Viral subversion of the host protein synthesis machinery

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Abstract | Viruses are fully reliant on the translation machinery of their host cells to produce the polypeptides that are essential for viral replication. Consequently, viruses recruit host ribosomes to translate viral mRNAs, typically using virally encoded functions to seize control of cellular translation factors and the host signalling pathways that regulate their activity. This not only ensures that viral proteins will be produced, but also stifles innate host defences that are aimed at inhibiting the capacity of infected cells for protein synthesis. Remarkably, nearly every step of the translation process can be targeted by virally encoded functions. This Review discusses the diverse strategies that viruses use to subvert host protein synthesis functions and regulate mRNA translation in infected cells.

Despite the diverse functions that viruses encode for their propagation, they remain exquisitely dependent on the translational machinery of the host cell. No matter whether their genomes are RNA or DNA, and regardless of their mRNA production method, the goal remains the same: to ensure that cellular ribosomes are recruited to viral mRNAs. The ensuing synthesis of viral proteins is required for viral genome replication and progeny virion production. Typically, commandeering ribosomes to viral mRNAs involves subverting cellular translation factors and signalling pathways that control the host protein synthesis apparatus. Many discrete strategies have been uncovered by studying translation control in virus-infected cells. These investigations have not only revealed key steps in viral pathogenesis, but also defined paradigms for translation control in uninfected cells. In this Review, we discuss the underlying mechanisms by which viruses gain control over the cellular functions required for mRNA translation.

Translation regulation: the basics

Regulated mRNA translation is a post-transcriptional mechanism that controls gene expression and directly and rapidly varies protein abundance, both spatially and temporally. It has a major role in numerous biological processes, including cell growth, development, synaptic plasticity, stress responses and productive viral growth. Viruses not only need unrestricted access to the host translation machinery, but also must suppress host innate defences that are designed to cripple the protein production capacity of the infected cell. The translation process can be subdivided into three stages — initiation, elongation and termination — each of which requires specific factors (FIG. 1). Much of the regulation of this process focuses on the rate-limiting initiation step, which involves ribosome recruitment to mRNA.

Prior to their recruitment to mRNAs, 40S ribosome subunits bind to the eukaryotic translation initiation factor 1 (eIF1), eIF1A, the eIF3 complex and eIF5, along with eIF2-GTP, to assemble a 43S pre-initiation complex loaded with the charged initiator-methionine tRNA (Met-tRNA). Unlike bacterial mRNAs, most eukaryotic mRNAs cannot position ribosomes on their 5′ termini to initiate translation. Instead, eIFs recognize structural landmarks in the mRNA to load 40S subunits onto the transcript. The 7‑methylguanosine cap (m7G) that distinguishes the 5′ end of the eukaryotic mRNA is bound by eIF4E, a multisubunit complex comprising the cap-binding protein eIF4E and the DEAD box-containing RNA helicase eIF4A, both bound to the large molecular scaffold eIF4G. Cap recognition by eIF4E anchors the complex on the mRNA, and eIF4G binding enhances the affinity of eIF4F for the cap. Indeed, eIF4E binding to eIF4G represents a crucial step in which physiological inputs regulate eIF4F assembly and translation initiation. Integration of signals relating to nutrient availability and energy supply, as well as growth factor signals, by the kinase complex mTOR complex 1 (mTORC1) regulates the translation repressor eIF4E-binding protein 1 (4EBP1), which binds eIF4E and suppresses eIF4F activity. Hyperphosphorylation of 4EBP1 by activated mTORC1 liberates eIF4E, allowing eIF4G to bind eIF4E and stimulate cap-dependent translation (FIG. 2). Following eIF4E incorporation into eIF4F, eIF4E can be
The process of translation has three phases: initiation, elongation and termination. Each stage requires specific translation factors. 

**Initiation**
- The 40S ribosome bound to eukaryotic translation initiation factor 1 (eIF1), eIF1A, the eIF3 complex and eIF5 is loaded with initiator-methionine tRNA (Met-tRNAi).
- eIF4E is phosphorylated by an eIF4G-associated kinase (either MNK1 or MNK2). Whereas basal eIF4E phosphorylation requires MNK2, inducible p38 mitogen-activated protein kinase family-responsive and extracellular signal-regulated kinase (ERK)-responsive eIF4E phosphorylation is MNK1 dependent.

**Elongation**
- Ribosome-catalysed peptide bond formation proceeds until a stop codon prompts eRF1 recognition and hydrolysis of the peptidyl-tRNA ester bond linking the tRNA to the completed polypeptide, resulting in translation termination.
- Polypeptide release of mRNA and tRNAs. This ensemble of cellular termination ribosomes are dismantled into 60S and 40S subunits, eIF3 also prevents 60S subunits from joining during scanning and initiation.

**Termination**
- Stop codon recognition by eRF1 induces hydrolysis of the ester bond linking the tRNA to the completed polypeptide, resulting in translation termination.
- Post-termination ribosomes are dismantled into 60S and 40S components, promoting subunit recycling and the release of mRNA and tRNAs.

**Targeting initiation through eIF4F**
- Regulated eIF4F assembly is a fundamental step in controlling cap-dependent translation initiation in eukaryotes.

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Figure 1 | Overview of mRNA translation in eukaryotes. The process of translation has three phases: initiation, elongation and termination. Each stage requires specific translation factors. 

a | Initiation
- The 40S ribosome bound to eukaryotic translation initiation factor 1 (eIF1), eIF1A, the eIF3 complex and eIF5 is loaded with initiator-methionine tRNA (Met-tRNAi).
- eIF4E is phosphorylated by an eIF4G-associated kinase (either MNK1 or MNK2). Whereas basal eIF4E phosphorylation requires MNK2, inducible p38 mitogen-activated protein kinase family-responsive and extracellular signal-regulated kinase (ERK)-responsive eIF4E phosphorylation is MNK1 dependent. eIF4F assembly coordinates the interactions of the 5' and 3' mRNA ends, as a poly(A)-binding protein (PABP) recognizes the 3' terminus of the polyadenylated mRNA and associates with eIF4G to stimulate initiation. This interaction probably restricts recruitment of the 40S ribosome to mRNAs with intact 5' and 3' termini. Thus, in eukaryotes, regulated assembly of a specialized ribonucleoprotein complex including eIF4F and PABP facilitates 40S subunit loading onto mRNA (FIG. 1). This key initiation step is rate limiting, and the degree to which individual mRNAs are reliant on high or low eIF4F levels depends on the extent of secondary structure in the 5' untranslated region (UTR).

Although regulated eIF4F assembly marks the mRNA 5' end and controls 40S subunit recruitment, eIF4F does not directly tether ribosomes to mRNA. eIF3 bridges the eIF4F cap recognition complex and the 43S pre-initiation complex. After positioning the 40S subunit onto the 5' end of the mRNA, the AUG start codon is identified by a process termed scanning. By binding 40S subunits, eIF3 also prevents 60S subunits from joining during scanning and initiation.

