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.

7-methylguanosine cap
A 7-methylguanosine linked to the 5′ end of an mRNA, via a 5′–5′ triphosphate linkage, to mark the extreme 5′ terminus of a eukaryotic mRNA. In addition to having regulatory roles in pre-mRNA processing and mRNA stability, the cap structure controls ribosome recruitment to the mRNA 5′ end.

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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 ($Met\text{-}tRNA_i$). 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 (m^7G) that distinguishes the 5′ end of the eukaryotic mRNA is bound by eIF4F, 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[1]. Cap recognition by eIF4E anchors the complex on the mRNA, and eIF4G binding enhances the affinity of eIF4E 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 assembly. 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

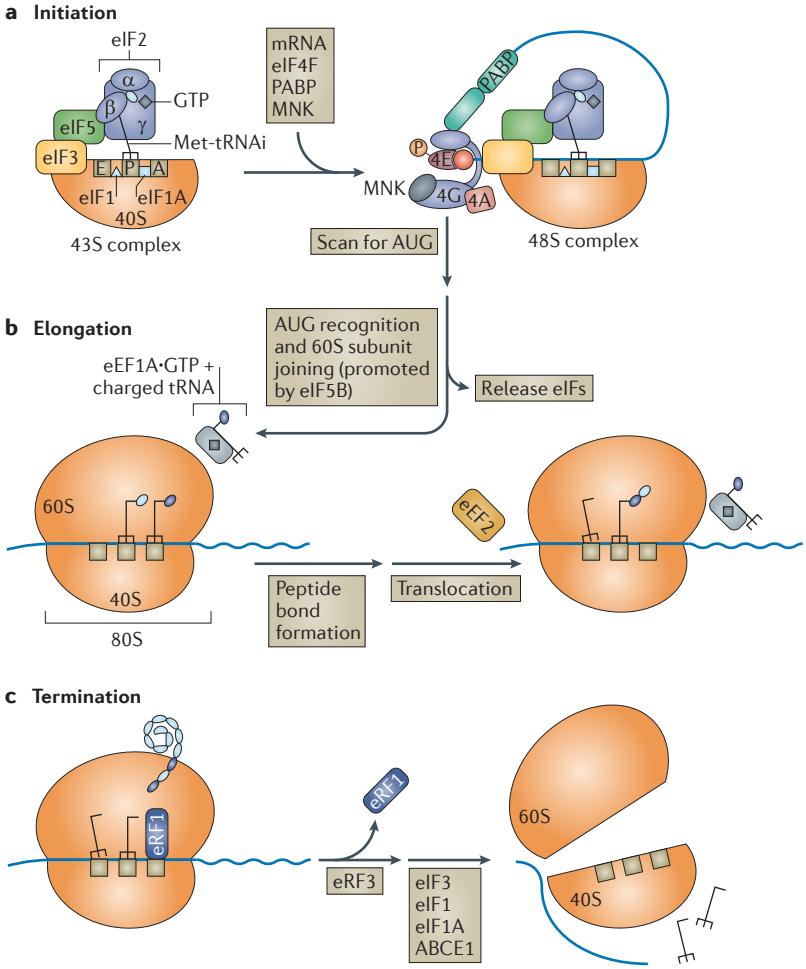


Figure 1 | **Overview of mRNA translation in eukaryotes.** The process of translation has three phases: initiation, elongation and termination. Each stage requires specific translation factors. **a** | Initiation. The 40S ribosome bound to eukaryotic translation initiation factor 1 (eIF1), eIF1A, the eIF3 complex and eIF5 is loaded with initiator-methionine tRNA (Met-tRNA$_i$) in the P site by eIF2·GTP, forming a 43S pre-initiation complex. Subsequently, the 43S complex is positioned onto the 5′ end of a capped (red circle), polyadenylated mRNA by eIF4F, a multisubunit complex composed of the cap-binding protein eIF4E, eIF4G and eIF4A (abbreviated here as 4E, 4G and 4A). The polyadenylated 3′ mRNA end is recognized by a poly(A)-binding protein (PABP), which also associates with eIF4G bound to the 5′ end. This results in a 'closed-loop' topology, linking 5′ and 3′ mRNA ends. One of the eIF4E kinases MNK1 and MNK2 binds eIF4G and phosphorylates eIF4E. The assembled 48S complex then scans the mRNA to locate the AUG start codon. After AUG recognition, facilitated by eIF3, eIF1 and 1A, 60S subunit joining triggers initiation factor release. **b** | Elongation. Each charged tRNA is delivered to the 80S ribosome A site by eEF1A·GTP. Following ribosome-catalysed peptide bond formation, eukaryotic elongation factor 2 (eEF2) catalyses 80S translocation, transferring the deacetylated tRNA to the E site, positioning the peptidyl-tRNA in the P site and re-exposing the A site. **c** | Termination. Eukaryotic release factor 1 (eRF1) recognizes the stop codon in the A site, triggering 80S arrest and polypeptide release. eRF3 releases eRF1 from the ribosome, and several initiation factors, together with ABCE1-directed nucleotide hydrolysis, dismantle the complex, thus recycling ribosome subunits.

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[1]. 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[1]. 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 (FIG. 1). 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[2].

Stop codon recognition by eRF1 induces hydrolysis of the ester bond linking the tRNA to the completed polypeptide, resulting in translation termination (FIG. 1). eRF3 then removes eRF1 from the ribosome[3]. 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 commandeer the host protein synthesis machinery.

