Viruses are obligate intracellular parasites, and their replication requires host cell functions. Although the size, composition, complexity, and functions encoded by their genomes are remarkably diverse, all viruses rely absolutely on the protein synthesis machinery of their host cells. Lacking their own translational apparatus, they must recruit cellular ribosomes in order to translate viral mRNAs and produce the protein products required for their replication. In addition, there are other constraints on viral protein production. Crucially, host innate defenses and stress responses capable of inactivating the translation machinery must be effectively neutralized. Furthermore, the limited coding capacity of the viral genome needs to be used optimally. These demands have resulted in complex interactions between virus and host that exploit ostensibly virus-specific mechanisms and, at the same time, illuminate the functioning of the cellular protein synthesis apparatus.

The dependence of viruses on the host translation system imposes constraints that are central to virus biology and have led to specialized mechanisms and intricate regulatory interactions. Failure to translate viral mRNAs and to modulate host mRNA translation would have catastrophic effects on virus replication, spread, and evolution. Accordingly, a wide assortment of virus-encoded functions is dedicated to commandeering and controlling the cellular translation apparatus. Viral strategies to dominate the host translation machinery target the initiation, elongation, and termination steps and include mechanisms ranging from the manipulation of key eukaryotic translation factors to the evolution of specialized cis-acting elements that recruit ribosomes or modify genome-coding capacity. Because many of these strategies have likely been pirated from their hosts and because virus genetic systems can be manipulated with relative ease, the study of viruses has been a preeminent source of information on the mechanism and regulation of the protein synthesis machinery. In this article, we focus on select viruses that infect mammalian or plant cells and review the mechanisms they use to exploit and control the cellular protein synthesis machinery.
VIRAL REPLICATION AND TRANSLATION STRATEGIES

The prodigious diversity of viruses, their unparalleled rate of evolution, and the wide repertoire of their interactions with their hosts, all contribute to their utility as biological tools to study the translation system. Thus, viral genomes are composed of DNA or RNA, either of which may be single- or double-stranded; replication may take place in the nucleus or cytoplasm of the cell; infection may give rise to acute or persistent infection; viruses may be agents of disease or innocuous; and the consequences of infection may vary in different organisms or cell types. For a discussion of the underlying biological principles, you are referred to virology reviews (e.g., Pe’ery and Mathews 2007). Here, we cannot do more than briefly introduce the relationship between virus genome structure and mRNA biogenesis.

Viruses are classified into families according to their genome structure, which dictates the mode of synthesis of their mRNA, its structure, and often its translation. In some viral families, the viral RNA is single-stranded and of the same sense as the mRNA, termed (+)-stranded, and thus it can be directly translated. Viruses with RNA genomes that are of the opposite polarity, that is, (−)-stranded or double-stranded (ds), require virus-encoded RNA-dependent RNA polymerases to generate their mRNA. Exceptionally, retroviruses use viral reverse transcriptase to convert their (+)-stranded RNA genomes into a dsDNA form, which then serves as template for mRNA synthesis via cellular pathways. Most viruses with DNA genomes take advantage of the cellular machinery for mRNA production, but others (such as the poxviruses) use their own enzyme systems. As a consequence, virus families are characterized by mRNAs that have a range of structures at their 5′ ends (capped, not capped, cap-substituted) and 3′ ends (polyadenylated or not), and carry various cis-acting sequences and elements (internal ribosome entry sites [IRES], protein binding sites, etc.)—features that determine many aspects of viral mRNA translation (Fig. 1).

IMPAIRING HOST TRANSLATION

The vast majority of eukaryotic mRNAs are translated in a cap-dependent manner that involves regulated recruitment of a 40S ribosome-containing pre-initiation complex (43S complex) by eukaryotic translation initiation factors (eIFs) (Hershey et al. 2012; Hinnebusch and Lorsch 2012). By impairing cap-dependent ribosome recruitment to host mRNAs, many viruses globally interfere with host mRNA translation—a phenomenon termed “host shut-off”—thereby crippling host antiviral responses and favoring viral protein synthesis. Viral mRNA translation in these instances proceeds via an alternative initiation strategy that relies on cis-acting RNA elements. Other viruses target host mRNA metabolism, impairing host mRNA processing, stability, and/or export to the cytoplasm.