The recognition of AUG and the joining of the 60S subunit triggers the release of initiation factors, and the 80S ribosome subsequently begins polypeptide chain elongation. As well as maintaining the correct reading frame, elongation requires a limited set of eukaryotic elongation factors (eEFs). eEF1A delivers each selected aminoacylated tRNA to the 80S ribosome A site. Ribosome-catalysed peptide bond formation precedes eEF2-mediated ribosome translocation along the mRNA. To regulate elongation, phosphorylation by CK2 (also known as casein kinase II) and protein kinase C (PKC) family kinases stimulates eEF1A, whereas phosphorylation by eEF2 kinase inhibits eEF2 activity. Chain elongation proceeds until a stop codon prompts termination.

Stop codon recognition by eRF1 induces hydrolysis of the ester bond linking the tRNA to the completed polypeptide, resulting in translation termination. eRF3 then removes eRF1 from the ribosome. Post-termination ribosomes are dismantled into 60S and 40S components, promoting subunit recycling and the release of mRNA and tRNAs. This ensemble of cellular translation initiation, elongation and termination factors is regulated by an intricate web of signals, providing viruses with numerous potential targets through which they can commande the host protein synthesis machinery.
Figure 2 | Control of cap-dependent translation by regulated assembly of a multisubunit initiation factor. By binding to the cap-binding protein eukaryotic translation initiation factor 4E (eIF4E; abbreviated here to 4E), eIF4E-binding protein 1 (4EBP1) represses translation and prevents assembly of the multisubunit initiation factor eIF4F (composed of eIF4E, eIF4A (labelled 4A) and eIF4G (labelled 4G)). The GTPase-activating protein TSC (composed of subunits hamartin (TSC1) and tuberin (TSC2)) represses mTOR complex 1 (mTORC1) by promoting RHEB$^*\cdot$GDP accumulation. Receptor tyrosine kinase signalling, AMP-activated protein kinase (AMPK) and hypoxia regulate TSC activity. Inhibiting TSC allows RHEB$^*\cdot$GTP accumulation and mTORC1 activation, and results in p70 ribosomal protein S6 kinase (p70 S6K) and 4EBP1 phosphorylation. 4EBP1 hyperphosphorylation relieves translational repression and releases eIF4E, allowing eIF4E to bind eIF4G and assemble eIF4F on 7-methylguanosine (m$\text{G}$; red circle)-capped mRNA. eIF4F assembly typically results in eIF4E phosphorylation by the eIF4G-associated kinases (the MNK proteins) and recruits the 43S complex (see FIG. 1a) containing the 40S ribosome. A poly(A)$^*$-binding protein (PABP) is depicted bound to the 3$'$ poly(A) tail, and this PABP associates with eIF4G to stimulate translation. In addition to stimulating ribosomal protein S6 (RPS6) phosphorylation, p70 S6K activation by mTORC1 stimulates the eIF4A accessory factor eIF4B and inhibits eukaryotic elongation factor 2 (eEF2) kinase, thereby stimulating elongation. Importantly, by repressing phosphoinositide 3-kinase (PI3K) activation, p70 S6K activation prevents constitutive mTORC1 activation. Viral strategies for activating (green) and inhibiting (yellow) eIF4F are indicated; see main text for details and abbreviations.
replication. Other viruses stimulate eIF4F to translate their mRNAs, or change the subcellular distribution of eIF4F subunits to suit their needs.

Targeting eIF4F recruitment. Translation of most host mRNAs via a cap-dependent mechanism allows viruses to impair cellular protein synthesis by altering the recognition of host mRNAs by eIF4F. For example, poxviral decapping enzymes remove the m'G cap\(^1\), whereas influenza viruses and hantaviruses ‘steal’ caps together with a 5'‐proximal 10–18‐nucleotide host mRNA segment that is used to prime viral mRNA synthesis\(^2\). Despite this removal of eIF4F‐binding determinants on host mRNAs, eIF4F components can still be recruited to viral transcripts. For instance, influenza virus RNA polymerase and NS1 interact with eIF4G to recruit eIF4F to viral mRNAs. Other viral genomes contain genes encoding cap substitutes. The 5' ends of mRNAs from mammalian caliciviruses (such as noroviruses and plant potyviruses) are not capped but, instead, are covalently linked to a viral protein, VPg, that binds host initiation factors to recruit ribosomes\(^3\). The 5' mRNA leader of potyviruses, which are related to picornaviruses, contains eIF4G‐binding pseudoknots that direct cap‐independent translation\(^4\). Other plant viruses contain 3' cap‐independent translational elements (CITEs), which interact with the 5' end of the mRNA and bind initiation factors, including eIF4F and eIF4G, to recruit ribosomes\(^5\). For example, the turnip crinkle virus (TCV) CITE contains tRNA‐like structures that bind the 60S ribosome\(^6\). 3' CITEs also suppress mRNA translation on positive‐strand RNAs to promote genome replication\(^7\). Finally, hantavirus N protein reportedly has cap‐binding, RNA‐binding, helicase and ribosome‐binding activities, substituting for eIF4F to promote translation of viral mRNAs\(^8\).

Targeting eIF4F directly. eIF4F can be inactivated or modified in infected cells. Proteases of enteroviruses, (including rhinoviruses), retroviruses and caliciviruses (including noroviruses) (TABLE 1) cleave eIF4F, severing the eIF4E‐bound amino terminus from the eIF4A–eIF3–ribosome‐associated carboxyl terminus. Although multiple eIF4G1 isoforms and eIF4G2 are cleaved by viral proteases in infected cells, inhibition of cap‐dependent translation by poliovirus (an enterovirus) correlates with cleavage of eIF4G2 only, suggesting that different cellular mRNAs vary in their requirements for eIF4G family members\(^9\). Inhibiting host cap‐dependent translation does not block viral mRNA translation, as many virus RNAs contain specialized internal ribosome entry sites (IRESs) (BOX 1) that direct cap‐independent translation\(^10\). Although all IRESs recruit ribosomes independently of a cap, they differ in their requirements for initiation factors and ancillary IRES transactivating factors (ITAFs). DNA viruses, including simian virus 40 (SV40) and herpesviruses, also encode rare, IRES‐containing polycistronic mRNAs\(^11,17\).

Targeting eIF4F binding partners. Instead of eIF4G proteolysis, the picornavirus encephalomyocarditis virus (EMCV) suppresses cap‐dependent translation by activating the translational repressor 4EBP1 (REF. 22). Hypophosphorylated 4EBP1 binds eIF4E and prevents eIF4E binding to eIF4G, inhibiting eIF4F assembly. Precisely how EMCV activates 4EBP1 remains unclear, although vesicular stomatitis virus (VSV) M protein promotes hypophosphorylated 4EBP1 accumulation by inhibiting the kinase AKT\(^7,24\). Small t antigens from murine polyomavirus and SV40 promote 4EBP1 hypophosphorylation via a poorly understood protein phosphatase 2A (PP2A)‐dependent strategy\(^25\). Preventing 4EBP1 hyperphosphorylation helps viruses to suppress cap‐dependent translation of host defence mRNAs, including interferon‐regulatory factor 7 (IRF7), which regulates interferon production. Thus, replication of interferon‐sensitive RNA viruses is suppressed in cells that are deficient in both 4EBP1 and 4EBP2\(^26\). Other viruses (discussed below) that promote 4EBP1 hyperphosphorylation to stimulate eIF4F use different strategies to suppress translation of host defence‐related mRNAs.