Targeting initiation through eIF4F

Regulated eIF4F assembly is a fundamental step in controlling cap-dependent translation initiation in eukaryotes. Given the importance of protein synthesis in the biology of viruses, it is no wonder viruses target eIF4F to subvert and gain control of the host translational apparatus (FIG. 2). Some viruses impair host translation by removing key structural elements in the mRNA, such as the m^{7}G cap, by inactivating eIF4F subunits or by manipulating eIF4F-binding proteins, thus preventing synthesis of host defence molecules that antagonize viral

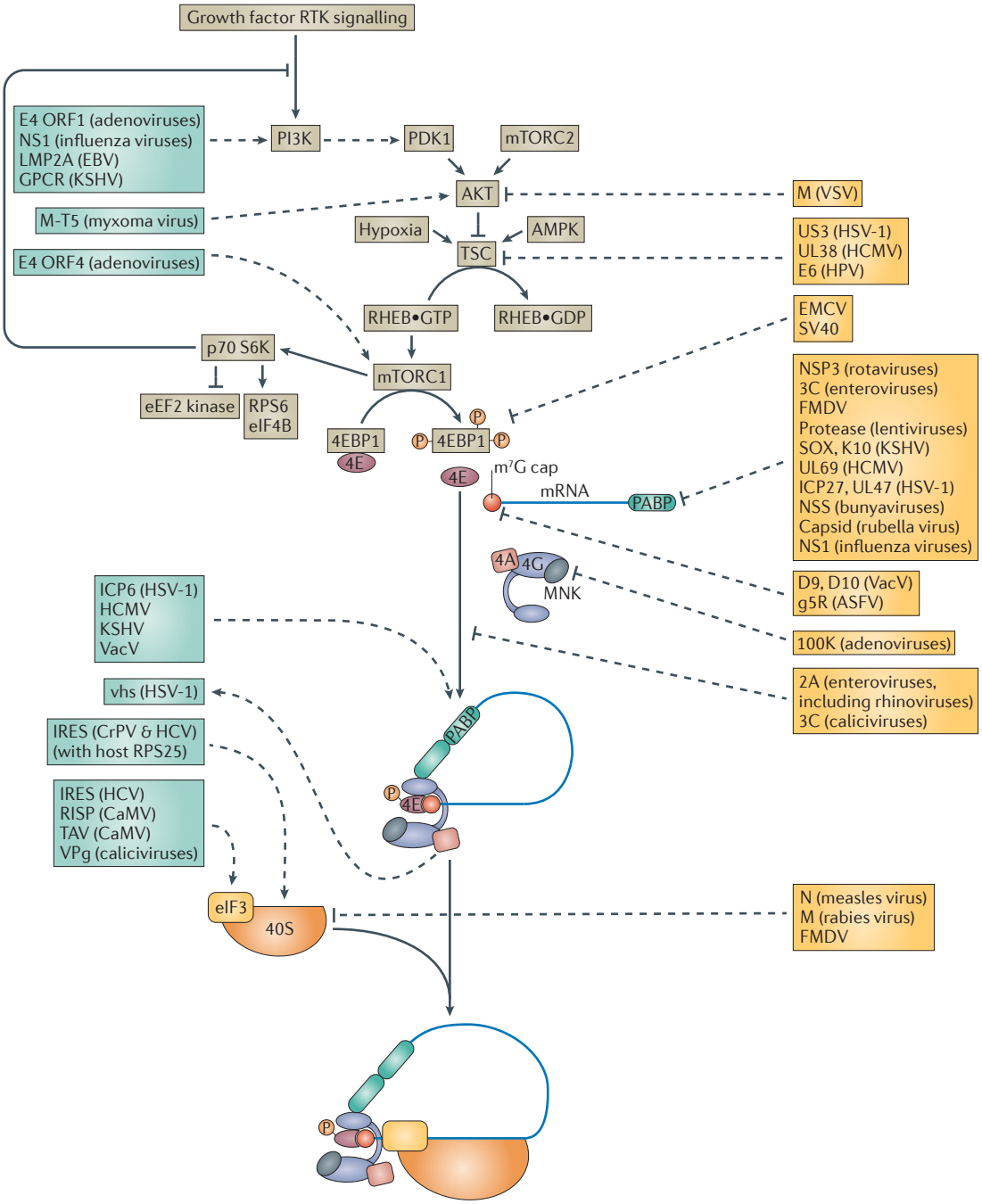


Figure 2 | **Control of cap-dependent translation by regulated assembly of a multisubunit initiation factor.** By binding to the cap-binding protein eukaryotic translation initiation factor 4E (eIF4E; abbreviated here to 4E), eIF4E-binding protein 1 (4EBP1) represses translation and prevents assembly 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•GDP accumulation. Receptor tyrosine kinase signalling, AMP-activated protein kinase (AMPK) and hypoxia regulate TSC activity. Inhibiting TSC allows RHEB•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^7G; 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^7G cap[4,5], 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[6–8]. 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[9]. 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[10–12]. The 5′ mRNA leader of potyviruses, which are related to picornaviruses, contains eIF4G-binding pseudoknots that direct cap-independent translation[13]. Other plant viruses contain 3′ cap-independent translational elements (CITEs), which interact with the 5′ end of the mRNA and bind initiation factors, including eIF4E and eIF4G, to recruit ribosomes[14]. For example, the turnip crinkle virus (TCV) CITE contains tRNA-like structures that bind the 60S ribosome[15]. 3′ CITES also suppress mRNA translation on positive-strand RNAs to promote genome replication[14]. Finally, hantavirus N protein reportedly has cap-binding, RNA-binding, helicase and ribosome-binding activities, substituting for eIF4F to promote translation of viral mRNAs[16].

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 eIF4G, 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[17]. Inhibiting host cap-dependent translation does not block viral mRNA translation, as many RNA viruses contain specialized internal ribosome entry sites (IRESs) (BOX 1) that direct cap-independent translation[18]. 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[19–21].

