizutani et al. 2004; Walsh and Mohr 2004, 2006; Walsh et al. 2005, 2008; Royall et al. 2015; Roth et al. 2017; Proud 2019; Zhan et al. 2020), which stimulates translation of virus mRNAs (Walsh and Mohr 2004) and mRNA encoding the NF- κ B inhibitor I κ B (Herdy et al. 2012). Mnk1 recruitment by eIF4F is regulated by eIF3 subunit e, and eIF4E phosphorylation is eIF3e-dependent, consistent with eIF4F assembly preceding eIF4E phosphorylation. It further illustrates how modifying a cap recognition complex in response to eIF3-bound 40S loading regulates mRNA translation. (Walsh and Mohr 2014). Although how eIF4E phosphorylation influences selective mRNA translation is unknown, RNA binding activities displayed by eIF3 subunits (Hinnebusch 2006) could play a role. Reduced I κ B mRNA translation, NF- κ B activation, and IFN production result when unphosphorylated eIF4E accumulates in infected cells (Ad and many RNA viruses) (Jan et al. 2016). At late times in Ad-infected cells, binding of Ad 100K to eIF4G displaces Mnk1 and results in unphosphorylated eIF4E accumulation (Cuesta et al. 2004), which correlates with reduced host cell mRNA translation while allowing high-level virus mRNA translation via a cap-dependent, noncanonical ribosome shunting mechanism discussed below. Exiting virus latency is also stimulated by eIF4F assembly and eIF4E phosphorylation, as inhibiting the eIF4E kinase Mnk1 reduced accumulation of the KSHV transactivator RTA needed for lytic replication (Arias et al. 2014). Thus, whether latent infection persists or productive, lytic reproduction is triggered can be determined by critical cell signaling pathways (MAPK and PI3K–Akt–mTOR) that regulate translation.

Once loaded onto capped mRNA, 40S-containing complexes search for the AUG start codon by translocating along the 5' UTR in an ATP-dependent process termed "scanning" (Merrick and Pavitt 2018). Ribosome shunting *cis*-elements that mediate nonlinear 40S translocation, whereby a 5' UTR section is bypassed and scanning resumed downstream, have been identified in virus (Ad, HPV, and HBV) and host (hsp70) mRNAs (Kwan and Thompson 2019). Shunting supports initiation on capped mRNAs, which typically requires 5' UTR unwinding by eIF4A, when initiation is suppressed by stress such as heat shock or infection that interferes with eIF4F. Ad 100K protein facilitates shunting by binding to the 5' non-coding region of virus late mRNA (called the tripartite leader) and eIF4G, which in turn enhances PABP and 40S loading (Xi et al. 2004). A different *cis*-element surrounding the AUG codon mediates translation initiation on leaderless mRNAs (TILM) that are capped and have very short or no 5' UTRs. HPV E6 oncoprotein expression uses TILM-directed initiation, which requires the cap structure, eIF4E, and eIF4A1 and could drive E6 production by cancer cells (García et al. 2021).

While eIF4E stimulates translation, a related host cap recognition protein, 4EHP, directs transcript-specific repression. Up-regulation of miR34a, which targets IFNB1, in RNA virus-infected cells, results in 4EHP-dependent translational repression of IFN β (Zhang et al. 2021). Besides demonstrating 4EHP's role in translational silencing and cell-intrinsic immunity, this illustrates how distinct cellular cap-binding proteins manipulate infection outcomes.