Influenza virus, VSV or adenovirus infection decreases the abundance of phosphorylated eIF4E, potentially helping to suppress host translation\(^27,28\). Although this process is not understood in influenza virus‐infected cells, protein 100K from adenoviruses binds eIF4G and displaces the eIF4E kinase MNK1, thus reducing the abundance of phosphorylated eIF4E\(^7\). By binding late viral mRNA sequences in the 5' end of the mRNA, 100K promotes 'ribosome shunting', enabling the 40S ribosome, after loading onto a capped mRNA, to bypass large 5' UTR segments and translocate to the initiation codon\(^29,30\). Complementarity between adenoviral mRNA and 18S ribosomal RNA is important for shunting, suggesting a role for mRNA structure or mRNA–rRNA interactions\(^30\). Shunting also occurs on cauliflower mosaic virus (CaMV) 35S mRNA, but in this case it requires an upstream ORF (uORF) and specific mRNA structures\(^31\).

Viruses also target the eIF4F‐associated PABP proteins. Besides binding 3' terminal sequences of non‐polyadenylated viral mRNAs, rotavirus NSP3 interacts with eIF4G and displaces PABP to inhibit host translation\(^32\). However, silencing NSP3 expression in infected cells does not detectably diminish viral‐protein synthesis\(^33\). In addition, enterovirus, lentivirus and calicivirus proteases cleave PABP, and the rubella virus capsid protein binds PABP to suppress translation\(^34,35\). Although PABP stimulates some IRESs, PABP inactivation by RNA viruses does not always correlate with host shut‐off, but rather suppresses viral mRNA translation to foster positive‐strand genome replication\(^36\).

Innate host defences may impair eIF4F function in infected cells through ISG15, an interferon‐induced, ubiquitin‐like modifier. The cap‐binding activity of the eIF4E family member 4EHP (also known as eIF4E2) is enhanced by ISG15 conjugation\(^36\). 4EHP, however, cannot bind eIF4G and competes with eIF4E, suppressing cap‐dependent translation. Although virus‐induced suppression of interferon‐stimulated gene expression limits ISG15 production, specific viral ISG15–4EHP conjugation antagonists, or the consequences of ISG15 conjugation to 4EHP in infected cells, remain unknown.
| Viruses | Viral functions | Effects on target |
|---------|----------------|------------------|
| **eIF4E** | Caliciviruses and TMV | VPg | Binds eIF4E and recruits factors to viral mRNA |
| | Enteroviruses | Unknown | Induces host miR-141 and suppresses eIF4E mRNA translation |
| **4EBP1** | VSV | M protein | Dephosphorylate 4EBP1 (via inactivation of AKT–mTOR) |
| | Reoviruses | p17 | Dephosphorylates 4EBP1 (PP2A dependent) |
| | SV40 | Small t antigen | Dephosphorylates 4EBP1 (PP2A dependent) |
| | HSV-1 | US3 | Phosphorylate 4EBP1 (via TSC2 inactivation) |
| | HCMV | UL38 | Phosphorylate 4EBP1 (via PI3K–AKT–mTOR pathway activation) |
| | KSHV | v-GPCR | Phosphorylate 4EBP1 (via PI3K–AKT–mTOR pathway activation) |
| | EBV | LMP2A | Phosphorylate 4EBP1 (via PI3K–AKT–mTOR pathway activation) |
| | Adenoviruses | E4 ORF1 and E4 ORF4 | Phosphorylate 4EBP1 (PP2A dependent) |
| | HCV | NS5A | Phosphorylates 4EBP1 (via FKBP38 binding to activate mTOR) |
| | HPV | E6 | Phosphorylates 4EBP1 (via PDK1 activation and TSC2 degradation) |
| **eIF4G** | Enteroviruses | 2A protease | Cleave eIF4G |
| | Caliciviruses | 3C protease | Cleave eIF4G |
| | Retroviruses | Protease | Cleave eIF4G |
| | FMDV | Leader protease | Cleave eIF4G |
| | Influenza viruses | Polymerase NS1 | Binds eIF4G and promotes viral-mRNA translation |
| | Adenoviruses | 100K | Binds eIF4G, dephosphorylates eIF4E (via competitive displacement of MNK1) and promotes ribosome shunting on viral mRNAs |
| | Rotaviruses | NSP3 | Binds eIF4G and competitively displaces PABP |
| | HSV-1 | ICP6 | Binds eIF4G and increases its interaction with eIF4E |
| | Enteroviruses | IRES | Interacts with eIF4G to recruit the 40S ribosomal subunit |
| **eIF4A** | HSV-1 | vhs | Binds eIF4A and either eIF4H or eIF4B, and this targets vhs endoribonuclease activity to mRNAs, accelerating mRNA turnover |
| | HCMV | UL69 | Binds eIF4A (consequence unknown) |
| **eIF5B** | Enteroviruses | 3C protease | Cleave eIF5B |
| **PABP** | Enteroviruses | 3C and 2A proteases | Cleave PABP |
| | Caliciviruses | 3C-like protease | Cleave PABP |
| | Lentiviruses | Protease | Cleave PABP |
| | Rubella virus | Capsid | Binds PABP and suppresses translation |
| | Influenza viruses | NS1 | Binds PABP (consequence unknown) |
| | HSV-1 | ICP27 | Binds PABP and stimulates translation of a viral mRNA subset |
| | | ICP27 and UL47 | Cause nuclear PABP accumulation |
| | HCMV | UL69 | Binds PABP (consequence unknown) |
| | KSHV | SOX and K10 | Bind PABP and causes its nuclear accumulation |
| | Bunyaviruses | NSS protein | Causes nuclear PABP accumulation |
| | Rotaviruses | NSP3 | Displaces PABP from eIF4G, and interacts with ROXAN to cause nuclear PABP accumulation |
| **eIF3** | Measles virus | N protein | Binds eIF3g and impairs translation |
| | Rabies virus | M protein | Binds eIF3h and impairs translation |
| | SARS CoV and IBV | Spike protein | Binds eIF3f and impairs translation |
| | Caliciviruses (including noroviruses) | VPg | Binds eIF3 and recruits factors to viral mRNA |
| | CaMV | RISP | Binds eIF3a and eIF3c, binds the 60S ribosomal subunit L24 and recruits ribosomes for re-initiation |
| | | TAV | Binds and activates TOR, and recruits RISP |
| | HCV, CSFV and HIV | IRES | Interacts with eIF3 and recruits translation machinery |
Stimulating eIF4F activity. In contrast to viruses that inhibit eIF4F and use cap-independent translation, many DNA viruses, the mRNAs from which are structurally similar to host mRNAs (with a 5′ m7G cap and 3′ poly(A) tail) rely on cap-dependent translation and stimulate eIF4F activity. Herpesviruses (herpes simplex virus type 1 (HSV-1), human cytomegalovirus (HCMV), Epstein–Barr virus (EBV) and Kaposi’s sarcoma-associated herpesvirus (KSHV)), vaccinia virus (VacV) (a poxvirus) and asfarviruses all activate mTORC1, promoting 4EBP1 phosphorylation, eIF4F assembly, viral protein synthesis and viral replication. Indeed, inhibitors of the mTOR active site (targeting both mTORC1 and mTORC2) suppress protein synthesis in infected cells and inhibit replication of a representative alphaherpesvirus (HSV-1), betaherpesvirus (HCMV) and gamma-herpesvirus (murine herpesvirus 68) [42–44]. In addition to promoting eIF4F assembly, 4EBP1 phosphorylation stimulates HSV-1 and HCMV replication, as a dominant 4EBP1 repressor with alanine substitutions at the Thr37 and Thr46 phosphorylation sites represses viral protein synthesis for these species [44,45]. To activate mTORC1 and stimulate 4EBP1 hyperphosphorylation, the HSV-1 Ser/Thr kinase US3 acts as an AKT surrogate.
by phosphorylating tuberin (TSC2)\(^4\). HCMV UL38 also binds to TSC2 and thus inhibits the TSC complex to activate mTORC1 [REF. 46]; in addition, the substrate specificity of mTOR-containing complexes is modified in HCMV-infected cells\(^25,47\). Although human papilloma virus (HPV) E6 and adenovirus E4 ORF1 activate mTORC1 either at or upstream of TSC, a second adenoviral function stimulates mTORC1 in a TSC-independent manner that may involve PP2A\(^25,48,49\) (FIG. 2, TABLE 1). Although additional viruses stimulate phosphoinositide 3-kinase (PI3K)–AKT signalling, it is not clear whether this regulates translation in infected cells\(^50\). Finally, steady-state 4EBP1 levels decrease in HSV-1 and VacV-infected cells\(^50,52,53,54\), as 4EBP1 hyperphosphorylation can result in proteasome-mediated degradation. 4EBP1 degradation is not restricted to virus-infected cells and also occurs in uninfected cells\(^51,52\).