Direct Effects on Cellular Translation Factors

Some viruses directly target cellular translation factors to prevent ribosome recruitment by host mRNAs (Fig. 2A). Poliovirus (an enterovirus), feline calicivirus, and retroviruses encode proteases that cleave eIF4G, separating its (amino-terminal) eIF4E-interacting domain from its eIF4A- and eIF3-binding segment (Etchison et al. 1982; Ventoso et al. 2001; Alvarez et al. 2003; Willcocks et al. 2004). In poliovirus-infected cells, both eIF4GI and eIF4GII are cleaved, and host shut-off correlates more closely with the protracted cleavage of eIF4GII (Gradi et al. 1998). In addition to eIF4G proteolysis, enterovirus 71 infection induces host micro-RNA (miRNA) miR-141 expression, which reduces eIF4E abundance and suppresses host protein synthesis (Ho et al. 2010). Vesicular stomatitis virus (VSV), influenza virus, and adenovirus (Ad) decrease eIF4E phosphorylation (Huang and Schneider 1991; Feigenblum and Schneider 1993; Connor and Lyles 2002). By binding to eIF4G, the Ad 100K protein displaces the kinase Mnk1 (see below), resulting in the accumulation of unphosphorylated eIF4E late in infection (Cuesta et al. 2000b, 2004). This stimulates selective late viral mRNA translation (discussed below) and may contribute to host
shut-off (Huang and Schneider 1991). During infection with some RNA viruses, however, accumulation of unphosphorylated eIF4E represents a host antiviral response, which induces interferon (IFN)-β production through translational activation of NF-κB (Herdy et al. 2012). Enteroviral, apthoviral, caliciviral, and retroviral proteases also cleave the poly(A)-binding

<table>
<thead>
<tr>
<th>Virus mRNA</th>
<th>RNA structure</th>
<th>Primary eIF target(s) for 40S recruitment/virus</th>
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<tbody>
<tr>
<td>m7Gppp</td>
<td>5’ cap</td>
<td>eIF4F/herpesvirus, poxvirus, ASFV</td>
</tr>
<tr>
<td>m7Gppp</td>
<td>Cap-stealing</td>
<td>eIF4G/influenza, eIF3?/hantavirus</td>
</tr>
<tr>
<td>m7Gppp</td>
<td>Cap-substitute</td>
<td>eIF4E/TEV, eIF3/calicivirus, eEF1A/TuMV</td>
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</table>

**Figure 1.** Recruitment of 40S ribosome subunits to viral mRNAs: structural features and initiation factor targets. RNA structural elements involved in recruiting cellular 40S ribosome subunits to the 5’ end of viral mRNAs are shown on the left, with their corresponding name immediately to the right. The primary eukaryotic translation initiation factor (eIF) targets involved in recognizing each structural element and recruiting additional factors or mediating 40S subunit binding are indicated, with representative viruses that use them. (?) indicates that the precise factor targeted by hantavirus N protein remains unknown. Abbreviations: MNeSV, Maize necrotic streak virus; BYDV, Barley yellow dwarf virus; PEMV, Pea enation mosaic virus.
protein (PABP) (Kuyumcu-Martinez et al. 2004a,b; Alvarez et al. 2006; Rodriguez Pulido et al. 2007; Zhang et al. 2007; Bonderoff et al. 2008). PABP cleavage in enterovirus-infected cells does not always correlate with host shut-off, however (discussed below). Rather than cleaving PABP, the rotavirus NSP3 protein disrupts the PABP–eIF4G association (Piron et al. 1998; Groft and Burley 2002), allowing viral mRNA translation to proceed while host mRNA translation, which requires PABP, is suppressed (Montero et al. 2006). The large DNA-containing poxviruses produce small non-coding polyadenylated RNAs (POLADs) that have been reported to impair host PABP-dependent translation, but their precise function in infected cell biology remains unknown (Cacoullos and Bablanian 1991; Lu and Bablanian 1996).

Some RNA viruses also induce eIF2α phosphorylation to impair host responses (see below), or—in the case of rabies virus (M protein) (Komarova et al. 2007), measles virus (N protein) (Sato et al. 2007), and coronavirus (spike protein) (Xiao et al. 2008)—impair cap-dependent translation via virus-encoded eIF3-interacting proteins. How viral mRNAs are translated under the latter conditions remains unknown, as are the contributions of the eIF3-binding proteins to viral biology.

Indirect Effects on Cellular Translation Factors

Other viruses impact initiation factors indirectly (Fig. 2B). Many RNA viruses, including encephalomyocarditis virus (EMCV), poliovirus, cricket paralysis virus (CrPV), VSV, Sindbis virus (SINV), Dengue virus (DENV), and reovirus (Gingras et al. 1996; Connor and Lyles 2002; Villas-Boas et al. 2009; Garrey et al. 2010; Mohankumar et al. 2011), as well as small DNA viruses such as SV40 (Yu et al. 2005), induce the accumulation of hypophosphorylated 4E-BP1, which sequesters the cap-binding subunit eIF4E and prevents eIF4F assembly (Hinnebusch and Lorsch 2012; Roux and Topisirovic 2012). In the case of VSV, this requires the viral M protein, which suppresses Akt-signaling to prevent mTORC1-mediated inactivation of 4E-BP1 (Dunn and Connor 2011). SV40 small T-antigen, however, uses a protein phosphatase 2A (PP2A)–dependent mechanism to dephosphorylate 4E-BP1 (Yu et al. 2005). Inhibition of eIF4F via 4E-BP1 can also suppress host antiviral responses. Mouse embryo fibroblasts (MEFs) lacking 4E-BP1 and 4E-BP2 produce high levels of type I IFN because of increased IRF7 mRNA translation, and 4E-BP1/2-deficient knockout mice are more resistant to EMCV, VSV, influenza, or SINV infection (Colina et al. 2008).