In lieu of stimulating eIF4F, certain viruses obstruct eIF4F, which restricts host cap-dependent translation to achieve host shutoff and requires alternative strategies to initiate translation on virus mRNAs. Many RNA viruses that replicate in the cytoplasm rely on *cis*-elements termed internal ribosome entry sites (IRESs) to load 40S subunits onto viral mRNA in a cap-independent manner (Jaafar and Kieft 2019; Stern-Ginossar et al. 2019). IRES-directed initiation allows virus mRNAs to evade host defenses that repress cap-dependent translation, such as 4E-BP1; prevent synthesis of host antiviral proteins; and ensure selective virus mRNA translation proceeds while host protein synthesis is impaired. Comprised of stable and dynamic RNA structures that form 40S high-affinity ligands, IRESs are classified by structure, initiation factor requirements, and initiation mechanism (Jan et al. 2016; Johnson et al. 2017; Jaafar and Kieft 2019; Stern-Ginossar et al. 2019; Arhab et al. 2020). Type 1 and 2 IRESs are larger and require nearly all eIFs except eIF4E. IRES transacting factors (ITAFs) that remodel RNA structure are also required. Initiation by type 1 or 2 IRESs depends on binding to full-length eIF4G (EMCV) or an eIF4G fragment lacking the N-terminal eIF4E-binding domain (PV) that interacts with eIF4A. Whereas type 1 IRESs recruit 40S upstream of coding regions and scan to locate the start codon, type 2 IRESs secure the initiation complex to the start codon without scanning (Yu et al. 2011a; Sweeney et al. 2014). Structurally similar to type 1 and 2 IRESs, the hepatitis A virus (HAV) type 3 IRES requires eIF4E binding to eIF4G, which increases IRES binding and stimulates eIF4A unwinding (Avanzino et al. 2017). Despite needing all eIF4F subunits unlike other IRESs, HAV RNAs are not capped, precluding a role for cap recognition by eIF4E. Somehow, eIF4E binding to eIF4G stimulates high-affinity binding of eIF4G to the HAV IRES and facilitates IRES structural remodeling (Avanzino et al. 2017). This could involve eIF4E altering eIF4G conformation or impacting the interaction of eIF4F with the HAV IRES (Ali et al. 2001; Borman et al. 2001). Type 4 IRESs (HCV and CSFV) directly bind 40S and eIF3, displacing eIF3 from its normal position on 40S, altering 40S conformation, and positioning the AUG without scanning (Spahn et al. 2001; Siridechadilok et al. 2005; Hashem et al. 2013; Quade et al. 2015). The HCV IRES also associates with the 40S subunit of a translating 80S ribosome without disrupting protein synthesis, and this captured 40S is likely hijacked for subsequent IRES-directed initiation (Yokoyama et al. 2019). Delivery of met-tRNA_i either by eIF2 or by eIF2A or eIF2D enables IRES function during physiological stress when canonical eIF2-mediated delivery is impaired (discussed later). Uniquely dependent on

DDX29, which likely remodels a stem–loop that sequesters the initiating AUG, the aichivirus (AV) type 5 IRES eIF4G-binding domain is structurally distinct from type 1 and 2 IRESs (Yu et al. 2011b). In contrast, dicistroviruses such as CrPV contain two IRESs. The 5' UTR IRES requires eIF3 but docks very differently with 40S subunits compared with type 4 IRESs (Neupane et al. 2020). The CrPV intergenic region (IGR) type 6 IRES, however, does not require eIFs for 40S binding and 80S assembly, can initiate translation from a non-AUG codon (Wilson et al. 2000; Muhs et al. 2015; Murray et al. 2016), and repositions some ribosomes to bypass 12 codons and resume +1 frame translation at a non-AUG codon (Kerr et al. 2018). Dicistrovirus IGR IRESs share similar structures consisting of a ribosome recruitment domain and a smaller domain containing pseudoknot I (PK I). Unlike canonical initiation, where the ribosome P-site is occupied by Met-tRNA_i and elongator tRNAs load into the A-site, the IGR IRES PK I-containing domain docks into the P-site. While CrPV IRES codon–anticodon mimicking PK initially occupies the ribosome A-site, 40S rotation and eEF2-dependent translocation into the P-site are required to expose the A-site for elongation to commence (Costantino et al. 2008). By imitating an intermediate ribosomal state with hybrid tRNAs, IRES PK I from Israeli acute paralysis virus (IAPV) within the A-site blocks eIF1/eIF1A binding and promotes 60S joining followed by codon translocation to the P-site in a related elongation factor recruitment strategy (Costantino et al. 2008; Acosta-Reyes et al. 2019). A simpler mechanism used by Halastavi árva virus positions the IRES PK into the P-site, averting the need for eEF2-mediated translocation prior to commencing decoding (Abaeva et al. 2020).