Simply inactivating 4EBP1 is not always sufficient for eIF4F assembly. In HSV-1-infected cells, eIF4E binding to eIF4G requires a virally encoded eIF4G-binding protein, ICP6 (also known as R1)\(^55\). ICP6 is multifunctional and is also a subunit of the viral ribonucleotide reductase. When associated with eIF4G, however, ICP6 stimulates eIF4E binding to eIF4G and drives eIF4F assembly. Strikingly, in cells infected with an ICP6-deficient virus, eIF4E is released from the repressor 4EBP1 but increased eIF4F assembly is not observed\(^56\). This identified a new step controlling eIF4F formation, in addition to 4EBP1 hyperphosphorylation, that may be required under stressful conditions such as viral infection. Indeed, ICP6 contains a segment related to small heat shock proteins that can remodel translation factor complexes and can promote eIF4G binding. Notably, the hepatitis A virus IRES is unusual in that it requires intact eIF4F with the cap binding slot of eIF4E unoccupied, suggesting that eIF4E interacts with the viral mRNA or induces the conformational changes in eIF4G that are necessary for IRES binding. Type III IRESs, typified by those of hepatitis C virus and the pestiviruses, bypass requirements for eIF4F altogether by interacting with both eIF3 and the 40S ribosome\(^51\), analogous to ribosome recruitment through Shine–Dalgarno sequences in bacteria. These IRESs also require eIF5B, eIF2 and Met-tRNA, although the requirement for these factors may be reduced in some cases (see main text). Finally, type IV IRESs of the family Dicistroviridae completely obviate the need for canonical initiation factors\(^57,58\). Remarkably, these IRESs interact with the 40S subunit directly, inducing conformational changes and facilitating 60S subunit joining to form 80S ribosomes independently of initiation factors. In addition, a CCU sequence is positioned in the ribosomal P site while the A site is occupied by a CGU (encoding alanine). An initial ‘pseudo-translocation’ of the Ala-tRNA P site while the A site is occupied by a CGU (encoding alanine) is unchanged or reduced\(^51,52\), depending on cell type. However, PABP can stimulate the translation of a subset of viral mRNAs by interacting with ICP27 [REF. 56]. Further studies on PABP function in HSV-1-infected cells will resolve these findings.
Compared with HSV-1, HCMV has a protracted life cycle and does not impair host translation. elf4F assembly and binding to PABP are stimulated in HCMV-infected cells. Furthermore, elf4E, elf4G, elf4A and PABP steady-state levels increase, and for PABP proteins this involves a translational control mechanism.70,71 Thus, whereas picornaviruses impair cap-dependent translation by reducing the abundance of full-length initiation factors, HCMV stimulates the cap-dependent translation machinery and increases initiation factor concentration. How this is achieved and its contribution to viral replication remain unknown. Nevertheless, raising the concentration of elf4F subunits may potentiate complex assembly. Instead of increasing host initiation factor levels, mimiviruses — large (2 Mb) DNA viruses that infect Acanthamoeba spp. — are the only viruses known to encode putative translation factors, one of which is elf4E.72 However, the capacity of mimiviral homologues to function in translation initiation and their contribution to protein synthesis in infected cells are unknown.

**Redistributing elf4F and PABP.** Although their abundance remains constant, changes in the local concentration of translation factors probably regulate protein synthesis in poxvirus- or asfarvirus-infected cells. Both types of DNA virus replicate in specialized cytoplasmic compartments and promote elf4F assembly.73,74 Remarkably, elf4E and elf4G are redistributed and concentrated in viral replication compartments.75,76,77 Increasing the local concentration of initiation factors in discrete regions could favour elf4F assembly and sequester factors from host mRNAs to suppress cellular translation. Similarly, tobacco mosaic virus (TMV)-encoded VPg binds elf4E, concentrating elf4F and elf4G on membrane-associated replication sites, whereas Sindbis virus, an RNA virus that replicates in the cytoplasm and employs cap-independent translation, recruits elf3 and elf2 to viral compartments but excludes elf4G.78

Redistribution of elf4F and PABP is not limited to concentration in replication compartments. For instance, elf4E is redistributed to the nucleus by poxvirus,79 possibly helping to suppress host translation. PABP, which normally shuttles between nucleus and cytoplasm, accumulates in the nucleus in bunyavirus-, rotavirus-, HSV-1- and KSHV-infected cells.80,81,82,83 Interestingly, these viruses impair host protein synthesis. HSV-1 and KSHV in particular promote elf4F assembly without stimulating PABP binding to elf4F.84,85,86,87 By contrast, PABP does not accumulate in the nucleus but is recruited to elf4E and host protein synthesis proceeds unimpared, in cells infected with the related herpesvirus HCMV.88,89 PABP redistribution and exclusion from elf4F might help to inhibit host translation in HSV-1- and KSHV-infected cells. Whether HSV-1 and KSHV mRNAs have reduced dependence on PABP to initiate translation, despite being polyadenylated, is unknown.

