Cold Spring Harbor Perspectives in Biology
www.cshperspectives.org

Translational Control in Virus-Infected Cells

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As obligate intracellular parasites, virus reproduction requires host cell functions. Despite variations in genome size and configuration, nucleic acid composition, and their repertoire of encoded functions, all viruses remain unconditionally dependent on the protein synthesis machinery resident within their cellular hosts to translate viral messenger RNAs (mRNAs). A complex signaling network responsive to physiological stress, including infection, regulates host translation factors and ribosome availability. Furthermore, access to the translation apparatus is patrolled by powerful host immune defenses programmed to restrict viral invaders. Here, we review the tactics and mechanisms used by viruses to appropriate control over host ribosomes, subvert host defenses, and dominate the infected cell translational landscape. These not only define aspects of infection biology paramount for virus reproduction, but continue to drive fundamental discoveries into how cellular protein synthesis is controlled in health and disease.

A defining attribute of virus infection biology is its absolute reliance on the host translation machinery to produce the polypeptides needed for virus reproduction. This feature cannot be overstated, as virus replication and spread depend on conscripting host ribosomes to translate viral messenger RNAs (mRNAs). Failure to engage ribosomes would have dire consequences for virus reproduction and evolution. To ensure translation of their mRNAs, virus-encoded functions dominate cell signaling pathways that control the host protein synthesis machinery. Commandeering these regulatory circuits preserves the functionality of components that recruit ribosomes to viral mRNAs. Although many host cell intrinsic immune defenses target translation factors to incapacitate the protein synthesis apparatus of the infected cell, viral factors have evolved to limit host antiviral responses. Exploiting virus model systems continues to reveal fundamental parameters governing how mRNA translation is controlled in infected and uninfected cells. Here, we review molecular interactions between select plant and animal viruses and their hosts that regulate protein synthesis in infected cells, and recent developments in the field are highlighted.

A PRIMER ON VIROLOGY AND VIRUS REPRODUCTION STRATEGIES

Viruses are vastly diverse, and although a comprehensive discussion of virus biology is not our purpose, an overview of select principles is war-

Editors: Michael B. Mathews, Nahum Sonenberg, and John W.B. Hershey
Additional Perspectives on Translation Mechanisms and Control available at www.cshperspectives.org

 doi: 10.1101/cshperspect.a033001
Cite this article as *Cold Spring Harb Perspect Biol* 2019;11:a033001

ranted. Viruses are obligate intracellular parasites with varied lifestyles. Whereas acute infections are often cytolytic and destroy the cell, persistent infections can be tolerated. Some viruses establish permanent infections, in which viruses continually replicate or, alternatively, remain latent within cells and reproduce only periodically. These distinct reproduction strategies differentially impact the host translation machinery and translated mRNA landscape. Viruses replicate within and may remodel the cytoplasm or nucleus. Not all infections cause clinical disease, and infection outcome varies among organisms or cell types and is dependent on immune status. Finally, viruses have diverse genome structures comprised of single- or double-stranded (ds) DNA or RNA, and RNA virus genomes can be composed of single or multiple nucleic acid segments. Viral genome size varies from less than 10 Kb for small RNA viruses to greater than 200 Kb for large human DNA viruses and megabase genomes of DNA viruses that infect *Acanthamoeba* (Schultz et al. 2017). Notwithstanding genome size, viruses are under selective pressure to optimize coding capacity, and tactics like polyprotein processing, where proteases generate multiple proteins from one open reading frame (ORF; e.g., in picornaviruses and flaviviruses) and recoding (e.g., frameshifting as in retrovirus Gag-Pol) are frequently observed (Jan et al. 2016; Atkins et al. 2016).

Genome structure largely informs mRNA biogenesis and mRNA features impact translation. Single-strand RNA virus genomes having an identical polarity to mRNA, termed plus (+)-strand RNA viruses, function as mRNA and are directly translated on infection. RNA virus genomes of opposite polarity, designated minus (−)-strand RNA viruses, and dsRNA virus genomes require an RNA-dependent RNA polymerase to produce mRNA. Discrete structural elements within 5′ and 3′ untranslated regions (UTRs) support RNA virus genome replication and mRNA translation. Viral mRNA 5′ ends may be uncapped, protein-linked, modified by viral capping enzymes to contain a 5′ methyl-7-GTP (m^7GTP) cap, or derived from host mRNA 5′ terminal fragments that are naturally capped (Decroly et al. 2012). Uncapped viral mRNAs deploy specialized genome elements to recruit 40S ribosomal subunits that support translation even when canonical cap-dependent translation is impaired (Kwan and Thompson 2018). Polyadenylated 3′ ends are generally template-encoded for RNA viruses or replaced by an element that recruits a viral 3′ terminal binding protein (Poon et al. 1999; Deo et al. 2002; Kempf and Barton 2015). After converting (+)-strand RNA genomes into dsDNA using reverse transcriptase, retroviruses produce mRNA using the host RNA polymerase II transcriptional machinery. Whereas most DNA viruses replicate within the nucleus and use host enzymes for mRNA biogenesis, others, including poxviruses and asfarviruses, replicate in the cytoplasm, encoding their own transcription, capping, and 3′ end processing machinery (Van Etten et al. 2010).

STRESS RESPONSES AND INFECTION BIOLOGY

Controlling gene expression by mRNA translation enables swift responses to environmental and physiological insults, including infection. Indeed, many host proteins and mechanisms regulating protein synthesis in response to stress in uninfected cells (reviewed by Wek 2018) play significant roles during infection. Likewise, features of translational control in virus-infected cells resemble and perhaps were co-opted from host cell stress responses.

Host Defenses and Antiviral Immunity

While hijacking ribosomes enables virus protein production, it also is a vulnerability exploited by the host. Significantly, many innate host defenses limit mRNA access to ribosomes by selectively or globally impairing the translation machinery. The struggle between viruses and their hosts to control ribosomes occupies the front lines in the innate immune response to virus infection.

By detecting conserved viral nucleic acid features, including uncapped single-stranded RNA, dsRNA, or cytoplasmic DNA, host sentinel pattern recognition receptors trigger type I interferon (IFN) production (Chiang and Gack 2017). The resulting IFN-induced host proteins

establish an "antiviral state" that is not permissive for virus reproduction. Many IFN-induced proteins impact translation and ribosome recruitment to mRNA (Diamond and Farzan 2013; Schoggins 2014). Central among these are PKR, a eukaryotic initiation factor (eIF)2α kinase, and oligoadenylate synthetase (OAS), which are both activated by dsRNA. Importantly, dsRNA accumulates in cells infected with RNA or DNA viruses. Although some viruses have dsRNA genomes, dsRNA is an obligatory intermediate in RNA virus genome replication and can be present as secondary structures in single-strand RNA. dsRNA also accumulates in cells infected with DNA viruses, which produce mRNAs from opposing strands of the viral genome. Upon activation by dsRNA, PKR phosphorylates the α subunit of eIF2 (Fig. 1). This inactivates eIF2, a GTP-regulated, three-subunit complex that loads 40S ribosomal subunits with initiator methionyl-transfer RNA (Met-tRNA$_i^{Met}$) (Merrick and Pavitt 2018; Wek 2018). Normally, GTP hydrolysis is stimulated by eIF5 following start codon recognition enabling 60S subunit joining. Subsequent eIF2•GDP recycling to the GTP-bound form requires guanine nucleoside exchange factor (GEF) eIF2B (Merrick and Pavitt 2018; Wek 2018). However, phosphorylated eIF2 binds tightly to eIF2B, inhibiting its GEF activity (Fig. 1). Because eIF2B is limiting, small changes in phosphorylat-