Changing the subcellular distribution of translation factors in virus-infected cells represents another way in which host cap-dependent mRNA translation can be altered by viruses. SINV redistributes eIF3 and eIF2 to cytoplasmic replication compartments while excluding eIF4G (Sanz et al. 2009). Because SINV mRNAs contain an IRES, this selective redistribution likely suppresses host translation and fosters selective viral protein synthesis. eIF4E is redistributed to the nucleus by poxvirus (Sukarieh et al. 2010). Although the 2A protein encoded by EMCV, another picornavirus, has a nuclear localization signal and binds to eIF4E (Groppo et al. 2010), whether eIF4E accumulates within the nuclei of infected cells remains unknown. PABP distribution can be similarly altered upon virus infection. Bunyavirus NSS (Blakqori et al. 2009) and rotavirus NSP3 proteins (Harb et al. 2008) cause nuclear PABP accumulation. Herpes simplex virus 1 (HSV-1) and Kaposi’s sarcoma–associated herpesvirus (KSHV) do not stimulate PABP recruitment into eIF4F complexes but redistribute it to the nucleus, which may contribute to host shut-off by some herpesviruses. PABP redistribution in HSV-1-infected cells involves the viral proteins ICP27 and UL47 (Dobrikova et al. 2010; Salaun et al. 2010), and SOX and/or K8.1 in KSHV-infected cells (Arias et al. 2009; Covarrubias et al. 2009; Lee and Glaunsinger 2009; Kumar and Glaunsinger 2010; Kumar et al. 2011). Notably, both viruses induce host shut-off and, in the case of KSHV, SOX mutants that fail to redistribute PABP to the nucleus do not impair host translation (Covarrubias et al. 2009). In contrast, human cytomegalovirus (HCMV), a β-herpesvirus that does not impair host translation, does...
not redistribute PABP to the nucleus but does recruit it into eIF4F complexes (Walsh et al. 2005; Perez et al. 2011). Redistribution of host factors also occurs in cells infected with vaccinia virus (VaccV), a poxvirus, or African swine fever virus (ASFV), an asfarvirus (Katsafanas and Moss 2007; Walsh et al. 2008; Castelló et al. 2009). Both of these large DNA viruses replicate in the cytoplasm within specialized compartments termed viral factories. Redistribution of a number of eIFs to these sites may contribute to the suppression of host protein synthesis while at the same time favoring viral mRNA translation.

Controlling Translation by Manipulating RNA

Beyond targeting translation factors, mRNA structures (Fig. 1), metabolism, and trafficking have all been targeted by viruses to interfere with cellular protein production. Capped mRNAs produced by influenza virus, hantavirus, and the yeast L-A virus contain m7GTP caps derived from host mRNAs (Plotch et al. 1981; Mir et al. 2008; Reguera et al. 2010; Fujimura and Esteban 2011). Although L-A virus transfers only the host cap to the viral mRNA 5′ end, influenza virus and hantavirus use a viral endonuclease to cleave host mRNAs 10–18 nucleotides downstream from the m7GTP cap (Plotch et al. 1981; Shih and Krug 1996; Guilligay et al. 2008; Mir et al. 2008; Dias et al. 2009). The resulting capped oligonucleotides prime viral RNA synthesis (Plotch et al. 1981; Garcin et al. 1995; Reguera et al. 2010). At this same time, this process destabilizes host mRNAs and inhibits cellular mRNA translation. Notably, the severe acute respiratory virus (SARS) coronavirus protein Nsp1 associates with 40S ribosomes and selectively cleaves host mRNAs to induce host shut-off (Kamitani et al. 2006, 2009; Huang et al. 2011). An alternate strategy used by VSV, which replicates in the cytoplasm, suppresses nuclear export of cellular mRNAs to preclude the synthesis of host defense-related proteins (Faria et al. 2005).

Among DNA viruses that produce capped, polyadenylated mRNAs, poxvirus and asfarvirus decapping enzymes destabilize mRNAs (Parrish and Moss 2007; Parrish et al. 2007). In Ad-infected cells, cellular mRNA nuclear export is inhibited, and the E1B 55K and E4 ORF6 proteins selectively export viral mRNAs from the nucleus via an NXX1/TAP-dependent mechanism (Krätzer et al. 2000; Yatheramaj et al. 2011). The endoribonuclease encoded by the HSV-1 virion host shut-off (vhs) gene associates with eIF4F by interacting with eIF4A and eIF4B/eIF4H to increase mRNA turnover of host and viral mRNAs (Feng et al. 2005). Although stimulating mRNA decay impairs translation of host mRNAs, including those encoding host defense functions, accelerating viral mRNA turnover helps demarcate different kinetic populations of virus-encoded mRNAs expressed at immediate-early, early, or late times post-infection. The KSHV SOX protein also cleaves mRNA but recruits XRN1 to mediate target mRNA degradation (Covarrubias et al. 2011; Richner et al. 2011). The HSV-1-encoded protein ICP27 inhibits host mRNA splicing and transport, while promoting intronless viral mRNA export (Sandri-Goldin 2011). ICP27 also reportedly interacts with PABP to mediate selective translation of a small subset of viral mRNAs (Ellison et al. 2005; Larralde et al. 2006; Fontaine-Rodríguez and Knipe 2008), but the precise mechanism is unclear. A related protein encoded by KSHV ORF57 binds a host factor, PYM, to load ribosomes onto viral mRNAs, potentially coupling viral mRNA export and translation (Boyne et al. 2010; Jackson et al. 2011). Herpesviruses also encode miRNAs that selectively suppress translation of cellular and viral target mRNAs (Pfeffer et al. 2004; Cai et al. 2005; Murphy et al. 2008; Tang et al. 2008; Umbach et al. 2008; Wang et al. 2008; Bellare and Ganem 2009; Nachmani et al. 2009; Santhakumar et al. 2010). For HSV-1, these miRNAs may prevent lytic transcript accumulation in latently infected cells.