Although elf4E binding to elf4G regulates initiation, elf4F assembly can induce elf4E phosphorylation by the elf4G-associated elf4E kinase MNK1.80,81,82,83 ERK activation stimulates elf4E phosphorylation in cells infected with herpesviruses (HSV-1 [REF. 35], HCMV84 and KSHV85), poxviruses86, asfarviruses87 and coronaviruses88. Furthermore, inhibition of MNK proteins impairs HSV-189, HCMV90 and VacV91 productive replication 100- to 300-fold, and suppresses KSHV reactivation.92 VacV replication is similarly reduced in MNK1-deficient cells.93 Although MNK-dependent elf4E phosphorylation is not absolutely required for protein synthesis and is poorly understood, it is associated with increased viral protein synthesis and viral replication in herpesvirus-, asfarvirus- and poxvirus-infected cells.

**Targeting 40S binding through elf3.** Excluding the mRNAs of cricket paralysis virus (CrPV), which dispense with initiation factors88,89, most viral mRNAs recruit 40S subunits directly or indirectly through elf3, irrespective of their requirement for elf4F or their use of cap-dependent versus cap-independent mechanisms. In fact, viruses that rely on cap-independent translation to circumvent elf4F often target elf3 and ribosomal proteins. elf3 is an adaptor that orchestrates how ribosomes, elf4F and mRNA communicate, and is composed of 13 subunits (elf3a–elf3m) that interact (via elf3e) with elf4G, bind mRNA and contact the 40S ribosome. elf3j is intimately involved with ribosome function and occupies the ribosomal decoding centre to facilitate scanning and AUG selection with elf1A.94 Some viruses directly recruit elf3 to viral mRNAs through cis-acting RNA elements or interactions with viral proteins that partially mimic elf4F (FIG. 2; TABLE 1). elf3 also functions in re-initiation following termination of uORF translation in polyribosomal mRNAs.95 Finally, elf3 is targeted both by viruses seeking to inhibit host protein synthesis and by host defences attempting to impair viral protein production.

**Recruiting elf3 to viral mRNA.** The VPg protein that is covalently linked to the 5′ end of the feline calcivirus (FCV) and human norovirus (HNV) positive-strand RNA genome, in place of a cap, recruits ribosomes by interacting with elf3 (REF. 11). Other viruses (hepatitis C virus (HCV), classical swine fever virus (CSFV), HIV and potentially Sindbis virus) use IRESs to replace elf4F function and directly bind elf3 and 40S subunits (BOX 1). Substantial conformational changes in 40S subunits occur on binding HCV and CrPV IRESs,96 and 40S binding similarly alters IRES conformation.97 Small ribosome subunit protein RPS25 is essential for initiation from the CrPV IRES98,99, which directly binds 40S subunits independently of elf3 (REFS 67,68). RPS25 is also required for HCV IRES-directed initiation but has minimal effects on cellular protein synthesis, demonstrating that a ribosomal protein is selectively required for IRES-mediated translation.99 This raises the possibility that other ribosomal proteins influence translation of non-IRES-containing mRNAs.

elf3 also contributes to termination and re-initiation events on downstream ORFs of polycistronic viral mRNAs. Re-initiation on CaMV polycistronic mRNA requires the viral protein transactivator viroplasmin...
(TAV), which binds to the same eIF3g site as eIF4B and interacts with the plant protein re-initiation supporting protein (RISP). By binding eIF3a, eIF3c and ribosomal protein L24, RISP tethers TAV with 60S and eIF3-bound 40S subunits. TAV also recruits TOR to phosphorylate RISP, promoting re-initiation and viral replication. FCV, however, uses an 87-nucleotide RNA cis-element to support eIF4F-independent re-initiation of eIF3-bound 40S ribosomes on viral subgenomic polycistronic mRNA.

Interfering with eIF3 via viral proteins and host antiviral functions can suppress protein synthesis in cells infected with RNA viruses. eIF3-binding proteins from measles virus and rabies virus inhibit host protein synthesis, whereas foot-and-mouth disease virus proteinase degrades eIF3a and eIF3b subunits. How viral mRNAs recruit ribosomes using modified eIF3 is not understood. Host antiviral defenses also target eIF3. Interferon-stimulated gene products ISG54K (also known as IFIT2) and ISG56K are induced by interferon, dsRNA or infection with VSV, EMCV or Sendai virus. By binding eIF3e and eIF3c, ISG56K and ISG59K block translation by antagonizing eIF2–GTP–Met-tRNA loading and ribosome association with eIF4F and mRNA, How cellular eIF3-inhibitory functions are controlled once they are produced is not known.

Targeting tRNA, loading via eIF2

Even before recruitment to mRNA, the 40S ribosome is preloaded with Met-tRNA. This requires delivery of a ternary complex involving eIF2, GTP and Met-tRNA, (FIG. 3). Importantly, the process of ternary-complex formation and 40S loading is targeted by an innate host response designed to globally inhibit protein synthesis in virus-infected cells. eIF2 is a heterotrimeric guanine-nucleotide-binding (G) protein composed of a regulatory α-subunit, a RNA-binding β-subunit and a GTP-binding γ-subunit. Following eIF2-GDP release on AUG recognition and 60S subunit joining, GTP is exchanged for GTP by eIF2B to recycle active eIF2-GTP for another initiation round. eIF2 is inactivated by phosphorylation of its α-subunit on Ser51 by any of four cellular kinases, each of which is activated by a discrete stress. GCN2 (also known as eIF2αK4) responds to amino acid starvation or ultraviolet light, haem deprivation activates HRI (also known as eIF2αK1), exceeding the protein-folding capacity of the endoplasmic reticulum triggers PERK (also known as eIF2αK3) and double-stranded (ds) RNA produced in virus-infected cells activates PKR (also known as eIF2αK2). Phosphorylated eIF2α has a greater affinity than its unphosphorylated counterpart for eIF2B and inhibits eIF2B guanine nucleotide exchange activity, thus depleting eIF2-GTP pools and inhibiting initiation. Because eIF2B is present in limiting quantities, small changes in eIF2α phosphorylation have large effects on protein synthesis. Although activation of any eIF2 kinase in virus-infected cells could inhibit protein synthesis and potentially result in autophagy, type I interferon production by virus-infected cells stimulates PKR accumulation in neighbouring cells. PKR activation following infection of interferon-primed neighbouring cells globally inhibits protein synthesis and curtails viral spread, making this activation a key player in the innate response to viruses. However, host efforts to inactivate eIF2 by phosphorylation in order to limit viral replication are matched by viral countermeasures to inhibit interferon production and therefore indirectly prevent PKR accumulation, to directly preserve eIF2 activity for viral protein production or to bypass eIF2 function entirely (FIG. 3).