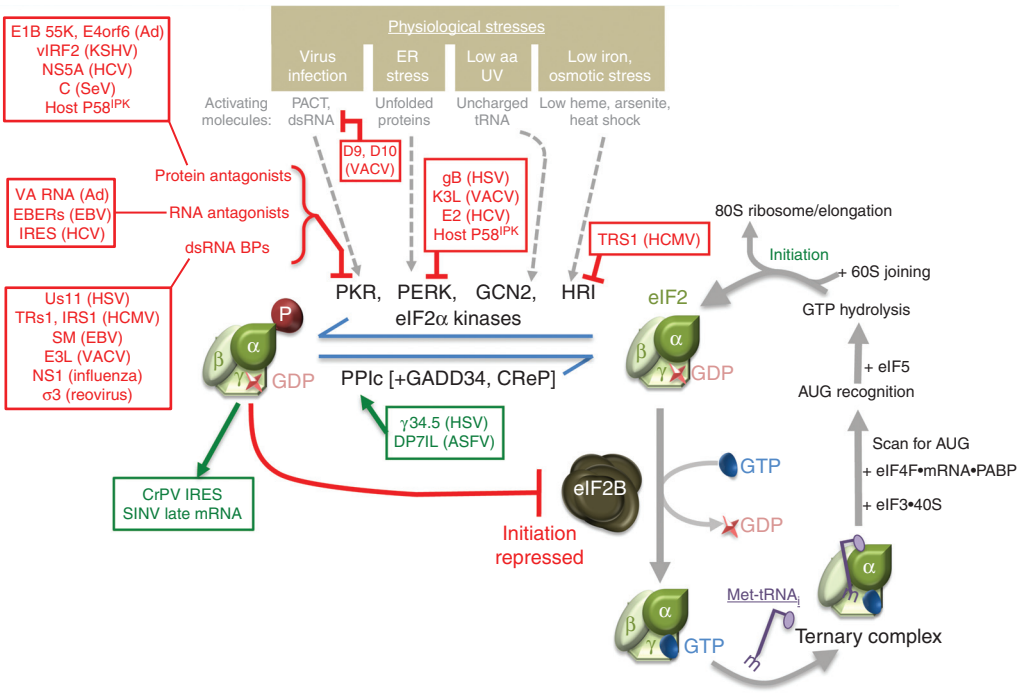

Figure 1. Targeting stress-responsive host defenses by viral functions controls eukaryotic initiation factor (eIF)2α phosphorylation and translation initiation. Composed of three subunits (α,β,γ), eIF2 is a GTP-binding translation initiation factor that loads eIF3-bound 40S ribosomal subunits with methionyl-transfer RNA (Met-tRNA$_i$) (*right* panel). Subsequent mRNA recruitment, AUG recognition, and eIF5-stimulated GTP hydrolysis is followed by 60S subunit joining and translation initiation by the 80S ribosome. Recycling inactive eIF2•GDP to the active GTP-bound form requires the GEF eIF2B. Phosphorylation of eIF2α on S51 blocks initiation by binding to and inhibiting eIF2B, preventing GDP-GTP exchange. Four eIF2 kinases, each of which is activated by specific molecules that accumulate in response to a discrete physiological stress, and the protein phosphatase 1 catalytic subunit (PP1c), partnered with an inducible (GADD34) or constitutively active (CreP) regulatory subunit, control eIF2α phosphorylation. Viral functions that activate (green), respond to (green), or repress (red) the indicated host effectors are shown. aa, amino acid.

ed eIF2α have a large impact on protein synthesis and globally inhibit initiation.

Whereas OAS is similarly activated by dsRNA, it interferes with protein synthesis via a different mechanism. OAS synthesizes short oligoadenylate (OA) polymers with a 2′–5′ linkage that stimulate RNase L, an endogenous ribonuclease whose activation is dependent on OA (Sadler and Williams 2008; Han et al. 2014). Active RNase L degrades ribosomal RNA (rRNA) and mRNA, inactivating both the translation machinery and its templates. RNase L cleavage products, which contain 2′–3′ cyclic phosphorylated termini, also stimulate inflammasome activation (Chakrabarti et al. 2015).

Viral Tactics to Counter Host Defenses

Viruses have acquired countermeasures that neutralize host dsRNA-activated defenses or allow their replication despite them. Coronavirus and rotavirus-encoded phosphodiesterases attack OA, limiting its accumulation and RNase L activation (Zhang et al. 2013). In addition, a picornavirus-encoded RNA and protein inhibit RNase L (Townsend et al. 2008; Sorgeloos et al. 2013), and Rift Valley fever virus (RVFV) triggers PKR degradation (Mudhasani et al. 2016). dsRNA-binding proteins encoded by a variety of viruses shield dsRNA from host sensors, foiling PKR and OAS activation (Fig. 1), and some physically interact with PKR to prevent its activation (Jan et al. 2016). Surprisingly, dsRNA accumulation and dsRNA-responsive immune effectors are regulated by the host Xrn1 mRNA exoribonuclease (Burgess and Mohr 2015). By accelerating RNA decay, viral enzymes like poxvirus decapping enzymes or coronavirus nsp15 endonuclease, which presumably produce Xrn1 substrates, limit dsRNA accumulation (Burgess and Mohr 2015; Liu et al. 2015; Deng et al. 2017; Kindler et al. 2017). Alternatively, an adenovirus (Ad) small RNA, VA RNA_I, binds PKR but is not large enough to support PKR dimerization, which is needed for activation (Mathews and Shenk 1991; Launer-Felty et al. 2015).

Broader strategies protect eIF2α from phosphorylation not only by PKR, but by the other stress-activated eIF2α kinases PERK, HRI, and GCN2 (Fig. 1) (Pavio et al. 2003; Berlanga et al. 2006; Won et al. 2012; Vincent et al. 2017). Examples include the poxvirus-encoded eIF2α pseudo-substrate K3L (Sood et al. 2000; Seo et al. 2008), the HCMV TRS1 protein that binds and inhibits PKR and HRI (Hakki et al. 2006; Vincent et al. 2017), and a phosphatase regulatory subunit encoded by herpes simplex virus (HSV)-1 (γ34.5) and African swine fever virus (ASFV) DP71L, which recruits the host protein phosphatase 1α catalytic subunit to eIF2α where it counteracts the activity of eIF2α kinases (Rojas et al. 2015; Barber et al. 2017). Induction of host $p58^{IPK}$ by infection can also limit PKR, PERK, and GCN2 activation (Goodman et al. 2011; Roobol et al. 2015). Multiple functions that act synergistically to restrict eIF2α phosphorylation are encoded by HSV-1 and poxviruses, illustrating the importance of preserving functional eIF2 (Mulvey et al. 2003, 2007; Seo et al. 2008; Rice et al. 2011; Sciortino et al. 2013; Burgess and Mohr 2015; Liu et al. 2015). Mutant viruses deficient in functions that subvert host dsRNA-activated defenses often have an altered host range (Haller et al. 2014; Carpentier et al. 2016; Peng et al. 2016), are hypersensitive to IFNs and in some cases are profoundly attenuated (Mulvey et al. 2004; White and Jacobs 2012; Liu et al. 2015). Activation of the unfolded protein response and PERK by hepatitis C virus (HCV) and vesicular stomatitis virus (VSV), however, may also favor virus replication by accelerating type I IFN receptor degradation to attenuate IFN responses (Liu et al. 2009). Finally, several RNA viruses including cricket paralysis virus (CrPV) and Sindbis virus (SINV) contain *cis*-elements that obviate the requirement for eIF2 altogether (Wilson et al. 2000; Spahn et al. 2004; Kerr et al. 2016; Sanz et al. 2017). Although in vitro studies suggested a mechanism in which eIF2A or eIF2D supply $Met\text{-}tRNA_i^{Met}$, recent work using knockout cell lines shows that these factors are dispensable (Sanz et al. 2017; Gonzales-Almela et al. 2018). The role of RNA structures and contribution of other proteins to eIF2-independent initiation on CrPV and SINV remain to be established.

Stress responses, including those resulting from infection, impact mRNA and translation

factor subcellular distribution. Stalled initiation complexes containing messenger ribonucleoproteins (mRNPs), mRNA, 40S subunits, initiation factors, and RNA-binding proteins (RBPs) accumulate in phase-dense, non-membrane-bound aggregates called stress granules (SGs) (Protter and Parker 2016; Ivanov et al. 2018). Although eIF2α phosphorylation often accompanies SG formation, implying a reversible way of regulating initiation, SG accumulation can be inhibited or viral mRNAs released from SGs regardless of eIF2α phosphorylation (Montero et al. 2008; Qin et al. 2011). SG core components can directly interface with viral RNA genomes or mRNAs, repressing their translation (Albornoz et al. 2014). Host cytoplasmic RNA sensors including MDA-5, RIG-I, and PKR can be recruited to SGs in response to eIF2α phosphorylation, suggesting SGs are platforms for viral RNA detection (Reineke and Lloyd 2015; Oh et al. 2016; Sánchez-Aparicio et al. 2017). Indeed, many viruses interfere with SG formation (Emara and Brinton 2007; White et al. 2007; Finnen et al. 2014; Khaperskyy et al. 2014; Dauber et al. 2016; Humoud et al. 2016; Nelson et al. 2016; Rabouw et al. 2016; Amorim et al. 2017; Basu et al. 2017; Choudhury et al. 2017; Khong et al. 2017; Le Sage et al. 2017). In cells infected with Middle East respiratory syndrome (MERS) coronavirus, Kaposi sarcoma–associated herpesvirus (KSHV), or HSV-1, this is achieved in part by preventing PKR activation (Rabouw et al. 2016; Sharma et al. 2017; Burgess and Mohr 2018). Even though SG formation is inhibited by dengue virus (DENV) and Zika virus, host protein synthesis remains suppressed, uncoupling these processes (Roth et al. 2017). Depleting key SG components like G3BP reduces Zika virus replication, however, indicating that host SG components may be repurposed to benefit virus reproduction without SG formation (Hou et al. 2017). Whereas SGs can be dynamic platforms for staging host antiviral responses (Tsai and Lloyd 2014; McCormick and Khaperskyy 2017), SG formation is stimulated by rabies virus (Nikolic et al. 2016) and enhances respiratory syncytial virus replication (Lindquist et al. 2010). The rationale underlying this seemingly opposite strategy is unknown.