A key component of the cellular antiviral response relies on RNase L, which inactivates both rRNA and mRNA. In response to dsRNA, a molecular signature associated with virus infection, oligoadenylate (OA) polynucleotide chains with a unique 2′−5′ linkage, are generated by the IFN-inducible OA synthetase (OA5). 2′−5′ OA is a potent RNase L activator. To preserve the integrity of viral mRNAs and cellular rRNAs,
**Figure 2.** Control of translation by virus-encoded functions that regulate assembly of eIF4E (A) eIF4E (4E) is able to interact with eIF4G and assemble the multi-subunit eIF4F complex (4E, 4A, 4G) on the m’GTP-capped (orange ball) mRNA 5’ end. eIF4F assembly typically results in eIF4E phosphorylation by the eIF4G-associated kinase Mnk and recruits eIF3 bound to the 40S ribosome subunit together with associated factors in the 43S complex. PABP is depicted bound to the 3’-poly(A) tail and associates with eIF4G to stimulate translation. Virus-encoded factors that activate (green, on the left) and repress (red, to the right) cellular functions are shown. (B) Cell signaling pathways that control the activity of the translational repressor 4E-BP1 and regulate eIF4F assembly allow for rapid changes in gene expression programs in response to a variety of physiological cues, including viral infection. In response to growth factor–stimulated receptor tyrosine kinases (RTK), PI-3-kinase (PI3K) and mTORC2 activate Akt by phosphorylation on T308 and S473, which, in turn, represses the tuberous sclerosis complex (TSC) by phosphorylating the TSC2 subunit. (Legend continues on facing page.)
viruses have evolved an array of countermeasures discussed below (Banerjee et al. 2000; Sanchez and Mohr 2007; Silverman 2007; Chakrabarti et al. 2011). Cytoplasmic structures associated with mRNA degradation may also play roles in infection, although they remain poorly understood. Poliovirus and CrPV suppress processing (P)–body formation (Dougherty et al. 2011; Khong and Jan 2011), which could represent another strategy to antagonize host responses because P-bodies restrict human immunodeficiency virus (HIV) infection (Nathans et al. 2009). It should be noted, however, that P-bodies facilitate the replication of brome mosaic virus (Beckham et al. 2007).

**CAP-INDEPENDENT TRANSLATION**

For viruses that interfere with eIF4F to suppress host protein synthesis and antiviral responses, an alternative, non-canonical mode of translation initiation is required, releasing viral mRNAs...
from regulatory constraints that normally control cellular mRNA translation.

**Protein-Linked 5’ Ends**

Instead of a m7GTP cap, some viral mRNAs contain a small virus-encoded protein, VPg (viral protein genome-linked), covalently attached to the 5’ end of their (+)-strand RNA genomes (Fig. 1). Calicivirus VPg interacts with eIF4E or eIF3 to mediate ribosome recruitment to viral mRNAs (Daughenbaugh et al. 2003, 2006; Goodfellow et al. 2005; Chaudhry et al. 2006). Interestingly, distinct plant virus-encoded VPg proteins selectively associate with different translation factors (Khan et al. 2006, 2008; Beauchemin et al. 2007). Tobacco mosaic virus (TMV) VPg binds eEF1A and concentrates it in membrane-associated viral replication sites (Thivierge et al. 2008), which may promote viral protein synthesis and/or impair host translation, whereas potyvirus potato virus A VPg promotes both viral mRNA stability and translation, effectively functioning as a proteinaceous cap (Eskelin et al. 2011). Free VPg can also suppress reporter mRNA translation, suggesting that it may sequester host factors to dampen host translation (Khan et al. 2008; Eskelin et al. 2011).