Besides stimulating selective virus mRNA translation, IRES-directed translation proceeds when viral functions inhibit cap-dependent 40S loading. Thus, by subverting normal host translation regulatory circuits, viruses impose a potent host shutoff where virus IRES-mediated translation proceeds while host protein synthesis is suppressed (Fig. 2). Hypophosphorylated 4E-BP1 in PV- or EMCV-infected cells limits eIF4E binding to eIF4G, inhibiting eIF4F assembly (Gingras et al. 1996). By cleaving eIF4G to sever the eIF3- and eIF4A-binding segment from the N-terminal eIF4E-binding fragment, PV 2A proteinase selectively disables eIF4E-dependent 40S loading onto host capped transcripts (Gradi et al. 1998). Inhibition of host cap-dependent translation was better correlated with virus proteinase cleavage of eIF4G3 (formerly eIF4GII) rather than eIF4G1 (formerly eIF4GI), although eIF4G3 was less sensitive to 2A cleavage than eIF4G1 (Gradi et al. 1998). Cleavage of eIF4G by PV or group A rhinovirus 2A protease is stimulated by eIF4E (Aumayr et al. 2017; Avanzino et al. 2017). The 3C proteinase produced by PV and EMCV also cleaves host PABP1 (Rivera and Lloyd 2008; Kobayashi et al. 2012a). Finally, EV71 infection stimulates cellular microRNA miR-141 expression to diminish eIF4E levels and curb host protein synthesis (Ho et al. 2011).

Using a termination–reinitiation mechanism (Kronstad et al. 2013, 2014; Royall and Locker 2016), some vi-

ruses express multiple proteins from a polycistronic transcript. Following upstream ORF translation, a termination upstream ribosomal binding site (TURBS) in calicivirus RNAs retains 40S post-termination. TURBS promote reinitiation at a nearby AUG or non-AUG codon via 18S rRNA base pairing (Luttermann and Meyers 2014; Royall and Locker 2016). Reinitiation in vitro requires eIF2, eIF1, and eIF1A but not eIF3 (Zinoviev et al. 2015).

Preserving initiator tRNA loading onto 40S subunits and subverting the integrated stress response

By detecting nutrient insufficiency, proteostasis deficiencies, and virus infection, the integrated stress response (ISR) allows mammalian cells to re-establish homeostasis by reprogramming gene expression (Costa-Mattioli and Walter 2020). Once new protein synthesis initiation is arrested by stress, specialized mRNA translation produces proteins required to implement a new transcription program that restores homeostasis. Virus models have illuminated how translation initiation is globally repressed by stress and the fundamental importance of this process to innate immune responses.

Four mammalian Ser/Thr kinases, each activated by discrete physiological stressors, can globally inhibit protein synthesis by preventing 40S ribosomes from acquiring met-tRNA_i required to initiate translation from most mRNAs (Fig. 3). This is achieved by phosphorylating the α subunit of eIF2, a heterotrimeric initiation factor that assembles and delivers a ternary complex (TC) comprised of eIF2•GTP•met-tRNA_i to the 40S subunit. Upon AUG start codon recognition by TC-loaded 40S, GTP hydrolysis stimulated by eIF5 promotes 60S joining and translation elongation. Recycling eIF2•GDP into the active, GTP-bound form requires the guanine nucleotide exchange factor (GEF) eIF2B (Fig. 3). Phosphorylated eIF2, however, binds eIF2B with high affinity and inhibits its GEF activity (Fig. 3). Initiation is arrested as eIF2B is present in limiting amounts, allowing small changes in phospho-eIF2 to have large effects on protein synthesis (Jan et al. 2016; Adomavicius et al. 2019; Stern-Ginossar et al. 2019). Phosphorylation of eIF2 α also induces stress granule formation—cytoplasmic foci containing mRNA, RNA-BPs, eIFs, and 40S RPs whose roles in infection have been reviewed (McCormick and Khaperskyy 2017; Gaete-Argel et al. 2019).