Remodeling Host mRNA Translation in Infected Cells

By interfering with host translation, which overwhelmingly is cap-dependent, viruses antagonize host defenses. In its extreme form, termed "host shut-off," virus infection impairs ongoing host protein synthesis, limiting production of host defense molecules and allowing viral mRNAs to better compete for limiting factors (Mohr and Sonenberg 2012; Mohr 2016). Different mechanisms account for host shut-off (Fig. 2). Picornaviruses suppress host protein synthesis by inhibiting cap-dependent translation and often target eIF4F, a multisubunit initiation factor comprised of the cap-binding protein eIF4E, the eIF4G scaffold, and the DEAD-box-containing RNA helicase eIF4A, needed to load 40S subunits onto m^7GTP-capped mRNAs. Poliovirus 2A proteinase cleaves eIF4G, separating the eIF4E-binding domain from the eIF3-binding region (Gradi et al. 1998), whereas 3C proteinases cleave the poly(A)-binding protein (PABP) (Rivera and Lloyd 2008; Kobayashi et al. 2012a). Cleavage of eIF4G by poliovirus or group A rhinovirus 2A protease is stimulated by eIF4E (Aumayr et al. 2017; Avanzino et al. 2017). During encephalomyocarditis virus (EMCV) infection, hypophosphorylated 4E-BP1 repressor accumulates, inhibiting eIF4E binding to eIF4G and limiting eIF4F assembly (Gingras et al. 1996). Enterovirus 71 (EV 71) instead induces host microRNA miR-141 expression, which reduces eIF4E abundance to suppress host protein synthesis (Ho et al. 2010).

Remodeling the host mRNA pool available for translation by cytoplasmic ribosomes is another shut-off mechanism. By encoding virus factors that stimulate mRNA turnover, viral mRNAs, which are actively transcribed in acutely infected cells, dominate the mRNA pool. Accelerating mRNA decay also sculpts viral mRNA populations, facilitating temporal viral gene expression transitions (Jan et al. 2016). Viruses that produce mRNAs with m^7GTP-capped 5′ termini, like herpesviruses and poxviruses, rely on mRNA decay to liberate host ribosomes without impairing cap-dependent translation. Viral functions subsequently can stimulate

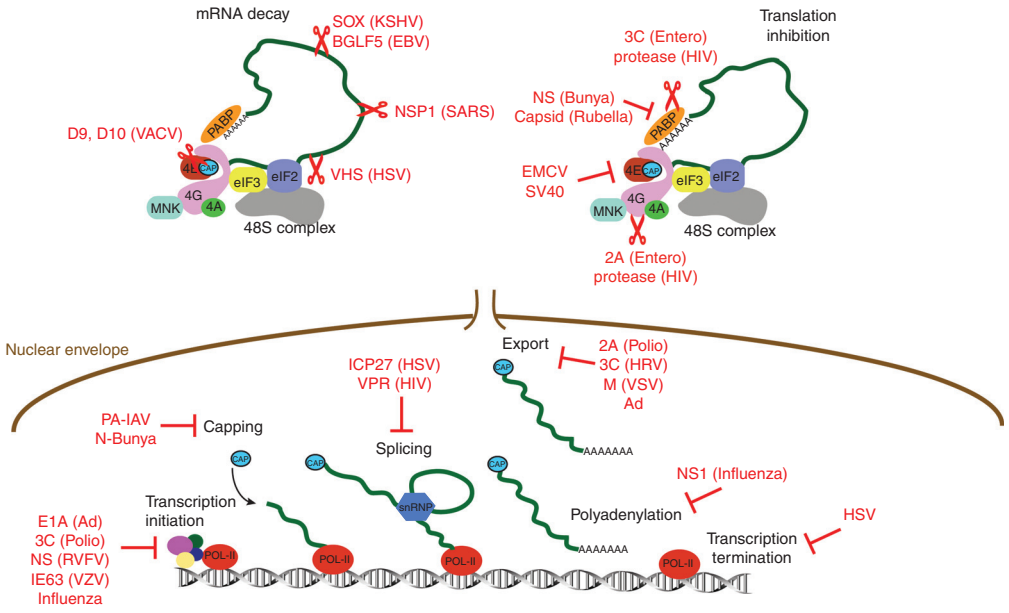

Figure 2. Viruses use multiple mechanisms to block host messenger RNA (mRNA) translation. Cellular mRNA biogenesis starts in the nucleus where RNA polymerase II generates primary transcripts that undergo several processing steps including 5′ capping, splicing, and polyadenylation before functional mRNAs are produced. Mature mRNAs are exported to the cytoplasm where they are translated. Initiation of cap-dependent mRNA translation typically requires recruitment of the multisubunit eukaryotic translation initiation factor (eIF)4F, which consists of the cap-binding protein eIF4E, the RNA helicase eIF4A, and the adaptor protein eIF4G. Binding of eIF4G to poly(A)-binding protein (PABP) mediates communication between 5′ and 3′ ends. Virus-encoded factors that degrade (*scissors*) cellular proteins and mRNAs or repress cellular functions are shown.

cap-dependent translation by subverting cell signaling (Walsh et al. 2005, 2008). To generate substrates for mRNA decay, some viruses encode endoribonucleases (influenza, HSV-1, coronavirus, KSHV) (Kamitani et al. 2009; Read 2013; Abernathy and Glaunsinger 2015; Khaperskyy et al. 2016), whereas others like poxviruses encode decapping enzymes (Parrish and Moss 2007). The HSV-1 endoribonuclease vhs interacts with eIF4B and eIF4H to target mRNA cleavage (Read 2013), the KSHV SOX protein directs host RNA decay components, including the exoribonuclease XRN1, to translating ribosomes (Abernathy and Glaunsinger 2015), and the coronavirus nuclease nsp1 associates with 40S ribosomal subunits (Kamitani et al. 2009). Viruses can also disrupt host mRNA biogenesis and nuclear export to remodel the host mRNA pool (Faria et al. 2005; Rutkowski et al. 2015; Gong et al. 2016).

Not all viruses impair ongoing host translation during their acute reproductive cycle, however. Notably, host protein synthesis proceeds in human cytomegalovirus (HCMV)-infected cells. Activation of the mechanistic target of rapamycin complex 1 (mTORC1) (see Proud 2018) by the viral UL38 protein promotes cap-dependent translation and stimulates synthesis of factors encoded by mRNAs containing a 5′ terminal oligopyrimidine (5′-TOP; see Proud 2018) sequence element including PABP (McKinney et al. 2012, 2014). Higher PABP levels allow HCMV to overcome a host response that increases PABP-interacting protein 2 (Paip2) abundance, which inhibits PABP binding to eIF4G and poly(A) RNA (Fig. 3). Interfering with the HCMV-induced PABP increase results in restriction of virus replication by Paip2, highlighting an unexpected antiviral role for Paip2 in host-cell-intrinsic defenses (McKinney et al.