Preserving eIF2. To directly target PKR, viruses encode dsRNA decoys that bind, but do not activate, PKR (such as the adenoviral VA RNA and the EBV EBERs), and PKR pseudosubstrates that divert activity from eIF2 (REF. 81). Other strategies include viral dsRNA-binding proteins that mask dsRNA and/or interact with and inhibit PKR (FIG. 3, TABLE 1), and phosphatase-regulatory subunits that bind cellular catalytic subunits to dephosphorylate eIF2α (such as African swine fever virus (ASFV) DP71L and HSV γ34.5 (also known as ICP34.5)). By targeting phosphorylated eIF2α, phosphatases can antagonize any eIF2α kinase. Often, viruses harness multiple strategies to prevent eIF2 phosphorylation, combining eIF2α-kinase-specific antagonists with a second function that broadly prevents phosphorylated-eIF2α accumulation. For example, HSV-1 US11 binds dsRNA and PKR to inhibit the kinase while the HSV-1-encoded eIF2α phosphatase subunit, γ34.5, removes phosphate that reaches eIF2α. As a third method, HSV-1 glycoprotein B (gB) counteracts another eIF2α kinase, PERK, preventing endoplasmic reticulum-stress-induced eIF2α phosphorylation. Similarly, VacV encodes both a dsRNA-binding PKR inhibitor (E3L) and a PKR and PERK pseudosubstrate (K3L). Although the eIF2α kinase GCN2 has antiviral effects, GCN2-specific antagonists have not been reported. Finally, the protein kinase-inhibiting molecular chaperone P56L (also known as DNAJ3K) limits eIF2α phosphorylation in influenza virus-, TMV- and tobacco etch virus-infected cells, illustrating the fact that viruses conscript host factors to prevent eIF2α phosphorylation.

Inactivating eIF2. Some viruses benefit from eIF2 inactivation. HCV, Sindbis virus, pestiviruses, reoviruses (including rotavirus), Semliki forest virus (SFV), poliovirus and CrPV induce eIF2α phosphorylation. Although eIF2α phosphorylation is not strictly required by rotaviruses or SFV, it helps to inhibit host translation. How viral mRNAs are translated without eIF2 or in the presence of phosphorylated eIF2 is beginning to emerge. Surprisingly, the CrPV IRES initiates translation without eIFs or Met-tRNA, and only requires an 80S ribosome and eIF4G. Sindbis virus late mRNAs are also insensitive to eIF2α phosphorylation, whereas CSFV employs both eIF2-dependent and eIF2-independent translation modes. Finally, PKR-mediated eIF2α phosphorylation blocks interferon-induced protein production in HCV-infected cells. Paradoxically, HCV proteins E2 and NS5A, as well as the HCV IRES, inhibit PKR and, in the case of E2, PERK. Perhaps the HCV IRES is eIF2 independent in the physiological, infected-cell system.
Indeed, high magnesium concentrations support HCV IRES function without eIF2 in vitro. Alternatively, the HCV IRES could require eIF2, provided that HCV prevents eIF2 phosphorylation in local replication compartments on intracellular membranes but allows activated PKR to phosphorylate eIF2 in the cytoplasm. Cellular factors — including ligatin (also known as the GTP-independent initiation factor eIF2D) and MCT1 (also known as MCTS1) –DNER (also known as DRP) — that are capable of recruiting Met-tRNA to 40S subunits and positioning the AUG start codon directly into the P site may explain the eIF2-independent initiation mechanisms used by HCV and Sindbis virus IRESs.

**Targeting elongation and termination**

Whereas translation initiation is rate limiting and involves numerous factors that are each subjected to intricate regulation, the processes of elongation and termination require a more limited set of factors, but viruses can nonetheless effectively target these factors. Increased elongation rates are required to cope with elevated initiation rates. Thus, viruses that activate mTORC1 to promote initiation also stimulate p70 ribosomal protein S6 kinase (p70 S6K) proteins, which phosphorylates and inhibits eIF2 kinase (Figs 1, 4). As eIF2 phosphorylation by eIF2 kinase inhibits elongation, p70 S6K stimulates elongation. By contrast, eIF2 kinase is stimulated by protein kinase A (PKA), Ca2+–calmodulin or AMP-activated protein kinase (AMPK), thus reducing elongation. Viruses can alter eIF function and subcellular distribution. Similarly, viral manipulation of termination factors can regulate polypeptide synthesis or couple termination to re-initiation.

**Elongation.** eIF5B has a key role in transitioning from initiation to elongation by promoting initiation factor displacement and 60S subunit joining. To control 60S recruitment and elongation, eIF5B, eIF1A and eIF2 are respectively inactivated by enterovirus 3C protease, severe acute respiratory syndrome (SARS) coronavirus (SARS CoV) N protein and avian reovirus p17 (REFS 102–104). Although these probably contribute to host shut-off, how viral mRNA translation proceeds without intact eIF5B or functional eEFs remains unknown. By interacting with eIF1A, HIV Gag inhibits viral mRNA translation and stimulates RNA packaging into virions. As an alternative method, TMV VPg binds to eIF1A and causes it to accumulate on intracellular membranes, where viral replication occurs. Similarly, eIF2 is recruited to cytoplasmic viral replication compartments in cells infected with Sindbis virus or ASFV. Finally, the eIF1Bα subunit (formerly known as eIF1B), which mediates GDP–GTP exchange on eIF1A, is hyperphosphorylated by a conserved herpesvirus kinase, although how this affects translational control in infected cells is unknown.

**Termination.** On stop codon recognition by eRF1, the completed polypeptide is released and the GTPase eRF3 removes eRF1 from the ribosome (Fig. 4). Termination and re-initiation may be linked through the interaction of PABP with ribosome-bound eRF3 and cap-bound eIF4E. Polycistronic mRNAs of RNA viruses, for example, employ coupled termination–re-initiation events to translate downstream ORFs, similarly to bacteriophage translational coupling (BOX 2). Murine norovirus VP2 is synthesized by such coupling.
A termination upstream ribosomal-binding site (TURBS) cis-element in FCV (70 nucleotides) and influenza B virus (45 nucleotides) positions the ribosome for re-initiation by base-pairing with 18S rRNA to allow translation of the FCV and influenza virus ORFs encoding VP2 and BM2 (also known as M), respectively. Retroviral reverse transcriptase binds eRF1 to modulate termination and re-initiation, and re-initiation protects HIV-1 mRNAs from nonsense-mediated decay. Finally, termination in small uORFs can have a regulatory role by restricting scanning ribosomes from re-initiating at downstream cistrons. A variation of this strategy operates in HCMV-infected cells, in which ribosomal stalling (which is dependent on the sequence of the uORF2 peptide) prevents scanning ribosomes from reaching the downstream UL4 ORF. By binding eRF1, uORF2 peptide inhibits translation at its own stop codon. Ultimately, the stalled ribosome disengages the mRNA.

Exploiting mRNA metabolism

Competition between virus and host for limiting translation components is influenced by mRNA availability in
the cytoplasm of the infected cell. Viruses can interfere with mRNA trafficking, altering mRNA steady-state levels to impair host protein synthesis while stimulating the cellular translation machinery. For example, in HSV-1-infected cells, transcription from cellular RNA polymerase II promoters is suppressed and the virally encoded protein ICP27 inhibits splicing, causing nuclear retention of most cellular mRNAs but allowing ICP27-mediated export of unspliced viral mRNA96. Although other, related herpesviruses (HCMV, KSHV and EBV) do not inhibit splicing, they all encode an ICP27-like protein that promotes nuclear export of viral mRNA. The HCMV protein UL69, which associates with PABP and eIF4A, is required to suppress eIF4E binding to 4EBP1 (REF. 114), suggesting that viral nuclear-export proteins associate with initiation factors to stimulate viral mRNA translation. In KSHV-infected cells, ORF57 protein facilitates export of intronless viral mRNA and associates with PYM, a cellular factor that stimulates recruitment of the ribosomal pre-initiation complex to newly exported mRNAs115. Other viruses that replicate in the nucleus, such as adenoviruses or influenza viruses, also inhibit host mRNA export116,117. Consequently, the adenovirus proteins E1B 55K and E4 ORF6 stimulate selective, nuclear RNA export factor 1 (NXF1; also known as TAP)-dependent nuclear export of viral late mRNAs. How influenza virus mRNAs reach cytoplasmic ribosomes remains unknown, although the TAP nuclear export pathway is required118. Despite replicating in the cytoplasm, HSV M protein inhibits RAE1 (also known as MRNP41)-mediated nuclear export to block host mRNA trafficking and prevent synthesis of host defence-related proteins119.