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[23,24]. 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[23,27,28]. 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[27]. By binding late viral mRNA sequences in the 5′ tripartite leader, 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[27,29]. 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[17,32]. 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[17,32].

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[34]. 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.

Internal ribosome entry sites (IRESs). *Cis*-acting structural elements that lie within mRNAs and mediate cap-independent ribosome recruitment. Different IRES elements have varying requirements for translation initiation factors.

IRES-transactivating factors (ITAFs). *Trans*-acting protein cofactors that are required by some internal ribosome entry sites (IRESs), in addition to canonical translation initiation factors, in order to promote IRES-dependent translation initiation.

Polycistronic
Of an mRNA: containing multiple ORFs or cistrons. In eukaryotes, most mRNAs are monocistronic, and specific *cis*-acting elements are required to efficiently translate polycistronic mRNAs. Polycistronic mRNAs, however, are relatively common in bacteria and archaea.

Table 1 | **Viral functions and their impact on host translation factor targets**

	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	
	SV40	Small t antigen	Dephosphorylates 4EBP1 (PP2A dependent)
	HSV-1	US3	Phosphorylate 4EBP1 (via TSC2 inactivation)
	HCMV	UL38	
	KSHV	v-GPCR	Phosphorylate 4EBP1 (via PI3K–AKT–mTOR pathway activation)
	EBV	LMP2A	
	Adenoviruses	E4 ORF1 and E4 ORF4	
	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	
	Retroviruses	Protease	
	FMDV	Leader protease	
	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	Cleaves eIF5B
PABP	Enteroviruses	3C and 2A proteases	Cleave PABP
	Caliciviruses	3C-like protease	
	Lentiviruses	Protease	
	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

Table 1 (cont.) | **Viral functions and their impact on host translation factor targets**

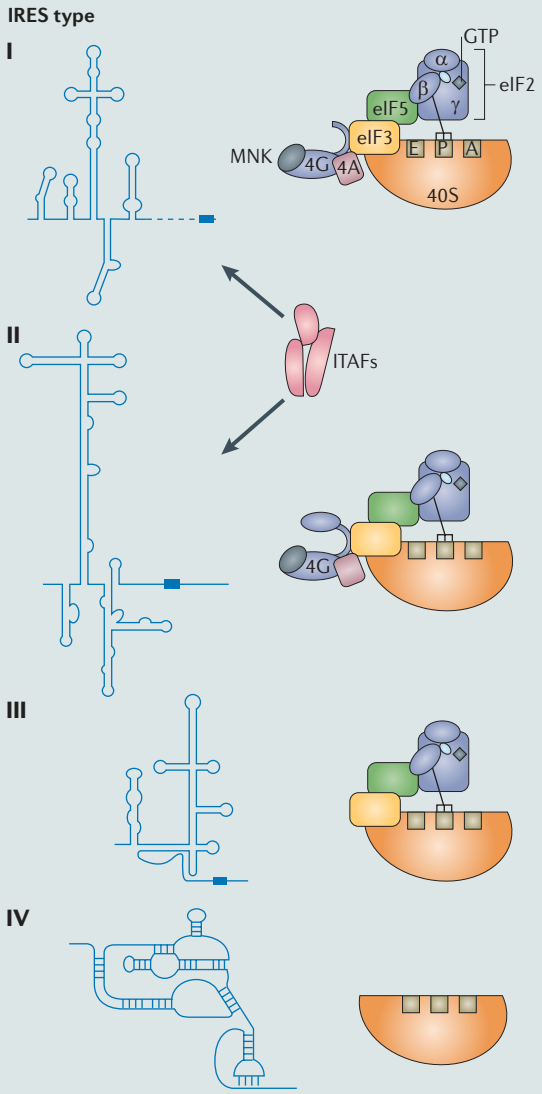
	Viruses	Viral functions	Effects on target
eIF2	HSV-1	US11	Inhibits PKR
		gB	Inhibits PERK
		γ34.5	Regulates eIF2α phosphatase
	EBV	SM	Inhibits PKR
		EBER RNAs	Bind PKR and prevent its activation
	HCMV	TRS1 and IRS1	Bind dsRNA and prevent PKR activation
	KSHV	v-IRF2	Binds PKR and prevents its activation
	VacV	E3L	Binds dsRNA and PKR
		K3L	Acts as a pseudosubstrate for PKR and PERK
	Adenoviruses	VA RNA	Binds PKR and prevents its activation
	ASFV	DP17L	Dephosphorylates eIF2α by recruiting PP2A
	HCV	NS5A	Inhibits PKR
		E2	Acts as a pseudosubstrate for PKR and PERK
		IRES	Inhibits PKR
	Influenza viruses	NS1	Sequesters dsRNA and prevents PKR activation
	Reoviruses	σ3	
	HPV	E6	Binds GADD34–PP1α to dephosphorylate eIF2α
eEF1A and eEF1B	TMV	VPg	Binds eEF1A so that it is redistributed to viral replication compartments
	SARS CoV	N protein	Binds eEF1A and impairs translation
	HIV-1	Gag	Binds eEF1A and impairs viral mRNA translation to stimulate packaging
	HSV-1	UL13	Phosphorylate eEF1Bα
	HCMV	UL97	
	EBV	BGLF4	
eRF1	HIV-1	Reverse transcriptase	Binds eRF1, modulates termination and re-initiation, and protects viral mRNAs from nonsense-mediated decay
	HCMV	uORF2	Binds eRF1 and inhibits translation at its own stop codon to regulate translation of the downstream HCMV ORF
Ribosome	HCV, CSFV and HIV	IRES	Binds the 40S ribosome in conjunction with eIF3
	CrPV	IRES	Binds the 40S ribosome to mediate initiation factor-independent translation
	FCV and influenza B virus	TURBS	Base-pairs with 18S ribosomal RNA to promote re-initiation
	KSHV	ORF57	Binds PYM to recruit 40S ribosomes to viral mRNAs