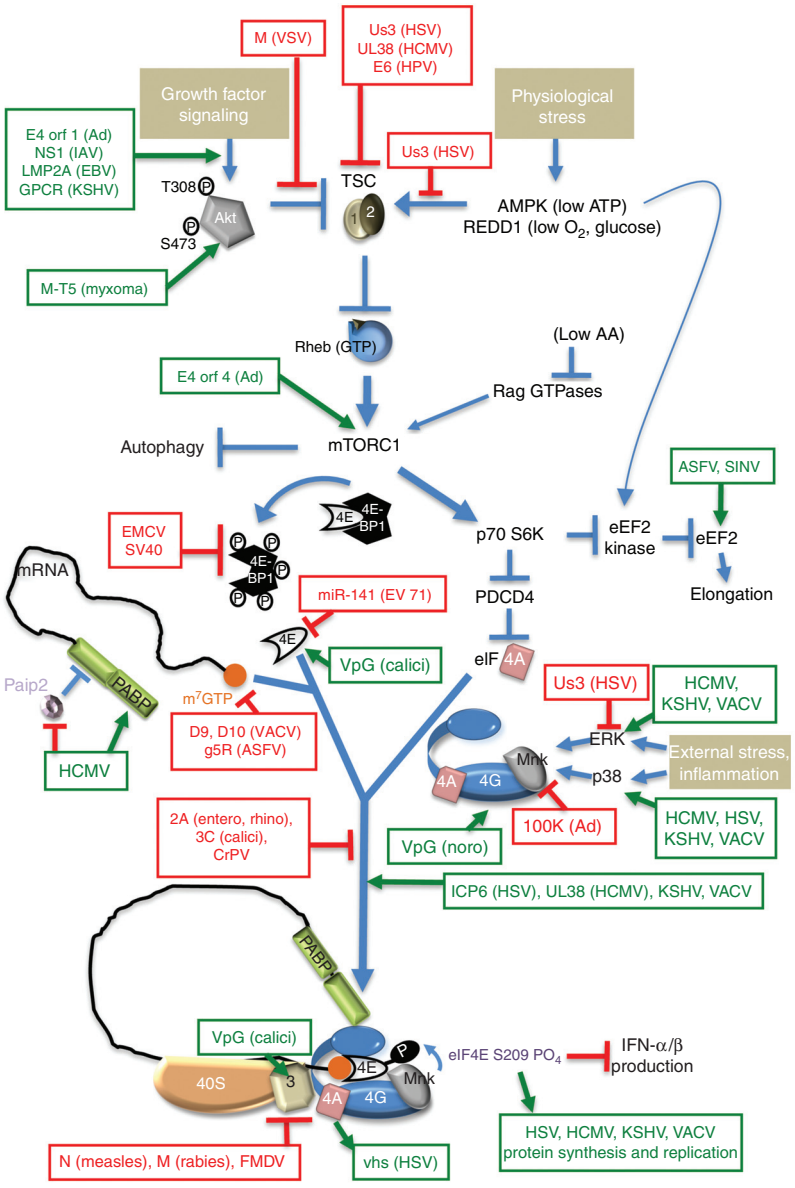

Figure 3. Subverting mechanistic target of rapamycin complex 1 (mTORC1) signaling to control translation in virus-infected cells. Occupying a nexus of intersecting signaling networks, the cellular ser/thr kinase mTORC1 plays a critical role stimulating anabolic programs, like protein synthesis, and repressing catabolic outcomes like autophagy. Briefly, growth factor–induced Akt phosphorylation (T308, S473) and activation represses TSC1/2, which, in turn, allows Rheb-GTP to activate mTORC1. Nutrient, energy, amino acid (aa), or oxygen insufficiency (physiological stress) all repress mTORC1 through discrete effectors. Signaling through mTORC1 allows swift changes in translational output in response to differing environmental and physiological inputs by controlling initiation and elongation. Initiation is stimulated by phosphorylating and inactivating 4E-BP translational repressor family members (e.g., 4E-BP1), which bind the cap-binding protein eIF4E to prevent its interaction with eIF4G. Through its substrate p70S6K, mTORC1 controls the DEAD-box-containing RNA helicase eIF4A, which together with eukaryotic initiation factor (eIF)4E and eIF4G comprises the multisubunit initiation factor eIF4F. Regulated eIF4F assembly controls cap-dependent mRNA translation as eIF4F recruits 40S subunits to the mRNA capped 5′ end. By repressing eEF2 kinase, mTORC1 stimulates eEF2 and elongation. The impact of mTORC1 activation on translation initiation and elongation is shown, as are viral factors that stimulate (green) and repress (red) the indicated cellular effectors. SV40, simian virus 40; calici, calicivirus; noro, norovirus; entero, enterovirus; rhino, rhinovirus.

2013). Avian herpesvirus microRNAs similarly repress Paip2 to stimulate translation of a specific viral mRNA (Tahiri-Alaoui et al. 2014). Additional host genes, like the IFN-induced C19orf66 (RyDEN) may also target PABP to restrict both DNA and RNA viruses, including DENV (Suzuki et al. 2016).

Regulating eIF4E phosphorylation impacts selective host mRNA translation and modulates IFN production, influencing host defenses. Coronaviruses, flaviviruses, noroviruses, and many large DNA viruses promote eIF4F assembly, positioning the eIF4G-associated kinase Mnk1 proximal to its substrate eIF4E (Fig. 3) (Mizutani et al. 2004; Walsh and Mohr 2004, 2006; Walsh et al. 2005, 2008; Royall et al. 2015; Roth et al. 2017; Proud 2018). This stimulates eIF4E S209 phosphorylation and translation of IκB mRNA, which encodes an NF-κB inhibitor (Herdy et al. 2012). Besides counteracting NF-κB-dependent IFN production, eIF4E phosphorylation stimulates viral mRNA translation (Walsh and Mohr 2004; Walsh et al. 2008). Significantly, eIF4E phosphorylation is dependent on eIF3 subunit e, showing how loading eIF3-bound 40S marks cap-bound eIF4F by phosphorylation to regulate selective mRNA translation (Walsh and Mohr 2014). Unphosphorylated eIF4E accumulates in cells infected with adenovirus and many RNA viruses (Jan et al. 2016), resulting in reduced translation of IκB-encoding mRNA, NF-κB activation, and IFN production.

Harnessing Stress Responses to Control Viral Persistence

Unlike acute infections, different viral lifestyles necessitate specialized interactions with host cells. Some, like herpesviruses, establish lifelong latency where virus reproduction is suppressed in specific cell types. Periodically, latent infections reactivate and reenter the productive growth cycle, which allows virus reproduction and spread to new hosts. Reactivation is influenced by host defenses and physiological stress responses induced by disrupting homeostasis. KSHV stimulates eIF4F assembly on inducible reactivation, and eIF4E phosphorylation is needed for optimal production of the lytic activator RTA (Arias et al. 2009). In contrast, HSV-1 establishes latency in neurons, where inactivation of the translation repressor 4E-BP1 by persistent mTORC1-dependent phosphorylation in response to neurotrophic factor sufficiency promotes latency (Camarena et al. 2010). Conversely, preventing 4E-BP1 phosphorylation stimulates reactivation presumably by restricting translation of eIF4E-responsive mRNAs that are repressed by 4E-BP1 (Kobayashi et al. 2012b). Whereas the mRNA targets remain unknown, monitoring host mRNA translation can gauge homeostasis in long-term, latent infections to support latency or trigger virus reproduction.

VIRAL STRATEGIES TO CAPTURE RIBOSOMES

The absolute dependence of viruses on host ribosomes for protein production demands tactics to ensure their recruitment to viral mRNAs. Shut-off mechanisms suppress host cap-dependent translation and effectively remodel the translation-ready mRNA pool. Ribosome recruitment, however, cannot be left to chance given its vital role in virus reproduction.

Mechanisms of Cap-Independent Translation Used by Viruses

When eIF4F becomes limiting, cap-dependent translation is restricted. Cleavage of eIF4G by poliovirus 2A proteinase shows a severe example of inactivating eIF4F. Uncapped poliovirus mRNA contains a specialized, *cis*-acting RNA internal ribosome entry site (IRES) in the 5′UTR. In contrast to canonical cap-dependent initiation where 40S ribosomes load onto the mRNA 5′ end, highly structured IRES elements enable ribosome recruitment to specific internal sites within viral RNA (Kwan and Thompson 2018). IRESs were first discovered in poliovirus and EMCV where they allow translation initiation of uncapped, single-stranded (+)-sense RNA viral genomes immediately upon release into the cytoplasm (Jang et al. 1988; Pelletier and Sonenberg 1988). Subsequently, IRESs have been identified in many virus genomes includ-

ing retroviruses like the human immunodeficiency virus (HIV)-1, which uses an IRES to express the Gag protein late in infection when cap-dependent initiation is impaired (Brasey et al. 2003; Amorim et al. 2014; Carvajal et al. 2016). Some DNA virus genomes like KSHV even contain IRES elements to facilitate translation of polycistronic mRNA (Othman et al. 2014).

Although they share the general capacity to direct initiation when canonical cap-dependent translation mechanisms are suppressed, different IRESs are structurally distinct and show varied functional requirements for eukaryotic initiation factors to load 40S subunits (Table 1) (Jan et al. 2016; Kwan and Thompson 2018). For example, the poliovirus IRES requires the eIF4G carboxy-terminal fragment, and selectively recruits 40S subunits to viral mRNA in a bona fide cap-independent manner (Sweeney et al. 2014). Even though the hepatitis A virus (HAV) RNA genome lacks an m^7GTP cap, it contains the only IRES found to require the cap-binding protein eIF4E (Table 1). Stimulation of the HAV IRES by eIF4E is independent of m^7GTP cap binding. Instead, eIF4E increases the affinity of eIF4G for several picornavirus IRESs, including HAV, and promotes IRES restructuring by the eIF4A helicase (Avanzino et al. 2017). In contrast, some IRESs, such as those in the CrPV intergenic region (IGR) and HCV, recruit 40S subunits without eIFs (Jan and Sarnow 2002; Pestova and Hellen 2003). Whereas the HCV IRES requires eIF3 and eIF2 to initiate translation (Fraser and Doudna 2007), the CrPV IGR can directly assemble 80S ribosomes and initiate translation in the absence of canonical initiation factors and even the initiator tRNA (Thompson et al. 2001; Jan et al. 2003; Pestova and Hellen 2003; Deniz et al. 2009).