**IRES-Dependent Mechanisms in Picornaviruses**

Several RNA viruses contain an IRES within their 5’-untranslated regions (UTRs) that directs initiation through interactions with eIFs and/or ribosomal proteins (Fig. 1) (Jackson 2012). First discovered in poliovirus (Pelletier and Sonenberg 1988; Trono et al. 1988) and subsequently identified in other viruses including related picornaviruses (rhinovirus, hepatitis A [HAV], EMCV) (Jang et al. 1988) and hepatitis C virus (HCV), IRESs are divided into four structurally distinct classes, although a fifth related to class I and II IRESs has recently been proposed (Sweeney et al. 2011). Both class I and class II IRESs interact with the carboxy-terminal half of eIF4G (Kolupaeva et al. 1998; Bordenave et al. 2006; de Breyne et al. 2009), which recruits the 40S pre-initiation complex through its binding to eIF3. Class I and II IRESs also use specific host factors, termed IRES trans-activating factors (ITAFs), which alter IRES conformation and enhance eIF4G binding to facilitate ribosome recruitment (Kolupaeva et al. 1996; Kafasla et al. 2010; Yu et al. 2011a). During infection with poliovirus, the viral 2A protease cleaves eIF4G, inhibiting host cap-dependent translation, whereas its class I IRES uses the large eIF4G fragment that contains eIF4A and eIF3 binding sites to promote selective viral mRNA translation (Krausslich et al. 1987; Kempf and Barton 2008; Willcocks et al. 2011). The related picornaviruses EMCV and HAV contain a class II IRES whose function does not involve eIF4G cleavage. Instead, hypophosphorylated 4E-BP1 accumulates in EMCV-infected cells, which, in turn, sequester the cap-binding protein eIF4E and suppresses cap-dependent translation (Gingras et al. 1996). The HAV IRES is unusual because it uses intact eIF4E. However, the eIF4E cap-binding slot must be unoccupied, rendering HAV IRES initiation cap-independent and suggesting that it interacts with eIF4E or that eIF4E induces conformational changes in eIF4G that facilitate interaction with the IRES (Ali et al. 2001; Borman et al. 2001). The Aichivirus IRES is unusual in its absolute requirement for the helicase DHX59 to expose the start codon buried in a stable hairpin (Yu et al. 2011b).

**Translation Mediated by Class III and IV IRES**

The class III IRES in HCV and pestivirus RNAs uses a prokaryote-like mode of translation initiation by positioning ribosomes on the mRNA through interactions with both eIF3 and the ribosome itself, thereby circumventing any need for eIF4F (Pestova et al. 1998; Sizova et al. 1998; Ji et al. 2004; Otto and Puglisi 2004; Pisarev et al. 2004; Fraser and Doudna 2007; Babaylova et al. 2009; Berry et al. 2010). Translation of HCV RNA is also enhanced by the binding of host miR-122 to two target sites in the 5’ UTR, thereby promoting ribosome recruitment (Jopling et al. 2005, 2008; Henke...
et al. 2008; Jangra et al. 2010). In HIV-1, an IRES within the Gag open reading frame (ORF) also interacts with eIF3 and the 40S ribosome (Locker et al. 2010). The simian picornavirus (SPV9) IRES binds eIF3 and the 40S ribosome, yet its activity is enhanced by eIF4F (de Breyne et al. 2008b). In a striking departure, the class IV IRESs of the Dicistroviridae, including CrPV, recruit 40S subunits, assemble 80S ribosomes, and direct initiation in the absence of any eIFs and even of the initiator Met-tRNAi, requiring only eEFs for polypeptide chain formation (Wilson et al. 2000; Jan and Sarnow 2002; Spahn et al. 2004; Cevallos and Sarnow 2005; Kamoshita et al. 2009). By positioning a CCU codon that is not decoded into the P-site, the CrPV IRES is able to initiate protein synthesis from an alanine codon positioned in the A-site after initial pseudotranslocation of the ribosome. The small ribosomal subunit protein RPS25 is essential for initiation from the CrPV and HCV IRES (Landry et al. 2009). RPS25 deletion in yeast or depletion in mammalian cells has minimal effects on cellular protein synthesis, implying that a ribosomal protein can be selectively required for IRES-mediated translation. Moreover, deficiencies in rRNA pseudouridylation reduce CrPV IRES binding to 40S ribosome subunits and inhibit IRES-dependent translation (Jack et al. 2011).

IRES-Like Mechanisms in Other Viruses

The 5' UTRs of some plant potyviruses contain IRES-like structures that bind initiation factors (Fig. 1). For example, tobacco etch virus (TEV) interacts with eIF4G (Gallie 2001). Plant viruses also contain cis-acting cap-independent translational elements (CITEs) in their 3' UTRs that interact with the 5' UTR, bind translation factors, and place them proximal to the 5' initiation site (Miller et al. 2007; Treder et al. 2008). The 3' CITE in RNA2 of pea enation mosaic virus contains a pseudoknot that occupies the cap-binding slot in eIF4E, showing another mode by which the cap-binding protein can recognize mRNA (Wang et al. 2011). The turnip crinkle virus (TCV) CITE contains a 102-bp trNA-like structural element that recruits ribosomes (Zuo et al. 2010). A related strategy for recruiting factors to the 3' UTR is used by DENV, where non-polyadenylated 3'-UTR sequences bind PABP to promote viral mRNA translation (Polacek et al. 2009).