4EBP, eIF4E-binding protein; ASFV, African swine fever virus; CaMV, cauliflower mosaic virus; CrPV, cricket paralysis virus; CSFV, classical swine fever virus; dsRNA, double-stranded RNA; EBV, Epstein–Barr virus; eEF, eukaryotic elongation factor; eIF, eukaryotic translation initiation factor; eRF, eukaryotic release factor; FCV, feline calicivirus; FMDV, foot-and-mouth disease virus; GADD34, growth arrest and DNA damage-inducible protein 34; HCMV, human cytomegalovirus; HCV, hepatitis C virus; HPV, human papilloma virus; HSV, herpes simplex virus; IBV, infectious bronchitis viruses; IRES, internal ribosome entry site; KSHV, Kaposi's sarcoma-associated virus; miR-141, mature microRNA 141; mTORC, mTOR complex; PABP, poly(A)-binding protein; PDK1, phosphoinositide-dependent protein kinase 1; PI3K, phosphoinositide 3-kinase; PP 1α, protein phosphatase 1α; PP2A, protein phosphatase 2A; RISP, re-initiation supporting protein; ROXAN, rotavirus 'X'-associated non-structural protein; SARS CoV, severe acute respiratory syndrome coronavirus; SV40, simian virus 40; TAV, transactivator viroplasmin; TMV, tobacco mosaic virus; TSC2, tuberin; TURBS, termination upstream ribosomal-binding site; uORF2, upstream ORF 2; VacV, vaccinia virus; v-GPCR, viral G protein-coupled receptor; vhs, virion host shut-off; VSV, vesicular stomatitis virus.

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′ m^7G cap and 3′ poly(A) tail) rely on cap-dependent translation and stimulate eIF4F activity. Herpesviruses (herpes simplex virus type 1 (HSV-1), human cytomegalomvirus (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[25,35–41]. 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 gammaherpesvirus (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

Box 1 | **Internal ribosome entry sites**

There are four types of internal ribosome entry sites (IRESs) (see the figure), each of which can directly interact with host translational components and circumvent conventional cap-dependent ribosome recruitment[18]. These sites can confer a potent competitive advantage to viral mRNAs, freeing them from host regulatory constraints and, in cases for which viral infection impairs cap-dependent translation, sustaining viral protein synthesis. Type I (for example, poliovirus) and II (for example, encephalomyocarditis virus) IRESs were first identified in picornaviruses. These two IRES types interact with the eukaryotic translation initiation factor 4G (eIF4G; labelled 4G) carboxy-terminal domain[18], which binds to eIF4A (labelled 4A) and eIF3. They require eIF5B, eIF2 and initiator-methionine tRNA (Met-tRNA$_i$), and are stimulated by the activity of eIF1, eIF1A and eIF4B. They also require IRES *trans*-acting factors (ITAFs), which are RNA-binding proteins that alter IRES conformation 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[71], analogous to ribosome recruitment through Shine–Dalgarno sequences in bacteria. These IRESs also require eIF5B, eIF2 and Met-tRNA$_i$, 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[67,68]. 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 to the P-site initiates translation, resulting in viral precursor polypeptides with amino-terminal alanine residues rather than methionine.



by phosphorylating tuberin (TSC2)[44]. 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[35,38,39,44], 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)[53]. 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[53]. 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[54]. Although eIF4E binding to eIF4G is stimulated in HSV-1-infected cells, PABP binding to eIF4F is unchanged or reduced[37,55], 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. eIF4F assembly and binding to PABP are stimulated in HCMV-infected cells. Furthermore, eIF4E, eIF4G, eIF4A and PABP steady-state levels increase, and for PABP proteins this involves a translational control mechanism[37,45]. 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 eIF4F 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 eIF4E[57]. However, the capacity of mimiviral homologues to function in translation initiation and their contribution to protein synthesis in infected cells are unknown.

Redistributing eIF4F 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 eIF4F assembly[38,41]. Remarkably, eIF4E and eIF4G are redistributed and concentrated in viral replication compartments[38,41,58]. Increasing the local concentration of initiation factors in discrete regions could favour eIF4F assembly and sequester factors from host mRNAs to suppress cellular translation. Similarly, tobacco mosaic virus (TMV)-encoded VPg binds eIF4E, concentrating eIF4E and eIF4G on membrane-associated replication sites[59], whereas Sindbis virus, an RNA virus that replicates in the cytoplasm and employs cap-independent translation, recruits eIF3 and eEF2 to viral compartments but excludes eIF4G[60].

Redistribution of eIF4F and PABP is not limited to concentration in replication compartments. For instance, eIF4E is redistributed to the nucleus by poliovirus[61], 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[32,40,55,62–65]. Interestingly, these viruses impair host protein synthesis. HSV-1 and KSHV in particular promote eIF4F assembly without stimulating PABP binding to eIF4F[37,40,55,63]. By contrast, PABP does not accumulate in the nucleus but is recruited to eIF4F, and host protein synthesis proceeds unimpaired, in cells infected with the related herpesvirus HCMV[37,45]. PABP redistribution and exclusion from eIF4F 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 eIF4E binding to eIF4G regulates initiation, eIF4F assembly can induce eIF4E phosphorylation by the eIF4G-associated eIF4E kinase MNK1. p38 and/or ERK activation stimulates eIF4E phosphorylation in cells infected with herpesviruses (HSV-1 (REF. 35), HCMV[37] and KSHV[40]), poxviruses[38], asfarviruses[41] and coronaviruses[66]. Furthermore, inhibition of MNK proteins impairs HSV-1[35], HCMV[37] and VacV[38] productive replication 100- to 300-fold, and suppresses KSHV reactivation[40]. VacV replication is similarly reduced in MNK1-deficient cells[38]. Although MNK-dependent eIF4E 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 eIF3