In an alternative strategy, some RNA viruses like norovirus and calicivirus rely on a 5′ terminal protein covalently linked to the 5′ end of the

Table 1. Major types of IRESs

IRES	Examples	Required initiation factors[a]	References
Picornaviruses			
I. Enterovirus	Poliovirus, EV71, bovine enterovirus	eIF1A, eIF2, eIF3, eIF4A, eIF4B, central domain eIF4G, ITAFs (PCBP1/2, PTB)	Martinez-Salas et al. 2015
II. Cardio-/apthovirus	EMCV, FMDV	eIF2, eIF3, eIF4A, eIF4B, central domain eIF4G, ITAF PTB)	Martinez-Salas et al. 2015
III. HAV-like	Hepatitis A virus	eIF2, eIF3, eIF4A, eIF4B, eIF4E, eIF4G, ITAF (PTB, PCBP2)	Martinez-Salas et al. 2015
IV. HCV-like picornaviruses	Simian picornavirus type 9 (SPV9), porcine teschovirus I (PTV-1), Avian encephalomyelitis virus	eIF2, eIF3	Pisarev et al. 2004; Chard et al. 2006; Martinez-Salas et al. 2015
V. Aichivirus	Aichivirus	eIF2, eIF3, eIF4A, central domain eIF4G, ITAF (DHX29, PTB)	Yu et al. 2011
HCV-like	HCV, CSFV	eIF2, eIF3, binds to 40S directly	Fraser and Doudna 2007
Dicistrovirus intragenic (IGR)	CrPV, DCV, IAPV, PSIV	No initiation factors, binds 40S and assembles 80s directly	Hertz and Thompson 2011b
Retrovirus	HIV-1, HTLV-1, SIV, FIV	Central domain eIF4G, hypusine-eIF5A, eIF4A, likely other eIFs, ITAF (hnRNPA1, hRIP, DDX3), viral proteins (Rev)	Ohlmann et al. 2014; Plank et al. 2014; Caceres et al. 2016
KSHV vFLIP	KSHV vFLIP	eIF4A, eIF4G, eIF4E, eIF3, eIF2	Othman et al. 2014

[a]ITAFs: IRES transacting factors.

genome to recruit eIF4E, eIF4G, and/or eIF3 (Daughenbaugh et al. 2003; Leen et al. 2016). Different *cis* elements mediating long-range RNA interactions have been identified in plant (+)-strand RNA viruses (barley yellow dwarf virus, maize necrotic streak virus, carnation Italian ringspot virus, tomato bushy stunt virus, saguaro cactus virus). These cap-independent translation enhancers (CITEs) reside within 3′UTRs where they recruit 40S ribosomes directly or via eIF4F subunits eIF4E or eIF4G (Simon and Miller 2013). Functional base-pairing subsequently repositions 3′-CITE-loaded ribosomes proximal to 5′UTR structural elements (Nicholson and White 2014). Multiple 3′-CITEs in pea enation mosaic virus recruit both 40S and 60S subunits (Gao et al. 2014, 2017). By adopting alternate conformations induced by viral RNA polymerase binding, CITEs also repress translation to facilitate RNA replication (Le et al. 2017).

Strategies and Mechanisms Used by Viruses that Produce m^{7}GTP-Capped mRNAs

Viral mRNAs with a 5′-m^{7}GTP-cap and 3′-poly(A) tail are indistinguishable from host mRNAs and are typically translated by cap-dependent processes. A number of different strategies that are used to commandeer control over the translational machinery by dominating host cell signaling pathways (reviewed by Proud 2018) have been defined (Fig. 3). Herpesviruses and poxviruses constitutively stimulate mTORC1 to ensure that the 4E-BP1 translational repressor is inactivated (Moorman et al. 2008; Walsh et al. 2008; Arias et al. 2009; Chuluunbaatar et al. 2010). By targeting the host tuberous sclerosis complex (TSC), the HSV1 Us3 ser/thr kinase not only enforces mTORC1 activation by mimicking the cellular kinase Akt (Fig. 3), but also subverts host AMPK-dependent responses to energy insufficiency and supports virus replication during stress (Vink et al. 2017). In addition to inactivating 4E-BP1, these viruses rely on diverse mechanisms to promote assembly of eIF4F, the multisubunit initiation factor that recruits 40S ribosomes to m^{7}GTP-capped mRNA. These include an eIF4G-binding protein encoded by HSV-1 (ICP6) that stimulates eIF4E binding to eIF4G, promotes eIF4E phosphorylation, and stimulates viral mRNA translation (Walsh and Mohr 2006). To capitalize on limiting cytoplasmic PABP availability in HSV-1-infected cells, the viral ICP27 RNA-binding protein may stimulate initiation downstream of cap binding by harnessing PABP and eIF4G in a mechanism similar to that used by the cellular regulator Dazl (Deleted in azoospermia-like) (Smith et al. 2017). HCMV increases the overall abundance of eIFs and PABP. Moreover, preventing the virus-induced rise in PABP levels reduces eIF4F complex assembly and virus growth (McKinney et al. 2012). Instead of manipulating translation factor abundance, vaccinia virus (VACV) and ASFV, which replicate in the cytoplasm, increase the effective local concentration of eIFs by sequestering them within discrete replication compartments (Katsafanas and Moss 2007; Walsh et al. 2008; Castelló et al. 2009; Zaborowska et al. 2012; Desmet et al. 2014).

Following ribosome loading on capped viral mRNAs, AUG start codons are usually identified by 5′UTR scanning (Merrick and Pavitt 2018). However, some viruses use *cis* elements that allow ribosomes to bypass 5′UTR segments and resume AUG scanning further downstream. This nonlinear ribosome translocation, called ribosome shunting, is used to produce heat shock proteins in uninfected cells subjected to stress and involves base-pairing with 18S rRNA and mRNA *cis* elements (Yueh and Schneider 2000). In adenovirus-infected cells, ribosome shunting requires a *cis*-acting tripartite leader RNA sequence in late mRNAs, the virus-encoded 100K protein and eIF4G (Xi et al. 2004). Shunting also occurs in mRNAs encoded by cauliflower mosaic virus, human papillomavirus (HPV), DNA pararetrovirus, and a picorna-like virus (Remm et al. 1999; Pooggin et al. 2012).

Controlling Elongation

In comparison with initiation, our understanding of whether viruses control translation elongation is much less developed. Elongation factors are repurposed to function in RNA replication by many bacterial and plant viruses (Takeshita and Tomita 2012; Li et al. 2013). ASFV and SINV

concentrate eEF2 within virus replication compartments (Castelló et al. 2009; Sanz et al. 2009). Whereas mTORC1 activation by many viruses likely inhibits eEF2K (Fig. 3), stimulating elongation, the impact on infection biology remains largely unknown. Finally, expression of prokaryote-like elongation factors encoded by the giant mimivirus changes in response to nutrient availability (Silva et al. 2015), hinting that viral translation factors may supplant or supplement those resident in the host.

TACKLING THE RIBOSOME DIRECTLY

Viruses depend on host ribosomes regardless of whether they use cap-dependent or noncanonical translation initiation mechanisms. Whereas ribosome loading onto mRNAs in eukaryotes is typically reliant on initiation factors, a more direct role for the ribosome itself in regulating translation is emerging.

Dicistrovirus IRESs

Dicistroviruses are (+)-sense, single-stranded RNA viruses with two ORFs that are translated by two different IRESs. The 5′-IRES drives expression of the nonstructural proteins at a low level early in infection, whereas the IGR IRES drives robust structural protein expression late in infection (Garrey et al. 2010). IGR IRESs assemble 80S ribosomes without assistance from eIFs and initiate from the ribosomal A site at a non-AUG codon by priming the ribosome for elongation (Sasaki and Nakashima 2000; Wilson et al. 2000; Jan and Sarnow 2002; Jan et al. 2003; Pestova et al. 2004; Cevallos and Sarnow 2005; Yamamoto et al. 2007; Deniz et al. 2009; Zhang et al. 2016). By dissociating eIF4G from eIF4E to impair host protein synthesis, dicistroviruses subvert host ribosomes to translate viral IRES-containing RNAs (Garrey et al. 2010).