Some RNA viruses that produce mRNAs with m'GTP-capped 5' ends—either by encoding methyltransferases and other capping enzymes or by acquiring caps from host mRNAs—can still use cap-independent modes of translation initiation. SINV provides an example of this latter strategy. In contrast to many RNA viruses, all known DNA viruses produce capped, polyadenylated, predominantly monocistronic mRNAs and generally use canonical cap-dependent modes of translation initiation. Rare instances of cap-independent strategies occur, however, typically involving polycistronic viral mRNAs. Thus, initiation on the SV40 late 19S mRNA is mediated by an IRES (Yu and Alwine 2006), and IRES-mediated translation of several herpesvirus mRNAs has also been reported (Biesleski and Talbot 2001; Grundhoff and Ganem 2001; Low et al. 2001; Griffiths and Coen 2005; Grainger et al. 2010).

MODULATION OF CAP-DEPENDENT INITIATION

As noted above, most dsDNA virus mRNAs are translated by conventional mechanisms used by the majority of host mRNAs, and many, but not all, of these viruses suppress host mRNA translation by altering mRNA metabolism (Clyde and Glaunsinger 2010). Unlike many RNA viruses, numerous DNA viruses stimulate factors, such as eIF4F to foster viral protein synthesis and replication irrespective of whether they inhibit host protein synthesis (Kudchodkar et al. 2004; Walsh and Mohr 2004; Walsh et al. 2005, 2008; Arias et al. 2009; Castello et al. 2009). The mechanisms used in several viral families are discussed here.

Polyoma-, Papilloma-, and Adenoviruses

To activate mTORC1 and stimulate 4E-BP1 hyperphosphorylation, human papilloma virus (HPV) E6 inhibits the tuberous sclerosis
complex (TSC) (Lu et al. 2004; Zheng et al. 2008; Spangle and Munger 2010). Merkel cell polyomavirus small T antigen also activates mTORC1, and its activity is required for transformation (Shuda et al. 2011). Ad E4-ORF1 stimulates phosphatidylinositol 3-kinase (PI3K) (Feigenblum and Schneider 1996; Gingras and Sonenberg 1997; O'Shea et al. 2005). In addition, Ad E4-ORF4 stimulates mTORC1 via PP2A independently of TSC (O'Shea et al. 2005).

Late Ad mRNAs contain a common 200-nucleotide sequence at their 5' ends. Termed the tripartite leader (TPL), it contains sequences complementary to 18S rRNA that are critical for ribosome shunting (Yueh and Schneider 1996, 2000). After loading onto the capped mRNA, the 40S ribosome is able to bypass large segments of the 5' UTR via a nonlinear translocation mechanism before recognizing the AUG. Shunting is stimulated by the Ad 100 K protein, which binds TPL sequences and eIF4G (Xi et al. 2004, 2005). A shunting mechanism also controls production of the HPV E1 replication protein from a polycistronic mRNA (Remm et al. 1999).

Herpesviruses

Among the largest of the DNA viruses, herpesviruses replicate in the nucleus and exist in two discrete developmental states. Infection results in lifelong latency characterized by a restricted gene expression program, punctuated by episodic reactivation events in which productive, lytic viral replication ensues. Different herpesvirus subfamily members colonize specialized differentiated cell types. For example, α-herpesviruses such as HSV-1 are neurotrophic; HCMV, a β-herpesvirus, colonizes myeloid progenitors; and KHSV and Epstein-Barr virus (EBV), both γ-herpesviruses, colonize lymphoid cells and are associated with malignancies. During their productive or lytic replication cycle, these viruses induce 4E-BP1 hyperphosphorylation, eIF4F assembly, and eIF4E phosphorylation to promote viral protein production and virus replication (Kudchodkar et al. 2004; Walsh and Mohr 2004; Walsh et al. 2005; Arias et al. 2009). Remarkably, different mechanistic strategies are enlisted to achieve this goal (Fig. 2A,B). For example, both HSV-1 and HCMV stimulate mTORC1 by targeting TSC. The HSV-1 Us3 ser/thr kinase directly phosphorylates substrates on sites targeted by Akt, including TSC2, functioning as an Akt mimic (Chuluunbaatar et al. 2010). The HCMV UL38 protein, however, physically associates with TSC2 and inactivates it via an unknown mechanism that does not involve direct phosphorylation (Moorman et al. 2008). HCMV also alters mTOR substrate specificity and subcellular localization (Kudchodkar et al. 2006; Clippinger et al. 2011). Two γ-herpesvirus proteins, KSHV vGPCR (Sodhi et al. 2006; Nichols et al. 2011) and EBV LMP2A (Moody et al. 2005), also activate signaling pathways upstream of mTORC1. mTOR active-site inhibitors PP242 and Torin1, which target both mTORC1 and 2 (Feldman et al. 2009; Walsh and Mohr 2006), impair viral protein synthesis and replication (Moorman and Shenk 2010; McMahon et al. 2011), and their effect requires the translation repressor 4E-BP1 (Chuluunbaatar et al. 2010; Moorman and Shenk 2010; Perez et al. 2011). Besides stimulating cap-dependent initiation, mTORC1 activation during infection likely coordinately increases elongation rates by inhibiting eEF2 kinase (Browne and Proud 2002, 2004; Browne et al. 2004). Viruses can also directly modify elongation factors. A kinase conserved among different herpesviruses stimulates eEF1Bα phosphorylation (Kawaguchi et al. 1999); however, the significance to host or viral protein synthesis remains unknown.