Excluding the mRNAs of cricket paralysis virus (CrPV), which dispense with initiation factors[67,68], most viral mRNAs recruit 40S subunits directly or indirectly through eIF3, irrespective of their requirement for eIF4F or their use of cap-dependent versus cap-independent mechanisms. In fact, viruses that rely on cap-independent translation to circumvent eIF4F often target eIF3 and ribosomal proteins. eIF3 is an adaptor that orchestrates how ribosomes, eIF4F and mRNA communicate, and is composed of 13 subunits (eIF3a–eIF3m) that interact (via eIF3e) with eIF4G, bind mRNA and contact the 40S ribosome. eIF3j is intimately involved with ribosome function and occupies the ribosomal decoding centre to facilitate scanning and AUG selection with eIF1A[1,69]. Some viruses directly recruit eIF3 to viral mRNAs through *cis*-acting RNA elements or interactions with viral proteins that partially mimic eIF4F (FIG. 2; TABLE 1). eIF3 also functions in re-initiation following termination of uORF translation in polycistronic mRNAs[70]. Finally, eIF3 is targeted both by viruses seeking to inhibit host protein synthesis and by host defences attempting to impair viral protein production.

Recruiting eIF3 to viral mRNA. The VPg protein that is covalently linked to the 5′ end of the feline calicivirus (FCV) and human norovirus (HNV) positive-strand RNA genome, in place of a cap, recruits ribosomes by interacting with eIF3 (REF. 11). Other viruses (hepatitis C virus (HCV), classical swine fever virus (CSFV), HIV and potentially Sindbis virus) use IRESs to replace eIF4F function and directly bind eIF3 and 40S subunits[69,71–73] (BOX 1). Substantial conformational changes in 40S subunits occur on binding HCV and CrPV IRESs[69], and 40S binding similarly alters IRES conformation[74]. Small ribosome subunit protein RPS25 is essential for initiation from the CrPV IRES[75], which directly binds 40S subunits independently of eIF3 (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[75]. This raises the possibility that other ribosomal proteins influence translation of non-IRES-containing mRNAs.

eIF3 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[76]. 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[31].

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[77,78], whereas foot-and-mouth disease virus protease degrades eIF3a and eIF3b subunits[79]. How viral mRNAs recruit ribosomes using modified eIF3 is not understood. Host antiviral defences 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 ISGP54K block translation by antagonizing eIF2–GTP–Met-tRNA$_i$ loading and ribosome association with eIF4F and mRNA[80]. How cellular eIF3-inhibitory functions are controlled once they are produced is not known.

Targeting tRNA$_i$ loading via eIF2

Even before recruitment to mRNA, the 40S ribosome is preloaded with Met-tRNA$_i$. This requires delivery of a ternary complex involving eIF2, GTP and Met-tRNA$_i$ (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 tRNA-binding β-subunit and a GTP-binding γ-subunit. Following eIF2·GDP release on AUG recognition and 60S subunit joining, GDP 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[81]. 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[82], 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[1,81]. 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[83] and HSV γ34.5 (also known as ICP34.5)[84]). 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[85]. As a third method, HSV-1 glycoprotein B (gB) counteracts another eIF2α kinase, PERK, preventing endoplasmic reticulum-stress-induced eIF2α phosphorylation[86]. Similarly, VacV encodes both a dsRNA-binding PKR inhibitor (E3L) and a PKR and PERK pseudosubstrate (K3L)[87]. Although the eIF2α kinase GCN2 has antiviral effects[88], GCN2-specific antagonists have not been reported. Finally, the protein kinase-inhibiting molecular chaperone P58^{IPK} (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[89,90].

Inactivating eIF2. Some viruses benefit from eIF2 inactivation. HCV[91], Sindbis virus[92], pestiviruses[93], reoviruses[94] (including rotaviruses[95]), Semliki Forest virus (SFV)[96], poliovirus[97] and CrPV[98] 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$_i$ and only requires an 80S ribosome and eEFs[67,68]. Sindbis virus late mRNAs are also insensitive to eIF2α phosphorylation[92], whereas CSFV employs both eIF2-dependent and eIF2-independent translation modes[18,99]. Finally, PKR-mediated eIF2α phosphorylation blocks interferon-induced protein production in HCV-infected cells[91]. Paradoxically, HCV proteins E2 and NS5A, as well as the HCV IRES, inhibit PKR and, in the case of E2, PERK[81]. Perhaps the HCV IRES is eIF2 independent in the physiological, infected-cell system.

Autophagy
A catabolic process whereby cytoplasmic components (proteins or organelles) are targeted to lysosomes for recycling, providing the nutrients that are required during starvation, growth factor withdrawal, infection or oxidative stress.

Pseudosubstrates
Proteins that resemble a natural substrate sufficiently that they bind the target enzyme and subsequently inhibit recognition of the natural substrate by acting as decoys. The enzyme typically does not modify the pseudosubstrate. For example, virally encoded PKR pseudosubstrates are not phosphorylated by PKR, but they effectively bind PKR and prevent phosphorylation of eukaryotic translation initiation factor 2α, the natural PKR substrate.

Indeed, high magnesium concentrations support HCV IRES function without eIF2 *in vitro*[100]. 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[101]) and MCT1 (also known as MCTS1)–DENR (also known as DRP)[73] — that are capable of recruiting Met-tRNA$_i$ 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.