While all eIF2 α kinases may impact infection biology, the dsRNA-activated protein kinase PKR is a universal threat to animal viruses and a critical component of cell-intrinsic immune responses. Constitutively present but not activated, PKR is one of a suite of IFN-induced proteins needed to establish an antiviral state refractory to virus reproduction. PKR is activated by dsRNA and also by a protein, PACT (Stern-Ginossar et al. 2019). To neutralize PKR, viruses may produce dsRNA BPs to camouflage dsRNA from cellular sensors, degrade PKR as in Rift Valley fever virus (RVFV)-infected cells (Mudhasani et al. 2016), encode PKR inhibitory proteins, or produce a ncRNA (Ad VA-RNA) that associates with PKR to prevent

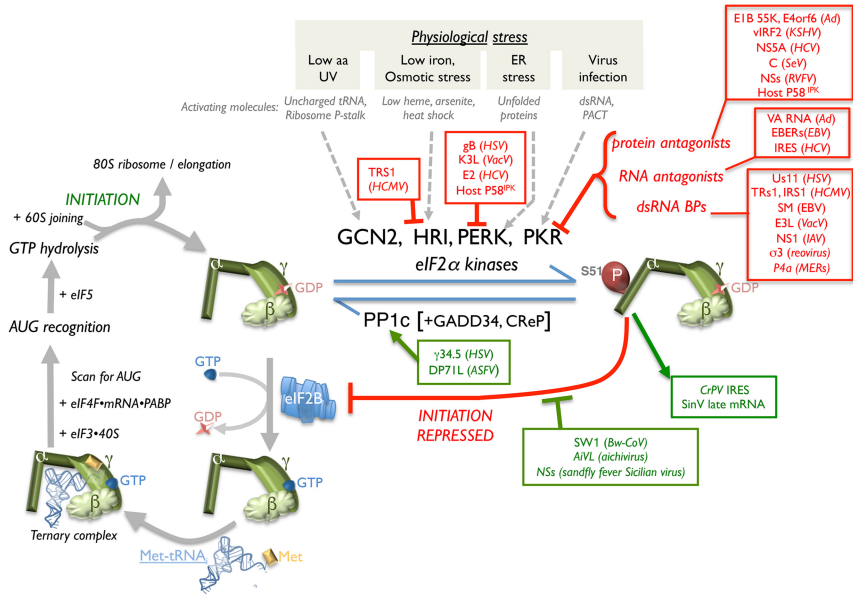


Figure 3. Viral strategies to preserve initiator tRNA loading onto 40S subunits. (Left panel) eIF2 is a GTP-binding initiation factor comprised of three subunits (α , β , and γ) that loads eIF3-bound 40S with Met-tRNA_i. After recruitment of mRNA containing eIFs and AUG identification, eIF5-dependent GTP hydrolysis is followed by 60S joining and initiation, and subsequent 80S-mediated elongation. The GEF activity of the eIF2B pentamer-dimer recycles inactive eIF2•GDP to the active GTP-bound form. S51 eIF2 α phosphorylation precludes initiation by associating with and inhibiting eIF2B, obstructing GDP-GTP exchange. eIF2 α phosphorylation is controlled by four eIF2 α kinases, each activated by distinct biological stress, and PP1c with its cognate constitutive (CrEP) or inducible (GADD34) regulatory subunit. Virus-encoded functions that antagonize (red) host eIF2 α kinases, stimulate PP1, or support translation despite phospho-eIF2 accumulation (green) are indicated. (aa) Amino acid.

kinase dimer formation needed for activity (Fig. 3; Jan et al. 2016; Stern-Ginossar et al. 2019). Similarly, dsRNA regions within host circular (circ) RNAs have been proposed to bind PKR and prevent its activation. Significantly, synthetic dsRNA exposure or EMCV infection triggered OAS/RNase L activation and rapid circRNA degradation (Liu et al. 2019a).