In addition to its phosphorylation, 4E-BP1 is degraded by the proteasome in cells infected with HSV-1 or VAcV (Walsh and Mohr 2004; Walsh et al. 2008). Ubiquitination and proteasomal degradation of 4E-BP1 are also observed in uninfected cells (Elia et al. 2008; Braunstein et al. 2009). Inactivation of 4E-BP1 is not sufficient to promote eIF4F assembly in HSV-1-infected cells, however. During virus-induced stress, binding of eIF4E to eIF4G requires the virus-encoded ICP6 protein (Walsh and Mohr 2006), which shares a small domain with homology to hsp27, a cellular chaperone that
regulates eIF4F formation during stress and recovery (Carper et al. 1997; Cuesta et al. 2000a). Thus ICP6 may represent a strategy to foster eIF4F formation under the stress of infection.

HCMV uses different strategies to control eIF4F activity. Although unchanged in HSV1-infected cells, the steady-state levels of eIF4E, eIF4G, eIF4A, and PABP are increased by HCMV (Walsh et al. 2005). Increased eIF4E, eIF4G, and eIF4A mRNA levels accompany the rise in abundance of the corresponding proteins, whereas PABP abundance, along with other TOP mRNA-encoded host proteins, increases through an mTORC1-dependent translational control mechanism that requires UL38 (Perez et al. 2011; McKinney et al. 2012) and promotes viral protein accumulation, eIF4F assembly, and viral replication. This represents the first example of a virus-directed increase in translation initiation factor concentration that contributes to viral replication, and it contrasts with poliovirus biology, where full-length translation initiation factor abundance is selectively reduced by virus-encoded functions. Additionally, an HCMV RNA-binding protein (UL69) important for viral mRNA export from the nucleus (Lischka et al. 2006) reportedly interacts with eIF4A and PABP and stimulates eIF4E release from 4E-BP1 (Aoyagi et al. 2010), although the underlying mechanism remains unknown.

Poxviruses and Asfarviruses

Unlike herpesviruses, poxviruses and asfarviruses (ASFV) cause acute infections and replicate in the cytoplasm. Both viruses encode their own mRNA capping enzymes (Ensinger et al. 1975; Dixon et al. 1994). Notably, VacV and ASFV redistribute eIF4E and eIF4G to cytoplasmic viral factories, where replication occurs (Katsafanas and Moss 2007; Walsh et al. 2008; Castelló et al. 2009). As neither virus increases eIF4F subunit abundance (unlike HCMV), redistribution raises the effective local concentration of these factors to promote eIF4F assembly, perhaps by altering the eIF4E:eIF4G interaction equilibrium. Consistent with this, inhibiting viral factory formation and eIF4G redistribution suppressed eIF4F assembly in poxvirus-infected cells (Zaborowska et al. 2012). In addition, 4E-Gi-1, an inhibitor of eIF4F and ribosome binding, has potent antiviral activity against VacV and HSV-1 (McMahon et al. 2011), and siRNA-mediated eIF4G depletion suppresses VacV infection (Welnowska et al. 2009). Concentrating eIF4G within replication factories may involve the VacV ssDNA-binding protein I3, which binds eIF4G and accumulates within replication factories (Zaborowska et al. 2012). VacV and ASFV infection also promotes 4E-BP1 hyperphosphorylation by mTORC1 (Walsh et al. 2008; Castelló et al. 2009). Although the mechanism by which VacV and ASFV stimulate mTORC1 signaling remains unknown, the rabbit poxvirus myxoma M-T5 protein directly activates Akt signaling (Werden et al. 2007), yet its potential role in translational control has not been explored.

Mimi- and Megaviruses

The recently discovered giant viruses that infect Acanthamoeba (mimivirus, megavirus) and zooplankton (Cafeteria roenbergensis virus) encode orthologs of translation factors, including eIF4E (Raoult et al. 2004; Saini and Fischer 2007; Fischer et al. 2010; Arslan et al. 2011). Whether these viral orthologs function to control translation in infected cells is unknown.

eIF4E Phosphorylation Promotes DNA Virus Replication

By stimulating eIF4F assembly, the eIF4G-associated kinase Mnk1 is positioned near its substrate eIF4E in poxvirus-infected (Walsh et al. 2008; Zaborowska and Walsh 2009), asfarvirus-infected (Castelló et al. 2009), and herpesvirus-infected (Walsh and Mohr 2004, 2006; Walsh et al. 2005; Arias et al. 2009) cells, resulting in eIF4E phosphorylation. Mnk1 activation and subsequent eIF4E phosphorylation is dependent on ERK and/or p38 MAPK signaling. The small molecule Mnk1 inhibitor, CGP57380, impairs HSV1 (Walsh and Mohr 2004), HCMV (Walsh et al. 2005), ASFV (Castelló et al. 2009), and VacV (Walsh et al. 2008) protein synthesis, and VacV replication is reduced in Mnk1-deficient MEFs (Walsh et al.
2008), indicating that this kinase plays an important role in controlling viral protein synthesis and replication. HSV-1 and V acV replication is also reduced in MEFs containing an eIF4E-substituted allele in which eIF4E cannot be phosphorylated, directly establishing that eIF4E phosphorylation regulates virus replication (Herry et al. 2012). For KSHV, Mnk1 activity is important in reactivation from latency because CGP57380 inhibits the transition from latency to lytic replication, suggesting a role for eIF4E phosphorylation in this developmental switch (Arias et al. 2009). Because Mnk1 is not essential for translation initiation but likely plays a regulatory role, it represents a potential target for therapeutic intervention against a wide range of large DNA viruses.