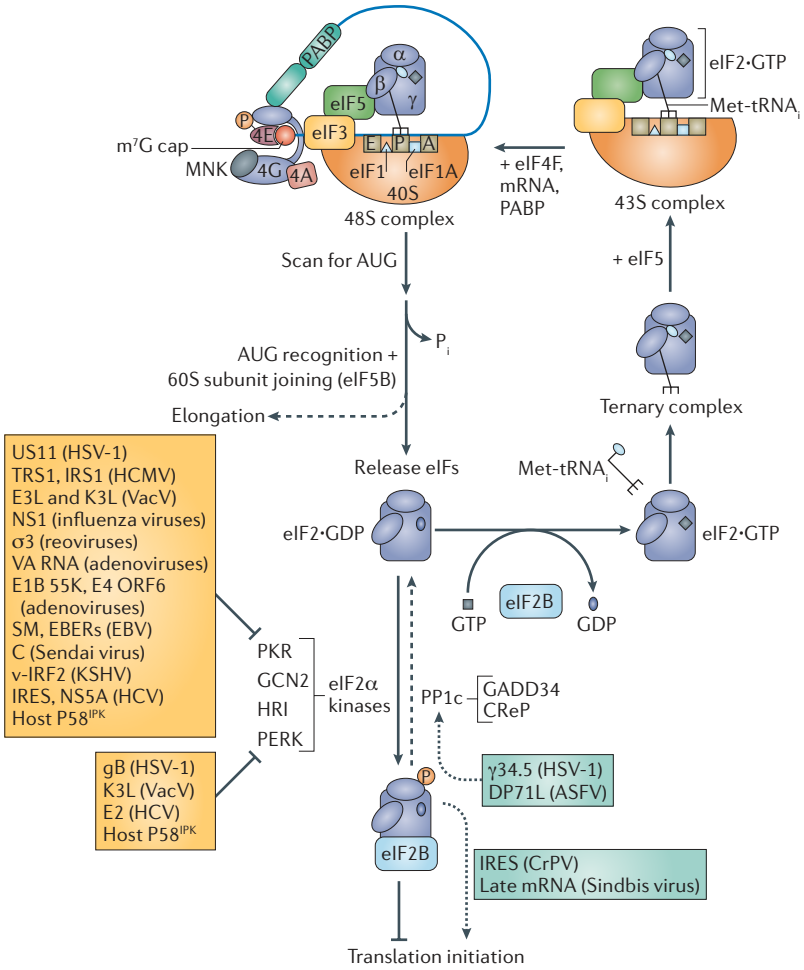


Figure 3 | **Eukaryotic translation initiation factor 2-dependent loading of 40S ribosomes with initiator tRNA regulates translation and is targeted by host antiviral defences.** Inactive eukaryotic translation initiation factor 2 (eIF2; with α-, β- and γ-subunits depicted) bound to GDP (eIF2·GDP) is recycled to the active GTP-bound form by the five-subunit guanine nucleotide exchange factor eIF2B. Once recycled, eIF2·GTP forms a ternary complex with initiator-methionine tRNA (Met-tRNA$_i$) and is loaded onto the 40S ribosome (see FIG. 1). A 43S pre-initiation complex assembles after the ternary complex loads Met-tRNA$_i$ into the ribosomal P site, and this converts to a 48S complex on recruitment to eIF4F- and poly(A)-binding protein (PABP)-bound mRNA. Following identification of the AUG start codon by scanning, the GTPase-activating protein eIF5 stimulates GTP hydrolysis, and 60S subunit joining triggers the release of eIF2·GDP and inorganic phosphate (P$_i$). The resulting 80S ribosome carries out the elongation phase (FIG. 1). Phosphorylation of eIF2 on its α-subunit by one of four different cellular eIF2α kinases (see main text for details), each of which is activated by a discrete stress, prevents eIF2 recycling. Phosphorylated eIF2 binds tightly to and inhibits eIF2B, blocking translation initiation. The host protein phosphatase 1 catalytic (PP1c) subunits can dephosphorylate eIF2 when partnered with either an inducible (growth arrest and DNA damage-inducible protein 34 (GADD34)) or constitutively active (CReP; also known as PPP1R15B) regulatory component. Viral strategies for inhibiting eIF2α phosphorylation (yellow), activating eIF2α dephosphorylation (green) or bypassing a requirement for eIF2 (green) are indicated. See main text for details and abbreviatons; eIF4A, eIF4E and eIF4G are labelled 4A, 4E and 4G, respectively.

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 eEF2 kinase (FIGS 1,4). As eEF2 phosphorylation by eEF2 kinase inhibits elongation, p70 S6K stimulates elongation. By contrast, eEF2 kinase is stimulated by protein kinase A (PKA), Ca^{2+}–calmodulin or AMP-activated protein kinase (AMPK), thus reducing elongation[2]. Viruses can alter eEF function and subcellular distribution. Similarly, viral manipulation of termination factors can regulate polyprotein 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[1]. To control 60S recruitment and elongation, eIF5B, eEF1A and eEF2 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 eEF1A, HIV Gag inhibits viral mRNA translation and stimulates RNA packaging into virions[105]. As an alternative method, TMV VPg binds to eEF1A and causes it to accumulate on intracellular membranes, where viral replication occurs[59]. Similarly, eEF2 is recruited to cytoplasmic viral replication compartments in cells infected with Sindbis virus[60] or ASFV[41]. Finally, the eEF1Bα subunit (formerly known as eEF1δ), which mediates GDP–GTP exchange on eEF1A, is hyperphosphorylated by a conserved herpesvirus kinase[106], 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[3] (FIG. 5). Termination and re-initiation may be linked through the interaction of PABP with ribosome-bound eRF3 and cap-bound eIF4F[32,107]. 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[108].