Besides interfering with cellular mRNA trafficking, viruses can stimulate mRNA turnover. Both the HSV-1-encoded eIF4F-associated RNase virion host shut-off (vhs) and a conserved function encoded by related gammaherpesviruses (KSHV SOX, murine herpesvirus 68 muSOX and EBV BGLF5) accelerate mRNA turnover to help suppress host protein synthesis114,119. Instead of a ribonuclease, poxviral decapping enzymes remove m’G caps from mRNAs, converting them into substrates for host mRNA decay pathways and contributing to host shut-off120. Thus, although HSV-1, KSHV and VacV stimulate eIF4F activity and assembly (as discussed above), their global assault on mRNA metabolism ensures that predominately viral mRNAs accumulate in the cytoplasm and are translated. Finally, host defences harness a powerful RNA decay pathway involving RNase L, which attacks mRNA and rRNA. To preserve cellular rRNA and viral mRNA, viruses often encode functions that antagonize RNase L activation, many of which also prevent PKR activation81.

Viral infection alters the distribution and composition of stress granules and processing bodies (P-bodies), which are discrete cytoplasmic structures associated with mRNA metabolism121. Stress granules contain translationally inactive mRNAs and accumulate in response to translation inhibition, including that mediated by eIF2α phosphorylation and eIF4G cleavage, whereas P-bodies are associated with mRNA degradation. Poliovirus in particular degrades factors involved in P-body formation (poly(A)-nuclease) and the exonuclease XRN1) and induces formation of modified stress granules that lack G3BP, which is cleaved by the viral 3C protease122,123. Although the function of modified stress granules in infected cells remains unclear, inactivating P-body components might protect viral mRNAs, which are uncapped, from degradation. Other RNA viruses (rotaviruses and CrPV) block the formation of stress granules and, in the case of CrPV, P-bodies, despite inducing eIF2α phosphorylation and eIF4G cleavage, whereas P-bodies are associated with mRNA degradation. Poliovirus in particular degrades factors involved in P-body formation (poly(A)-nuclease and the exonuclease XRN1) and induces formation of modified stress granules122,123. Although stress granule components can stimulate replication of some RNA viruses (respiratory syncytial virus, dengue virus and West Nile virus124), other viruses exploit P-bodies for viral assembly (HSV-1 and brome mosaics virus)125–127 or cap stealing (hantaviruses)128. DNA viruses can also target stress granules, as the PKR antagonist encoded by VacV, E3L, prevents their accumulation129.

MicroRNAs
Small, non-coding microRNAs (miRNAs) can regulate the stability and translation of both host and viral mRNAs via RNA interference (RNAi). After processing from a larger, primary transcript, a 22-nucleotide miRNA is loaded into the RNA-induced silencing complex (RISC). Perfect base pairing with target sequences commonly found in the 3′ UTR triggers mRNA degradation, whereas imperfect base pairing inhibits translation130. Although RNAi is a potent host antiviral defence mechanism in plants and invertebrates, virally encoded functions can antagonize the host miRNA machinery. Whether miRNAs contribute to mammalian innate antiviral responses remains less clear. However, herpesviruses in particular do express virally encoded miRNAs.

**Figure 5** | **Regulation of translation termination in virus-infected cells.** On recognition of a stop codon in the A site, eukaryotic release factor 1 (eRF1) triggers 80S arrest and polypeptide release. eRF3 subsequently releases eRF1 from the ribosome, and the 80S ribosome is dismantled into 40S and 60S subunits (see FIG. 1). Virally encoded functions that regulate termination are indicated. Notably, HIV reverse transcriptase and the termination upstream ribosomal-binding site (TURBS) RNA cis-elements in influenza B virus and feline calicivirus (FCV) allow eukaryotic ribosomes to efficiently re-initiate translation, a property normally associated with prokaryotic ribosomes. eIF, eukaryotic translation initiation factor; HCMV, human cytomegalovirus; uORF2, upstream ORF 2.
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Box 2 | Lessons in translation from bacteriophages

Differences in the physical structure, ORF organization, ribosome composition and initiation factors for bacterial mRNAs compared with eukaryotic mRNAs influence bacteriophage translation strategies136,137. Besides having smaller, 705 ribosomes and uncapped, predominately genome-collinear, non-polyadenylated mRNAs, bacteria mediate 305 ribosome recruitment without scanning, through 165 ribosomal RNA base-pairing with a Shine–Dalgarno (SD) cis-element proximal to the AUG start codon. Ribosomes also re-initiate translation efficiently in bacteria, enabling the translation of polycistronic mRNAs.

To regulate ribosome recruitment, phage RNA-binding proteins (RNA-BPs) recognize targets near SD sites, thus occluding ribosome binding to the translation initiation region (tir). This allows RNA replicates and coat proteins to suppress translation, fostering genome replication and RNA packaging, respectively. Phage T4 proteins involved in DNA replication autogenously repress translation of their own encoding mRNA by sequence-specific or, in the case of gp32 (which binds single-stranded DNA), cooperative structure-specific binding. Restricting the represorative activity of gp32 to unbound monomers that are superfluous for DNA replication serves as a rheostat, limiting gp32 accumulation148. Similarly, translation repression by free, unassembled phage P22 gene 8 scaffold protein maintains the scaffold-to-coat protein ratio that is required for phage assembly139-141. tir-binding proteins also remodel repressive RNA structures to stimulate translation, as phage Mu Com promotes the synthesis of DNA-modification enzyme Mom142.

Modifications of the mRNA structure also regulate phage mRNA translation. Processing of phage T7 1.1 and 1.2 gene mRNAs by host RNase III stimulates translation143. However, cleavage of the SD sequence of phage T4 early mRNA by an endoribonucllease comprising phage T4 RegB and host ribosomal protein S1 limits the accumulation of early proteins, stimulating translation of middle and late mRNAs144. Transit through an upstream cistron by translating ribosomes can modify the higher-order structure of a polycistronic transcript, regulating initiation for the downstream cistron by controlling SD exposure145. Such ‘translational coupling’ requires ribosome release factors when translation of a downstream cistron involves an upstream ribosome that must terminate before re-initiating (compared with entry of a new ribosome)150.