Ribosomal Proteins Control Translation in Virus-Infected Cells

Through discrete functions and modifications of specific protein subunits, ribosomes themselves selectively control viral and host mRNA translation (Fig. 4). Indeed, significant insight into how ribosome composition impacts translation has been gleaned from viral models. Two 40S subunit-associated proteins (eS25, RACK1) dispensable for cap-dependent initiation, but required for IRES activity, have been identified (Landry et al. 2009; Hertz and Thompson 2011a; Majzoub et al. 2014; Olivares et al. 2014; Carvajal et al. 2016). Whereas RACK1 is required by specific IRESs (dicistroviral 5′-IRES, HCV), it is not compulsory for the IGR IRES (Majzoub et al. 2014). In contrast, eS25 is essential for 40S subunit recruitment by numerous IRESs, including the dicistrovirus IGR and picornavirus, flavivirus, retrovirus, and cellular IRESs (Landry et al. 2009; Hertz et al. 2013; Olivares et al. 2014; Carvajal et al. 2016). Unexpectedly, eS25 is also important for ribosomal shunting, suggesting a potential shared mechanism between these two noncanonical initiation strategies (Hertz et al. 2013). Although RACK1 is not essential for cap-dependent translation of cellular mRNAs, poxvirus late mRNAs, which have 5′UTR adenosine tracts, require phosphorylated RACK1 for translation. By expressing a viral kinase that phosphorylates a loop region on RACK1, poxviruses remodel host ribosomes to confer a translational advantage on viral mRNAs that contain adenosine repeats in their 5′UTR (Jha et al. 2017). Consistent with this, adenosine-rich leaders enhance translation in plants where the RACK1 loop region is naturally negatively charged, suggesting that poxviruses have exploited a conserved mechanism to preferentially translate certain capped mRNAs (Jha et al. 2017).

A 60S subunit protein (eL40/RPL40) is required for VSV, rabies, and measles virus mRNA translation (Lee et al. 2013). These viruses produce capped, polyadenylated transcripts like cellular mRNAs, yet viral mRNAs are efficiently translated by an unknown mechanism even though host protein synthesis is suppressed. A screen for eL40-dependent mRNAs in yeast revealed that 7% of the yeast mRNAs required eL40, suggesting that VSV has usurped a highly conserved mechanism for translating a subset of cap-dependent mRNAs (Lee et al. 2013).

Dengue virus NS1 protein associates with ribosomal proteins from both the small and large subunits (Cervantes-Salazar et al. 2015).

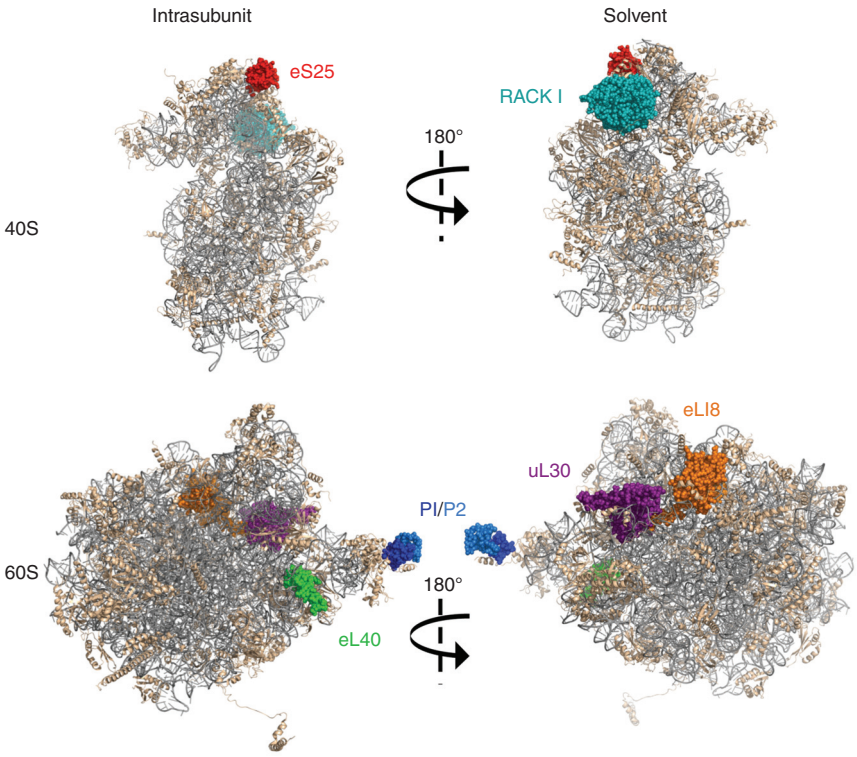

Figure 4. Ribosomal proteins are required for translation of viral RNAs. Locations of ribosomal proteins on 40S and 60S subunits that are important for viral messenger RNA (mRNA) translation are shown on the ribosome structure derived from PDB entry 4v88. (Figure based on data in Ben-Shem et al. 2011.) Both intrasubunit (*left*) and solvent surfaces (*right*) are shown. Ribsomal RNA (rRNA) (gray) and ribosomal proteins (tan) are depicted with the proteins implicated in viral mRNA translation in color: eS25 (red), RACK1 (turquoise), eL40 (green), uL30 (purple), eL18 (orange), and P1/P2 (dark blue/light blue).

Whereas the DENV RNA genome has a capped 5′ end, it lacks a poly(A) tail (Edgil et al. 2006). Two 60S ribosomal subunit proteins, eL18 and uL30 (previously called RPL18 and RPL7; Ban et al. 2014), were shown to relocalize with NS1 following DENV infection. Whether they play a direct role in translation is not known; however, knockdown of eL18 reduced viral titers by one log (Cervantes-Salazar et al. 2015). P1/P2 (RPLP1/2) are 60S subunit proteins that are part of the ribosome L1 stalk. They are also required for DENV protein expression early in infection (before replication) (Campos et al. 2017). Because the P1/P2 complex only associates with 80S ribosomes (not free subunits) and is important for eEF2 recruitment and GTPase activity, whether it effects elongation rather than initiation needs to be evaluated (Uchiumi et al. 2002; Bautista-Santos and Zinker 2014).

NEW INSIGHTS FROM GENOME-WIDE STRATEGIES

Recent progress using genome-wide, high-throughput technologies has reshaped our understanding of translational control. Besides uncovering new principles and mechanisms, these methodologies provide a global, unbiased view of the infected cell translational landscape.

Genome Annotation

Virus genomes contain densely packed coding information that is often accessed via specialized

translation strategies. Ribosome profiling (RP) (sequencing ribosome-protected fragments) allows global translation analysis and direct, experimental annotation of translation events (Ingolia et al. 2009, 2018). It couples classic nuclease footprinting with deep sequencing and indicates ribosome position with single-nucleotide resolution. Besides identifying precise boundaries of translated regions, the three-nucleotide footprint periodicity (reflecting translocation steps) indicates which reading frame is being decoded. Translational start sites can be mapped using conditions that preferentially capture initiating ribosomes (Ingolia et al. 2011; Lee et al. 2012; Stern-Ginossar et al. 2012). These approaches allow transcriptome annotation in areas translated in two overlapping reading frames, a frequent occurrence in virus genomes. Two herpesvirus genomes (HCMV, KSHV) (Stern-Ginossar et al. 2012; Arias et al. 2014), VACV (Yang et al. 2015), and a murine coronavirus (Irigoyen et al. 2016) have been annotated using RP, identifying numerous novel, mostly short ORFs translated upstream of, or within, known virus coding regions. Ribosome pause sites were identified in coronavirus A59, but their significance remains unknown (Irigoyen et al. 2016). RP also accurately measures virus gene expression kinetics throughout infection. During EMCV infection, RP exposed a temporally regulated frameshifting event. Although negligible early in infection, frameshifting efficiency increased to 70% at late time points, suggesting a new mechanism to modulate relative levels of EMCV structural and nonstructural proteins (Napthine et al. 2017).

Host Shut-Off

Application of genome-wide technologies to investigate host shut-off has clarified our understanding of underlying mechanisms and their relative contribution to impairing host translation. Concurrent measurement of translation and mRNA levels throughout influenza A virus (IAV), VACV, and coronavirus infections revealed that genome-wide changes to the host translation landscape are primarily driven by remodeling the mRNA pool (Bercovich-Kinori et al. 2016; Irigoyen et al. 2016; Dai et al. 2017). Although many viruses encode endoribonucleases, their specificity varies. In α (HSV-1) and γ (Epstein–Barr virus [EBV], KSHV) herpesvirus subfamily members, viral and cellular mRNAs are degraded, whereas viral mRNAs are spared by coronavirus and IAV (Rivas et al. 2016). A degenerate sequence motif was identified that enables cleavage of numerous RNA targets by a γ-herpesvirus endoribonuclease (Gaglia et al. 2015). Finally, transcription termination of cellular, but not viral, genes was unexpectedly disrupted by HSV-1, broadening our perception of the range of processes that potentially impact host shut-off (Rutkowski et al. 2015). Furthermore, γ-herpesvirus-induced mRNA degradation reduced host but not viral mRNA transcription, suggesting this cellular feedback mechanism empowers viral gene expression (Abernathy et al. 2015).