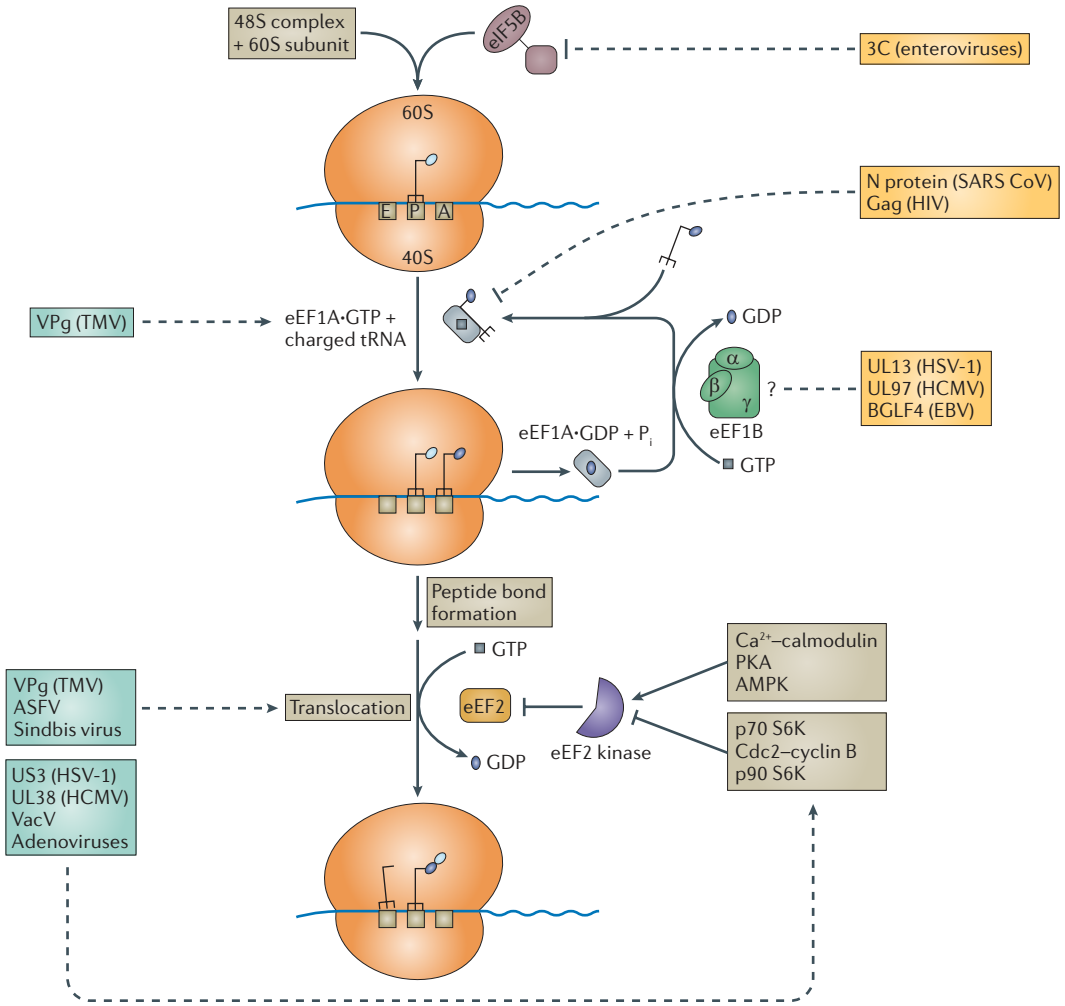


Figure 4 | **Regulation of translation elongation.** Although most translational control strategies operate at the rate-limiting initiation step, different regulatory mechanisms target elongation and termination. Translation elongation begins after eukaryotic translation initiation factor 5B (eIF5B)-mediated 60S subunit joining triggers eIF release, and the assembled 80S ribosome begins polypeptide chain extension. Each new aminoacylated tRNA is delivered to the A site by eukaryotic elongation factor 1A (eEF1A) bound to GTP. Following GTP hydrolysis, eEF1A·GDP is released, unable to bind aminoacylated tRNA until it is recycled to the active GTP-bound form by the multisubunit eEF1B guanine nucleotide exchange factor. Both eEF1A and eEF1B can be phosphorylated by cellular kinases, including CK2 and protein kinase C, which stimulate their activity. Ribosome-catalysed peptide bond formation precedes eEF2-mediated translocation of the peptidyl-tRNA into the P site and the de-acylated tRNA into the E site, exposing the unoccupied A site for successive rounds of elongation that form the polypeptide chain. eEF2·GDP exits the ribosome and is recycled to the active, GTP-bound form without the assistance of a guanine nucleotide exchange factor, owing to the high intrinsic GDP release rate. Phosphorylation by eEF2 kinase inhibits eEF2 activity. eEF2 kinase itself is phosphorylated and inhibited by p70 ribosomal protein S6 kinase (p70 S6K) proteins following mTOR complex 1 activation. By contrast, eEF2 kinase is activated by protein kinase A (PKA), Ca^{2+}–calmodulin and AMP-activated protein kinase (AMPK)[2]. Viral functions that regulate elongation are indicated; see main text for details and abbreviations. Pi, inorganic phosphate.

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)[109,110], respectively. Retroviral reverse transcriptase binds eRF1 to modulate termination and re-initiation[111], and re-initiation protects HIV-1 mRNAs from nonsense-mediated decay[112]. 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[113].