Besides coupling, other methods of maintaining subunit stoichiometry are recoding and bypassing. These processes also maximize codon usage by altering ribosome decoding of a contiguous ORF. Recoding via programmed frameshifting regulates protein levels or allows overlapping ORFs to produce fixed protein ratios, as in phage λ, phage HK97 and phage Mu tail assembly genes152. Bypassing joins the information in two ORFs into one polypeptide. Using a peptide-tRNA decoding mechanism, signals in the phage T4 gene 60 mRNA stimulate ribosome take-off, mRNA slippage without scanning, and ribosome landing, bypassing 50 nucleotides between two ORFs146.

Translation control provides a powerful physiological sensor that regulates the lytic phase–lysogenic phase developmental decision in temperate phages. Phage λ lysogeny requires synthesis of the repressor CI, which is positively regulated by CI and CII. Translation of both CI and CII mRNA is stimulated by host proteins binding near the 5’ end of the mRNA153. Translation of phage λ N mRNA, encoding a transcription elongation factor required for lytic replication, is also autogenously repressed by N protein binding to the 5’ untranslated region. Subsequent RNase III-mediated cleavage removes the N-binding site, stimulating N synthesis and phage λ replication155. Even more elaborate systems are found in phage P1 and phage P7, in which prophage C4 antisense RNAs indirectly antagonize the synthesis of anti-repressor by combining translational repression and coupling to regulate transcription156.

Bacterial antiviral responses also exploit the translation control mechanisms of phages. The Orf1 protein of phage bil66 activates translation of M operon mRNA by binding to an RNA structural element. A similar motif in the AbiD1 gene of the host, Lactococcus lactis, confers Orf1 responsiveness and results in an abortive infection157.

in latently infected cells, and these miRNAs are thought to suppress expression of lytic genes and help maintain latency. They also suppress host apoptotic and immune responses. Another DNA virus-encoded miRNA reduces translation of the SV40 large T antigen mRNA to limit the host immune response129. Poxviruses and most RNA viruses have not been reported to encode miRNAs. This may reflect their cytoplasmic replication, which could restrict access to nuclear miRNA-processing steps, or, for some RNA viruses, may reflect the potentially detrimental effects of miRNA processing on viral genome integrity. RNA viruses can, however, use miRNA-based strategies to manipulate the host translation machinery. Induction of a host transcription factor in enterovirus-infected cells promotes miR-141 expression, which impairs translation of eIF4E-encoding mRNA and inhibits cap-dependent protein synthesis150. The HCV RNA genome 5’ UTR contains two tandemly repeated, liver-specific miR-122 targets. Surprisingly, miR-122 enhances, rather than suppresses, both genome abundance151 and viral mRNA translation132,133, possibly through effects on the conformation of the HCV IRES. These target sites destabilize reporter mRNAs when placed in the 3’ UTR, suggesting that the functional outcome of miRNAs on their targets is influenced by the position of their recognition sites154. Finally, HCMV reduces the expression of host miRNAs that suppress ERK and PI3K–Akt–mTORC signalling129. Indeed, much remains to be learned about miRNA targets and their contribution to infection.

A potential Achilles heel to exploit for therapy?

The effectiveness with which viruses co-opt components of the host translation machinery represents an extraordinary example of parasitism and illustrates the importance of this process to viral replication. Nature validates this view, as initiation factors determine plant susceptibility to RNA viruses. Most recessive resistance genes from crop species encode eIF4E and eIF4G family members155, and host antiviral factors such as poxweed antiviral protein bind eIF4G and depurinate viral RNA156. Virus–host interactions that regulate protein synthesis in infected cells could potentially lead to novel broad-spectrum antiviral targets that are ripe for development. Even antagonizing a general factor such as eIF4F may be tolerated for limited periods to combat acute, life-threatening infections, as high eIF4F activity seems to be reserved for translating complex, growth-related mRNAs. 4EGi-1, a synthetic inhibitor that affects eIF4F and ribosome binding, has potent, non-cytotoxic antiviral properties against HSV-1 and VACV157; screens using small interfering RNAs suggest initiation factors and ribosomal proteins as potential antiviral targets135,158; and compounds that inhibit eIF2a dephosphorylation reduce HSV-1 replication159. Furthermore, a small-molecule inhibitor of the MNK protein reduces replication of VACV161, ASFV162 and several herpesviruses in culture133,134. The MNK proteins are interesting targets, as they are not essential, core initiation factors but instead have a regulatory role. Other targets, such as inhibitors of the mTORC1 active site (which disrupt eIF4F and impair herpesviral replication163), will probably have immunosuppressive side effects in vivo162. However, inhibiting a virally encoded mTOR activator, such as the HSV-1 kinase US3 (REF. 44), could prevent mTORC1 activation selectively in infected cells and circumvent this problem. IREs, which are relied on by many RNA viruses, also represent potential targets156,164-166. Finally, virus–host interactions that regulate translation have contributed to the development of oncolytic viruses144.
**Summary**

Viruses subvert virtually every step in the host translation process. From mRNA availability for cytoplasmic ribosomes, to cell-signalling pathways that regulate translation factor abundance, localization and activity, to ribosome recruitment, all are commandeered to stimulate and sustain viral mRNA translation. The diversity of strategies used by different viruses reflects the varied viral life cycles, the specialized host cells that viruses infect and the methods of translation control in their cellular hosts (which are probably the main evolutionary drivers behind the diverse strategies used for subversion). Similarities between the translation control strategies that are operative in infected cells and in stress-induced, uninfected cells have emerged. Adenovirus-infected and uninfected, heat-stressed cells use ribosome shunting. Related viral and cellular regulatory phosphate subunits are required to prevent accumulation of phosphorylated elf2α in HSV-infected cells and in uninfected cells recovering from endoplasmic reticulum stress. elf4G can be cleaved by virally encoded proteases and also by cellular caspas during apoptosis. Key integrators such as TSC and mTORC proteins, which enable rapid control of cap-dependent translation in response to physiological cues in uninfected cells, have important roles stimulating or repressing translation in virus-infected cells. IRESs were originally discovered as viral genetic elements, but they enable translation of cellular mRNAs when elf4F-mediated, cap-dependent translation is impaired by stress. By conveying elf2 independence, newly identified factors such as ligatin could expand the range of conditions that support viral mRNA translation. Roles for specific (that is, RPS25) or modified ribosomal proteins may emerge for different viral and cellular IRESs. Finally, IRESes with minimal initiation factor requirements (such as those of HCV and GrPV) highlight how viral models provide powerful cellular, biochemical and genetic tools that continue to expose surprising translation regulatory mechanisms.
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The demonstration that a retroviral protein interacts with eRF1 to regulate translation initiation has been thoroughly studied. For example, in their recent study, Luo et al. demonstrate that a retroviral protein interacts with eRF1 to regulate translation initiation. Their findings provide new insights into the mechanisms that regulate translation initiation in retroviruses. The authors highlight the importance of understanding the interplay between retroviral proteins and translation initiation factors to develop effective antiretroviral strategies.

In conclusion, the process of translation initiation is critical for viral replication and host cell function. Further research is needed to understand the complex interplay between retroviral proteins and translation initiation factors. The findings of Luo et al. add to our understanding of this complex process and may have implications for the development of novel antiviral therapies.

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Competing interests statement
The authors declare no competing financial interests.