Combinatorial tactics incorporating multiple viral effectors shield eIF2 from attack by other eIF2 α kinases activated by stresses distinct from dsRNA. HSV-1 (γ 34.5) and African swine fever virus (DP71L) encode a protein phosphatase 1 α (PP1 α) regulatory subunit, which engages the cellular PP1 catalytic subunit (PP1c) and broadly counteracts eIF2 α kinases by dephosphorylating phospho-eIF2 α (Rojas et al. 2015; Barber et al. 2017). Specific eIF2 α kinase antagonists including the HSV-1 Us11 dsRNA BP, which inhibits PKR, and glycoprotein B, which restricts PERK activation, synergize with the γ 34.5 PP1 α regulatory subunit to limit eIF2 α phosphorylation via discrete mechanisms. Using the viral eIF2 α pseudosubstrate K3L (Sood et al. 2000; Seo et al. 2008) and the dsRNA BP E3L, which limits PKR activation, poxviruses also restrict eIF2 α phosphorylation using independent effectors. Viral eIF2 α kinase antagonists also inhibit multiple kinases, like HCMV TRS1, which inhibits PKR and HRI (Vincent et al. 2017). Cellular p58IPK induction by stress also reportedly prevents PKR, PERK, and GCN2 activation (Roobol et al. 2015).

The extent of genome coding capacity and deployment of viral antagonists to preserve eIF2 activity emphasizes its importance in the virus reproductive cycle. Mutant viruses lacking functions to challenge host dsRNA-responsive defenses such as PKR are often hypersensitive to IFN, are attenuated (Mulvey et al. 2004; White and Jacobs 2012; Liu et al. 2015), and display an altered host range (Haller et al. 2014; Carpentier et al. 2016; Peng et al. 2016; Cao et al. 2020; Park et al. 2021). Host eIF2 α kinase

activation may at times benefit virus replication. By promoting type I IFN receptor degradation, which precludes IFN responses (Liu et al. 2009), activation of unfolded protein response and PERK in infected cells supports HCV and VSV replication. Conversely, RNA viruses CrPV and SINV dispense with any eIF2 requirement by relying on *cis*-elements that direct eIF2-independent initiation (Wilson et al. 2000; Spahn et al. 2004; Kerr et al. 2016; Sanz et al. 2019). How cellular proteins and RNA structures regulate and contribute to eIF2-independent initiation in CrPV- and SINV-infected cells remains actively investigated.

A distinctive mechanism that attacks eIF2B•phospho-eIF2 interaction dynamics, an integral ISR feature, was identified in RNA virus-infected cells. While unrelated in sequence or predicted structure, the beluga whale CoV (Bw-CoV SW1) multifunctional AcP10 protein and the AiVL protein (Fig. 3) encoded by human aichivirus, a picornavirus that infects the GI tract, prevent phospho-eIF2 from binding to the eIF2B GEF (Rabouw et al. 2020). Both viral factors, however, did not interfere with eIF2B binding to unphosphorylated eIF2 (Rabouw et al. 2020). This enables AiVL and AcP10 to antagonize the ISR. In contrast, nonstructural protein s (NSs), encoded by the arthropod transmitted sandfly fever Sicilian virus, associates with and modifies eIF2B such that the NSs-eIF2B complex resists inhibition by phospho-eIF2 (Wuerth et al. 2020). Future studies are needed to reveal how NSs association with eIF2B subunits achieves this and whether any host cell factor is capable of a related feat.

Ribosomal proteins and quality control processes regulate infected cell protein synthesis

While long considered as invariant mRNA decoding machines, ribosome composition and ribosome protein (RP) abundance and stoichiometry in different cells and tissues

may be heterogeneous and can regulate gene expression (Shi et al. 2017). Indeed, ribosome catalytic activity tolerates loss of several RPs, and specific RP requirements have been identified for discrete host mRNAs (Xue et al. 2015). Individual RPs also shape host responses to infection by regulating MHC class I peptide generation (Wei et al. 2019). Post-translational modifications (PTMs) of RPs and rRNAs and association with noncanonical RPs accentuate ribosome heterogeneity. Recent attention has focused on how virus infection impacts ribosomes and their role in regulating, as opposed to executing, protein synthesis (Fig. 4).