Exploiting mRNA metabolism

Competition between virus and host for limiting translation components is influenced by mRNA availability in

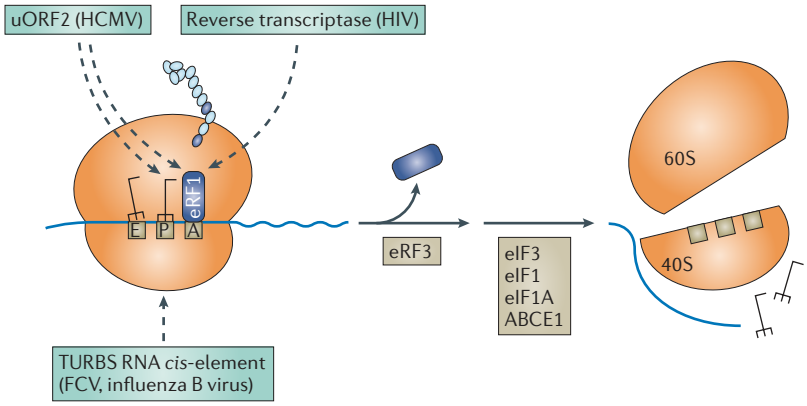


Figure 5 | **Regulation of translation termination in virus-infected cells.** On recognition of a stop codon in the A site, eukaryotic release factor 1 (eRF1) triggers 80S arrest and polypeptide release. eRF3 subsequently releases eRF1 from the ribosome, and the 80S ribosome is dismantled into 40S and 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.

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 mRNA[56]. 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 mRNAs[115]. Other viruses that replicate in the nucleus, such as adenoviruses or influenza viruses, also inhibit host mRNA export[116,117]. 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 required[118]. Despite replicating in the cytoplasm, VSV M protein inhibits RAE1 (also known as MRNP41)-mediated nuclear export to block host mRNA trafficking and prevent synthesis of host defence-related proteins[119].

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 synthesis[64,120]. Instead of a ribonuclease, poxviral decapping enzymes remove m^7G caps from mRNAs, converting them into substrates for host mRNA decay pathways and contributing to host shut-off[4]. 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 activation[81].

Viral infection alters the distribution and composition of stress granules and processing bodies (P-bodies), which are discrete cytoplasmic structures associated with mRNA metabolism[96]. 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 protease[121–123]. 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[95,124]. By contrast, stress granule induction by reoviruses may inhibit host translation[125]. Although stress granule components can stimulate replication of some RNA viruses (respiratory syncytial virus, dengue virus and West Nile virus)[126], other viruses exploit P-bodies for viral assembly (HIV-1 and brome mosaic virus)[96,127] or cap stealing (hantaviruses)[7]. DNA viruses can also target stress granules, as the PKR antagonist encoded by VacV, E3L, prevents their accumulation[128].

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 translation[129]. 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

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 strategies[145]. Besides having smaller, 70S ribosomes and uncapped, predominately genome-collinear, non-polyadenylated mRNAs, bacteria mediate 30S ribosome recruitment without scanning, through 16S 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 replicases 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 repressor activity of gp32 to unbound monomers that are superfluous for DNA replication serves as a rheostat, limiting gp32 accumulation[146]. Similarly, translation repression by free, unassembled phage P22 gene 8 scaffold protein maintains the scaffold-to-coat protein ratio that is required for phage assembly[147]. *tir*-binding proteins also remodel repressive RNA structures to stimulate translation, as phage Mu Com promotes the synthesis of DNA-modification enzyme Mom[148].

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 translation[149]. However, cleavage of the SD sequence of phage T4 early mRNA by an endoribonuclease comprising phage T4 RegB and host ribosomal protein S1 limits the accumulation of early proteins, stimulating translation of middle and late mRNAs[146]. 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 exposure[150]. 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)[151].

Besides coupling, other methods of maintaining subunit stoichiometry are recoding and bypassing. These processes also maximize coding capacity 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 genes[152]. Bypassing joins the information in two ORFs into one polypeptide. Using a peptidyl-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 ORFs[153].

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 CII and CIII. Translation of both *CII* and *CIII* mRNA is stimulated by host proteins binding near the 5′ end of the mRNA[154]. 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′ untranlsated region. Subsequent RNase III-mediated cleavage removes the N-binding site, stimulating N synthesis and phage λ replication[155]. 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 transcription[156].

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 infection[157].

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 response[129]. 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 synthesis[130]. The HCV RNA genome 5′ UTR contains two tandemly repeated, liver-specific miR-122 targets. Surprisingly, miR-122 enhances, rather than suppresses, both genome abundance[131] and viral mRNA translation[132,133], 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 sites[134]. Finally, HCMV reduces the expression of host miRNAs that suppress ERK and PI3K–AKT–mTORC signalling[129]. 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 members[135], and host antiviral factors such as pokeweed antiviral protein bind eIF4G and depurinate viral RNA[136]. 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 VacV[42]; screens using small interfering RNAs suggest initiation factors and ribosomal proteins as potential antiviral targets[137,138]; and compounds that inhibit eIF2α dephosphorylation reduce HSV-1 replication[139]. Furthermore, a small-molecule inhibitor of the MNK proteins reduces replication of VacV[38], ASFV[41] and several herpesviruses in culture[35,37]. 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 mTOR active site (which disrupt eIF4F and impair herpesviral replication[43]), will probably have immunosuppressive side effects *in vivo*[140]. 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. IRESs, which are relied on by many RNA viruses, also represent potential targets[141–143]. Finally, virus–host interactions that regulate translation have contributed to the development of oncolytic viruses[144].

Summary

Viruses subvert nearly 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 phosphatase subunits are required to prevent accumulation of phosphorylated eIF2α in HSV-infected cells and in uninfected cells recovering from endoplasmic reticulum stress. eIF4G can be cleaved by virally encoded proteases and also by cellular caspases 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 eIF4F-mediated, cap-dependent translation is impaired by stress. By conferring eIF2 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, IRESs with minimal initiation factor requirements (such as those of HCV and CrPV) highlight how viral models provide powerful cell-biological and genetic tools that continue to expose surprising translation regulatory mechanisms.

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