Infected Cell Translational Landscape

The notion of host shut-off as a blunt, indiscriminate instrument to halt host gene expression has been revised by genome-wide studies. While host shut-off curtails host antiviral responses, impairing overall cellular protein production could adversely impact virus reproduction. Precisely how the infected cell translational landscape impacts viral propagation is just beginning to be shown. Significantly, cellular mRNAs encoding critical maintenance functions like oxidative phosphorylation are spared from host shut-off and translated in IAV- and VACV-infected cells (Bercovich-Kinori et al. 2016; Dai et al. 2017). Although ongoing production of these proteins requires stable mRNA expression in IAV-infected cells, translation of mRNAs encoding oxidative phosphorylation effector proteins is stimulated by VACV. Continuous oxidative phosphorylation is important for viral propagation in both cases. Discrimination among targets during host shut-off is likely greater than previously anticipated. Similarly, numerous host mRNAs escape KSHV-mediated shut-off and affect viral pathogenesis (Glaunsinger and Ganem 2004). A different tactic was observed in HCMV-infected cells, where host

protein synthesis is not globally suppressed, so it was assumed that host protein synthesis proceeded uninterrupted. Using polysome profiling (McKinney et al. 2014) and RP (Tirosh et al. 2015), HCMV was shown to dramatically reshape the infected cell translation landscape. This translational reprogramming is dependent on mTOR activation, and expression of the virus-encoded UL38 mTORC1 activator in uninfected cells in part recapitulates these translational alterations. Importantly, interfering with the virus-induced activation of cellular mRNA translation can limit or enhance HCMV growth (McKinney et al. 2014). These examples show how genome-wide methodologies have revised our understanding of how viruses facilitate selective translation of host mRNAs needed for infection.

Synthetic Genome Recoding

Coding genes are biased in the relative frequencies of codons specifying the same amino acid. In some organisms, codon bias reflects optimization for specific tRNAs and elongation rates (Gingold and Pilpel 2011). Some synonymous codon pairs are used more or less frequently than expected, a phenomenon termed codon pair bias (Yarus and Folley 1985) that may influence translation efficiency (Tats et al. 2008). Indeed, altering codon pair frequencies reduced virus replication without affecting protein sequence (Coleman et al. 2008; Mueller et al. 2010; Martrus et al. 2013; Yang et al. 2013; Le Nouen et al. 2014). As the resulting virus attenuation depends on numerous mutations, reversion is markedly reduced, providing an exciting opportunity for live-attenuated vaccine development (Wimmer et al. 2009). However, in addition to codon pair bias and translation efficiency, other viral genome features, such as suppression of CpG and UpA dinucleotide frequencies, and variations in the propensity to mutate, which generate differential access to protein sequence space can contribute to the reduced replication phenotypes (Lauring et al. 2013; Tulloch et al. 2014; Kunec and Osterrieder 2016). Therefore, precisely how codon usage impacts virus attenuation and the relative contribution of translation repression requires further investigation.

RNA MODIFICATION AND INFECTION BIOLOGY

Although noncoding RNAs contain numerous modifications, only a few have been found in mRNAs. By far the most prevalent internal modified base on mRNAs is a methyl group on the N^6 position of adenosine (m^6A) (Yue et al. 2015; Peer et al. 2018).

Modulating Viral mRNA Metabolism by m^6A

The m^6A modification occurs predominantly in the nucleus and is mediated by the enzyme methyltransferase-like 3 (METTL3) together with METTL14, WTAP, KIAA1429, and RBM15/RBM15B. Following nuclear export, m^6A is recognized by cytoplasmic "reader" proteins, YTHDF1, YTHDF2, and YTHDF3 (Yue et al. 2015; Peer et al. 2018). m^6A modification reportedly influences mRNA splicing, export, translation and stability, all of which may impact virus biology.

Advances in genome-wide m^6A mapping on mRNAs and identification of the m^6A machinery fueled investigations into how this modification influences virus gene expression. m^6A modification was reported to enhance HIV-1 replication by regulating viral mRNA nuclear export or by stimulating viral gene expression (Kennedy et al. 2016; Lichinchi et al. 2016a; Tirumuru et al. 2016). YTHDF m^6A-reader proteins bind HIV-1 RNA at m^6A sites but their suggested function varies from promoting viral transcript abundance and translation to suppressing reverse transcription. Several m^6A-modified regions were identified in flaviviruses, such as HCV, Zika virus, DENV, yellow fever virus, and West Nile virus (Gokhale et al. 2016; Lichinchi et al. 2016b). Because these viruses replicate exclusively within the cytoplasm, the m^6A methyltransferase machinery is apparently active in this compartment. Knockdown of the host m^6A machinery enhances HCV and Zika virus production. HCV mRNA translation and replication are unaffected, but m^6A inhibits HCV RNA packaging into viral particles (Gokhale et al. 2016). Although the mechanism(s)

through which m^6A act remain unclear, virus model systems could help clarify how m^6A controls gene expression.

Discriminating Self versus Nonself mRNAs

Most eukaryotic mRNAs contain a Cap-0 (m^7GpppN) structure with a methyl group at the guanine N-7 position. In higher eukaryotes, the mRNA cap is further modified by ribose 2′-*O*-methylation on the first and sometimes second cap-proximal nucleotides, resulting in Cap-1 ($m^7GpppNmN$) or Cap-2 ($m^7GpppNmNm$). Although 2′-*O*-methylation does not affect translation directly, it provides a molecular signature of "self." Hence mRNAs that lack 2′-*O*-methylation are marked as "nonself," triggering type I IFN production (Zust et al. 2011), which induces transcription of IFN-stimulated genes (ISGs). Among the most highly upregulated ISGs are those encoding IFIT (IFN-induced proteins with tetratricopeptide repeats) proteins (Fensterl and Sen 2015). Viral 2′-*O*-methyltransferases encoded by coronavirus, flaviviruses, and VACV prevent recognition by IFIT1 (Daffis et al. 2010; Szretter et al. 2012; Menachery et al. 2014) and cap-proximal structural elements in α virus Cap-0 mRNA restrict IFIT1 action (Hyde et al. 2014). Mechanistically, IFIT1 can sequester eIF4F, inhibiting viral Cap-0 mRNA translation (Habjan et al. 2013). However, N1 methylation (Cap-1) may be insufficient to protect all mRNAs from IFIT1, as the second N2 methylation (Cap-2) and secondary structure may also impact IFIT1 activity (Daugherty et al. 2016; Young et al. 2016; Abbas et al. 2017). Most mammals encode several IFIT proteins with varying affinities for distinct RNA ligands (Hyde and Diamond 2015), suggesting that additional RNA determinants are recognized. Besides competing with eIF4E for cap binding, IFIT1 binds eIF3 subunits, preventing ribosome recruitment, and may inhibit 48S complex formation (Hyde and Diamond 2015). Because IFITs alter translation in uninfected cells (Guo et al. 2000) and increase following infection, IFITs might remodel the infected cell-translation landscape.

CODING CAPACITY

To maximize their genome coding capacity, viruses use multiple strategies, including leaky scanning, polyproteins, reinitiation, translational bypass (hopping), readthrough of stop codons, and programmed ribosomal frameshifting (PRF) (Fig. 5).

Coding and Recoding Strategies

PRF is a recoding event that shifts the reading frame of a translating ribosome one or two nucleotides in the + or − direction (Caliskan et al. 2015; Dever et al. 2018). PRF frequencies range from 1% to 80%, but are typically low. A 7-nucleotide slippery site sequence, the spacer region, and structural barriers that stall the ribosome, impact PRF efficiency. Retroviruses generate high levels of Gag and low levels of a Gag-Pol fusion from the same transcript via PRF or by readthrough of a stop codon (Hung et al. 1998; Csibra et al. 2014). Perturbations in this ratio affect viral assembly, RNA packaging and maturation. Mimiviruses use both PRF and readthrough to encode a polypeptide chain release factor homolog (Jeudy et al. 2012). West Nile virus, which encodes a single polyprotein, uses an efficient -1 PRF (∼30% to 70%) to generate additional structural proteins, which increases virus levels in birds and mosquitoes for efficient transmission (Melian et al. 2010, 2014). *Dicistroviridae* IGR IRESs induce a +1 frameshift during initiation by extending pseudoknot I by one base pair to translate a short protein, ORFx (Ren et al. 2012). In addition, +1 frameshifting in IAV gene segment 3, which encodes the viral RNA polymerase subunit PA, produces the PA-X endonuclease that coordinates host shut-off (Jagger et al. 2012). Rarer -2 PRF events, first reported in porcine reproductive and respiratory syndrome virus (PRRSV, an RNA virus), also occur (Fang et al. 2012). PRRSV -2 frameshifting is responsive to a viral protein transactivator that binds to a C-rich region downstream of the PRF (Li et al. 2014). Efficient +1/−2 PRF within repetitive sequence elements encoded by the DNA viruses EBV and KSHV also generates alternative reading frame versions of their re-