To translate their mRNAs, viruses may be more reliant on RPs that are not essential for bulk host protein synthesis. Virus IRESs require a different RP subset from transcripts that rely on cap-dependent initiation (Fig. 4). Structurally and functionally diverse IRESs require eS25 (RPS25) for 40S-IRES complex formation (Landry et al. 2009). Largely dispensable for cap-dependent translation, eS25 sits within the ribosomal E-site with a projection extending toward the P-site. CrPRV IRES binding to 40S requires eS25, as does an ensuing, stabilizing conformation change (Walters et al. 2020). Ribosome shunting also requires eS25 (Hertz et al. 2013). Host 40S RP RACK1 contributes to PV, EMCV, CrPV, and HCV IRES-mediated translation (Majzoub et al. 2014; LaFontaine et al. 2020). Insufficient RACK1 levels reduced PV plaque size and impaired virion release (LaFontaine et al. 2020). The HCV IRES binds to eL20 (RPL18A) and uS7 (RPS5) (Dhar et al. 2006), the latter required for IRES function (Fukushi et al. 2001; Bhat et al. 2015). Tethered to IRESs by binding to DDX3, eL13 (RPL13) stimulates translation from

FMDV, SVV, and CSFV IRESs with minimal impact on host translation (Han et al. 2020).

While not essential for cellular and IRES-driven translation, eL40 (RPL40) is needed for cap-dependent translation of VSV, rabies, and measles transcripts (Lee et al. 2013). P1 (RPLP1) and P2 (RPLP2) bind 60S to form the ribosomal stalk, which is anchored by uL10 (RPLP0) and needed for DENV, YFV, and ZIKV replication, but dispensable for host translation (Campos et al. 2017). P1/P2 mitigates ribosome pausing on DENV RNA (Campos et al. 2020), and DENV NS1 protein interacts with and relocalizes eL18 (RPL18), eL20, and uL30 (RPL7), although how this influences translation is unclear (Cervantes-Salazar et al. 2015). While some virus mRNAs require specific RPs dispensable for general host translation, the extent to which diverse viruses might rely on discrete individual RPs or combinatorial RP subsets to differentially impact virus mRNA translation in varied cell types, tissues, or host/vector systems remains unknown and ripe for investigation. In contrast, protein synthesis in HSV1-infected compared with uninfected cells is far less dependent on host RPs. Under conditions where RP insufficiency limits translation and ribosome availability, the HSV-1 late protein VP22 cosediments with initiating and elongating ribosomes, promotes polysome accumulation, and enforces translation (Vink et al. 2021). How VP22 compensates for RP insufficiency, which could support protein synthesis despite cell type and stress-induced RP variations, requires further study.

While it remains conceivable although unproven that virus mRNA translation might rely on a ribosome subpopulation with a specific RP stoichiometry, virus infection can modify ribosomes to impart selectivity for specific transcripts. One way host ribosomes are modified is through virus-encoded, ribosome-associated proteins. IAV NS1 protein associates with ribosomes and stimulates initiation on mRNAs, except those with a dicistrovirus IGR IRES (Panthu et al. 2017). By triaging which transcripts access ribosomes, SARS-CoV-1/2 Nsp1 promote host shutoff and virus protein synthesis (Huang et al. 2011; Lokugamage et al. 2015). SARS-CoV-1 Nsp1 inhibits cap-dependent and IRES-mediated translation by binding 40S via interactions with uS3 (RPS3), uS5 (RPS2), and 18S rRNA helix h18, and preventing 60S joining (Kamitani et al. 2009). Moreover, Nsp1 locks the 40S into a conformation that prevents mRNA loading and preinitiation complex formation by binding eIF1 and eIF3j (Thoms et al. 2020; Yuan et al. 2020; Lapointe et al. 2021). The Nsp1 C terminus occupies the mRNA entry channel, inhibiting translation by preventing most host mRNAs, including those encoding immune defenses, from entering ribosomes (Schubert et al. 2020). The SL1 hairpin within the virus mRNA 5' UTR interacts with and displaces Nsp1 (Shi et al. 2020; Mendez et al. 2021; Tidu et al. 2021) from the entry channel to selectively enable CoV mRNA translation. Not all host transcripts are excluded from ribosomes by Nsp1, as translation of mRNAs containing 5' TOP elements is stimulated (Rao et al. 2021). Further study is needed to discern whether this mechanism shares similarity to the one used by CoV mRNAs.

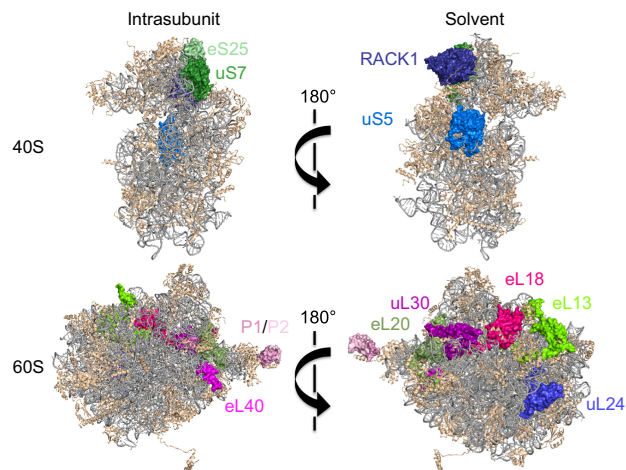


Figure 4. Ribosome proteins (RPs) that regulate translation in virus-infected cells. The figure depicts solvent and intrasubunit surfaces of 40S and 60S subunits with ribosomal RNA (gray) and RPs (tan). Highlighted RPs represent RPs important for virus IRES-mediated translation (green) or proviral functions (pink), or post-translationally modified during viral infection (blue). (Ribosome structure derived from PDB entry 4v88; figure based on data from Ben-Shem et al. [2011]).

Another way virus infection (VacV, HSV-1, and VSV) modifies ribosomes is through RP and ribosome-associated protein PTM, which could regulate infected cell protein synthesis (DiGiuseppe et al. 2020). The VacV protein kinase B1R phosphorylates uS5, a 40S RP located near the mRNA entry channel (Fig. 4), enabling VacV protein synthesis (Banham et al. 1993; Beaud et al. 1994; DiGiuseppe et al. 2020). By stimulating RACK1 (Fig. 4) phosphorylation, VacV remodels ribosome transcript selectivity. The resulting negative charge on RACK1 Ser/Thr residues within an extended loop increases the swivel motion of the 40S head domain and broadens the translational capacity of the human ribosome, enabling preferential translation of viral mRNAs containing A-rich 5' UTRs (Jha et al. 2017; Rollins et al. 2021). Finally, ubiquitin fold modifier (UFM1) conjugation to uL24 (RPL26) (Fig. 4) is required for HAV translation (Kulsuptrakul et al. 2021).

Rather than altering core RP stoichiometry, PV, ZIKV, and DENV remodel the host polysome-associated protein landscape. While host factors that trigger RNA sequestration, RNA degradation, antiviral responses, and eIFs were displaced, proteins required for proline hydroxylation were recruited to polysomes in ZIKV- and DENV-infected cells. (Aviner et al. 2021) This enables cotranslational proline hydroxylation of the viral polypeptide, which is essential for transmembrane domain folding and topology and is required for replication (Aviner et al. 2021)