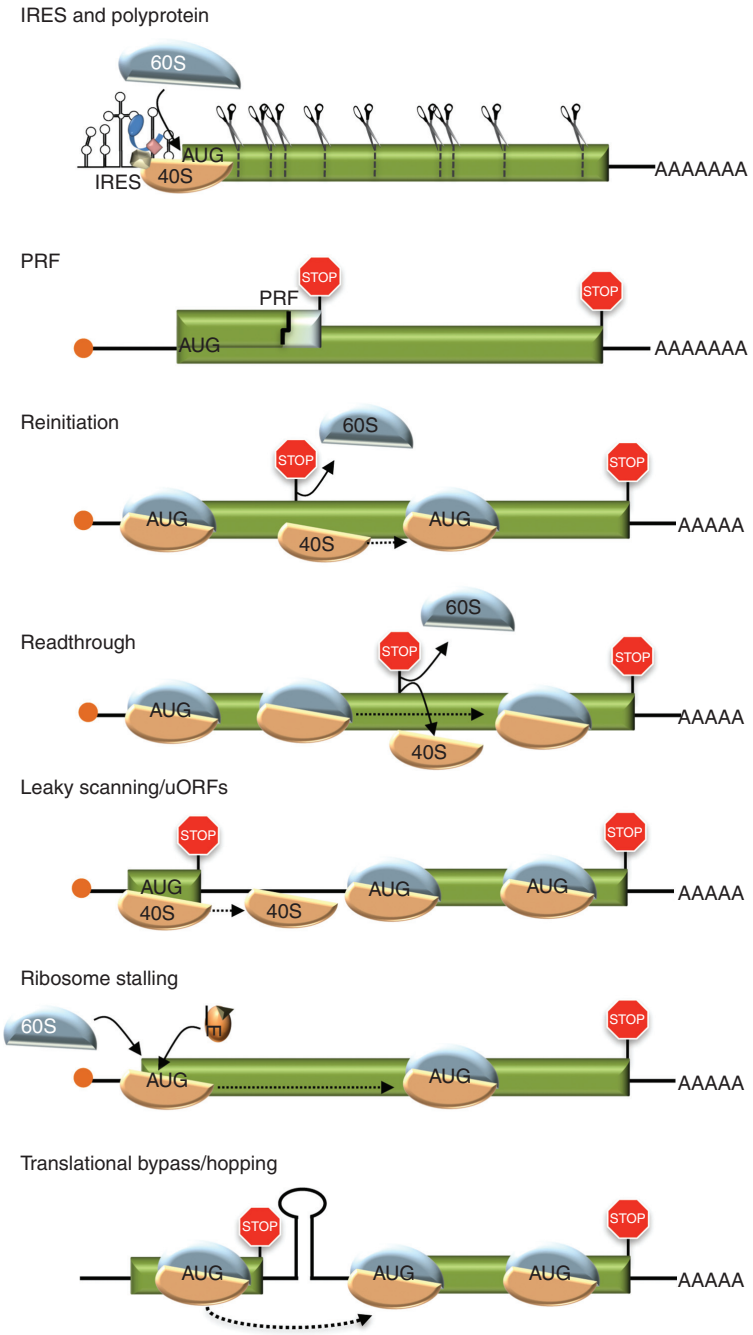

Figure 5. Strategies to maximize viral genome coding capacity. Internal ribosome entry site (IRES)-driven polyprotein production, programmed ribosome frameshifting (PRF), reinitiation, stop-codon readthrough, leaky scanning, ribosome stalling, and translational bypass/ribosome hopping are shown in the cartoon. (See the text for a detailed description.) Stop codons (stop signs), proteolytic cleavage sites (scissors), 5′-cap structure (orange circle), open reading frames (green), ribosome subunits (brown and blue), and initiation factor loaded with transfer RNA (tRNA) are shown.

spective latency proteins EBNA1 and LANA1, although their functions remain unknown (Kwun et al. 2014).

Polyproteins, which are proteolytically processed by viral and cellular proteases, are used by many (+)-stranded RNA viruses and allow for a single viral RNA to encode several different proteins. Alternatively, some DNA and RNA viruses express multiple proteins from a polycistronic transcript using a reinitiation mechanism (ribosomal termination-reinitiation or stop–start) (Wise et al. 2011; Kronstad et al. 2013, 2014; Royall and Locker 2016). For example, caliciviruses recruit ribosomes to the viral RNA 5′ end to translate an upstream ORF (uORF). Calicivirus RNAs contain a termination upstream ribosomal binding site (TURBS) that retains the 40S subunit after termination. By base pairing with 18S rRNA, TURBS facilitates efficient translation reinitiation at a nearby AUG or non-AUG codon (Luttermann and Meyers 2014; Royall and Locker 2016). In vitro, reinitiation by a terminated 40S ribosomal subunit requires eIF2, 1, and 1A but not eIF3 (Zinoviev et al. 2015).

To produce a single polypeptide from two discrete ORFs, bacteriophage T4 relies on a translational bypass or ribosome hopping. After translating a glycine codon that precedes a stop codon, the 80S ribosome "hops" over a stretch of sequences and resumes translation at a downstream glycine codon. This hopping mechanism likely requires a compact structure in the gap region to bring together the two glycine codons in the translating ribosome and to prevent the release factor from entering the A site (Todd and Walter 2013).

uORFs

Some DNA and RNA viral polycistronic transcripts contain upstream start codons that can translate short uORFs. The uORFs are a barrier to efficient initiation at a downstream ORF. Viruses modulate downstream ORF expression by leaky scanning, which transpires when the 40S subunit scans past an upstream AUG in a weak or moderate Kozak consensus sequence context before initiating at a downstream AUG (Wise et al. 2011; Kronstad et al. 2013, 2014). For example, members of the triple gene block (TGB) superfamily of movement proteins encoded by many plant viruses, which allow cell-to-cell movement and vascular spread needed to cause disease, are often produced by leaky scanning along a single mRNA transcript that contains overlapping ORFs (Lezzhov et al. 2015; Miras et al. 2017).

Ribosome Stalling

During cap-dependent initiation, the start codon is recognized when the Met-tRNA$_i^{Met}$ base-pairs with the start codon. When eIF2 is phosphorylated, levels of ternary complex (eIF2•GTP•Met-tRNA$_i^{Met}$) are reduced, which shuts down protein synthesis globally. Alphaviruses use a stable RNA stem-loop structure located within their coding sequence to stall the ribosome on the initiation codon of the 26S mRNA when ternary complex levels are low and rely on an as-yet-unknown initiation mechanism to avoid a major antiviral defense (Toribio et al. 2016, 2018). Once the 60S subunit joins the stalled ribosome, it is released to translate the viral RNA.

CONCLUDING REMARKS

The categorical requirement for host ribosomes to translate viral mRNAs continues to provide powerful opportunities to investigate how protein synthesis is regulated. Indeed, exploiting virus model systems has defined fundamental features of the cellular protein synthesis machinery, how it is regulated in uninfected cells, and how it responds to physiological stress. Insights gleaned from investigating viral mechanisms have implications for understanding how different forms of acute and chronic stress impact translational control of gene expression in health and disease. As virus reproduction is dependent on protein synthesis, the identity and roles of leading molecular actors during infection have been revealed. RNA structural elements and modifications detected by host sentinel molecules coordinate powerful antiviral responses intended to restrict virus access to

the translational apparatus. Further insights can be expected from functional analysis of the genes encoding certain translation system components in giant *Acanthamoeba* viruses (Abrahão et al. 2017; Schultz et al. 2017).

Virus–host interactions that control protein synthesis could potentially be valuable targets for new antiviral therapies and/or lead to new vaccines and biological treatments. Included among these are virus-encoded functions that counter host dsRNA-dependent, antiviral responses. By capitalizing on this biology, a replicating HSV-1 missing the ICP34.5 eIF2α phosphatase subunit, but producing a viral dsRNA-binding protein that inhibits PKR and OAS, was developed into the first oncolytic virus immunotherapy approved by U.S. and European regulatory agencies (Taneja et al. 2001; U.S. Food and Drug Administration 2015; European Medicines Agency 2016; Ribas et al. 2017). Potent innate defenses in normal cells, including IFN-induced functions like PKR and OAS, effectively limit replication of the oncolytic HSV-1 lacking the virus-encoded phosphatase subunit. However, impaired cell-intrinsic immune responses in cancer cells support preferential virus reproduction and spread through tumor tissue. This new class of biological therapeutics for cancer was an unexpected outgrowth of understanding and manipulating a translational control mechanism in virus-infected cells. New fundamental mechanisms of initiation and regulation have been revealed. In particular, roles for RNA modifications and the ribosome itself in regulating translation have emerged with discrete ribosomal proteins selectively controlling translation. Furthermore, application of genome-wide methodologies has revealed surprising insights into how host shut-off is achieved and how viruses that do not impair host protein synthesis globally impact the host translational landscape. While the underlying mechanisms remain unknown, viral systems continue to be instrumental in delineating how ribosomes differentially recruit or exclude messages and how discrete modifications of ribosomes and mRNAs comprehensively shape translation in response to physiological and environmental stress.

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