Virus mRNA translation is also regulated by ribosome quality control (RQC) surveillance. Upon identification of aberrant mRNAs, including those lacking in-frame stop codons due to premature poly(A) addition within coding sequences, or ribosome stall-inducing translation events, RQC triggers degradation of mRNA/nascent protein and recycles stalled ribosomes (Meydan and Guydosh 2021). Elevated protein synthesis in virus-infected cells may provoke ribosome stalling or stress responses resolved by RQC. The multifunctional host protein ABCE1, which also inhibits RNase L, is needed for translation termination and ribosome recycling and in part facilitates RQC (Anderson et al. 2019). Virus mRNA translation and replication in cells infected with (–)-strand RNA viruses (measles, mumps, and RSV) was more reliant on ABCE1 than host mRNAs. In response to detecting stall-inducing A-rich sequences on translating mRNA, ribosome-bound ZNF598 E3 ubiquitin ligase triggers RQC and restricts ribosome read-through by ubiquitination of select 40S RPs (Garzia et al. 2017; Juskiewicz and Hegde 2017; Sundaramoorthy et al. 2017). Unexpectedly, ZNF598 E3 ligase and uS10 (RPS20) site-specific ubiquitination were required for poxvirus replication and translation of virus mRNAs, many of which contain an unusual A-rich 5' UTR (DiGiuseppe et al. 2018; Sundaramoorthy et al. 2021). Stimulation of translation by ZNF598 is in contrast to its role in 80S stalling and RQC, although both might involve ZNF598-sensing poly(A) or A-rich sequences. Instead, ZNF598 might potentially impact scanning or possibly be repurposed to stimulate translation by poxviruses (DiGiuseppe et al. 2018). Virus infection might also induce ribosome collisions, and ZNF598-mediated RQC may rescue

stalled ribosomes and recycle the subunits to stimulate virus mRNA translation (Sundaramoorthy et al. 2021). Further studies are needed to elucidate the underlying mechanism. Finally, disrupting RQC stimulates cyclic GMP–AMP synthase (cGAS), a cytosolic DNA sensor that reportedly binds to collided ribosomes in vitro (Wan et al. 2021). Increased cGAS activity triggers ISG expression, which restricts virus replication. One such IFN-induced protein, IFIT2, is repurposed by IAV to prevent ribosome pausing on host and virus AU-rich mRNAs that could trigger RQC (Tran et al. 2020).

Closing thoughts

By appropriating and subverting cellular RNA decay and modification pathways together with unconditional reliance on host ribosomes, viruses remain enduring models to probe how gene expression is controlled post-transcriptionally and remodeled by physiological stress. Fundamental findings revealed by virus infection have implications for post-transcriptional mechanisms impacting health and disease including roles for eIF2 α kinase PKR in tuning protein synthesis to stress responses and new ways to subvert the ISR by phospho-eIF2 α –eIF2B, the control of innate immune responses by m⁶A, how 40S ribosomes are captured by a structured RNA without initiation factors, and how the cellular mRNA landscape is globally remodeled during infection stress. Understanding these processes offers new therapeutic possibilities to treat virus infections. Variants of the dsRNA sensor OAS1 are known to protect against severe COVID19 (Soveg et al. 2021; Wickenhagen et al. 2021). Inhibition of PA endonuclease activity by baloxavir represents a first in class new influenza antiviral (Heo 2018). SARs-CoV-2 Nsp1•40S interactions may also prove amenable to antiviral drug development. Cellular decay factors, including the SKI and TRAMP-like complex, and m⁶A modification by METTL3 on which viruses depend but whose short-term inhibition is tolerated by the host also present druggable targets less likely to be overcome by virus resistance (Weston et al. 2020; Burgess et al. 2021; Ho et al. 2021; Kulsuptrakul et al. 2021). By tinkering with functions that regulate eIF2 α phosphorylation, a safe, attenuated HSV-1 that preferentially replicates in cancer cells with impaired cell-intrinsic immune responses was engineered (Taneja et al. 2001). This unexpected property led to development of an approved immunotherapeutic oncolytic virus to treat melanoma (Ribas et al. 2017). Continued exploration of diverse animal virus models will undoubtedly drive our understanding of how infection and physiological stress regulate gene expression post-transcriptionally and fuel unanticipated future opportunities to treat a spectrum of unmet medical needs.

Competing interest statement

The authors declare no competing interests.

Acknowledgments

We apologize to colleagues whose work was not cited owing to space limitations. Work in the author's laboratories is supported by grants from the National Institute of Allergy and Infectious Diseases to H.M.B. (AI151436 and AI166638) and I.M. (AI073898 and AI152543), and from the National Institute of General Medical Sciences to I.M. (GM056927).

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