Cap-Dependent Translation in RNA Viruses
Some RNA viruses, including coronaviruses (SARS), orthomyxoviruses (influenza), rhabdoviruses (VSV, rabies virus), reoviruses, hantavirus, and alphaviruses, also produce capped mRNAs. Coronavirus mRNAs, which share a common capped 5′-leader and are polyadenylated, rely on eIF4F, because chemical inhibitors of the eIF4E-eIF4G interaction impair coronavirus replication in cultured cells (Cencic et al. 2011). Furthermore, coronavirus infection stimulates eIF4E phosphorylation (Banerjee et al. 2002; Mizutani et al. 2004). In influenza virus-infected cells, the viral cap-binding polymerase subunit proteins PB2 and NS1 reportedly interact with eIF4G and PABP (Aragon et al. 2000; Burgui et al. 2003, 2007; Yáñez et al. 2012), recruiting them to viral mRNAs. NS1 is not absolutely required for viral protein synthesis, however (Salvatore et al. 2002). Remarkably, the hantavirus N protein has been reported to have cap-binding, RNA-binding, RNA helicase, and ribosome-recruiting activities that functionally substitute for the entire eIF4F complex (Mir and Panganiban 2008, 2010). Finally, the dsRNA reoviruses and rotaviruses encode capping enzymes, and reovirus mRNAs are translated by a cap-dependent mechanism in vitro (Muthukrishnan et al. 1976; Sonenberg et al. 1979). Recently, modest reductions in eIF4E, eIF4G, eIF4B, and 4E-BP1 phosphorylation, along with enhanced eEF2 phosphorylation, have been reported in avian reovirus-infected cells or in cells expressing the viral p17 protein (Ji et al. 2009; Chulu et al. 2010). These modifications, which suppress translation, have been proposed to selectively impair translation of host mRNAs, although further investigation is required to test this hypothesis.

eIF2: A CENTRAL PLAYER IN THE INNATE IMMUNE RESPONSE TO INFECTION
For most host and viral mRNAs, the methionine-charged initiator tRNA is loaded into the ribosome by a ternary complex (TC) composed of eIF2, GTP, and an initiator tRNA (Met-tRNAi) (Fig. 3). In addition to its critical role in initiation and AUG selection (Hinnebusch and Lorsch 2012), TC formation is targeted by innate host antiviral immune defenses. Like OAS (discussed above), the IFN-induced eIF2α kinase PKR acts as a pattern recognition sentinel that detects dsRNA or viral replication intermediates. Once activated, phosphorylated eIF2 accumulates and binds with high affinity to the eIF2B guanine nucleotide exchange factor (GEF), preventing exchange of GDP for GTP and inhibiting translation initiation. Small changes in eIF2α phosphorylation can result in a large suppression of ongoing protein synthesis and even incapacitate the cellular translation machinery because eIF2B is present in limiting quantities.

Eukaryotes contain three additional eIF2α kinases (Fig. 3), each of which responds to a discrete set of stresses. Both GCN2, which responds to UV irradiation and amino acid deprivation, and PERK, which can be triggered by ER overload in infected cells (Pavitt and Ron 2012), can have antiviral effects (Berlanga et al. 2006; Won et al. 2011). eIF2α kinases have also been implicated in autophagy induction (Talloczy et al. 2002). This powerful host response has forced viruses to evolve countermeasures such that they can sustain protein synthesis and complete their growth cycles in infected cells. Although many of these functions target PKR, others have broader capabilities and can
Figure 3. Antagonism of host antiviral defenses that inactivate eIF2 by viral functions. eIF2-GTP forms a ternary complex (TC) with Met-tRNAi and is loaded into the P-site in the 40S ribosome to form a 43S pre-initiation complex (top right). Upon engaging mRNAs via other initiation factors (e.g., eIF4F) or via a specialized cis-acting RNA element (e.g., an IRES), the AUG start codon is identified (typically via scanning), the GTPase-activating protein eIF5 stimulates GTP hydrolysis, and 60S subunit joining triggers eIF2-GDP + phosphate (P_i) release. Translation elongation is executed by the resulting 80S ribosome. Inactive eIF2 (α, β, γ subunits depicted in center) bound to GDP (eIF2-GDP) is recycled to the active GTP-bound form (eIF2-GTP) by the five-subunit guanine nucleotide exchange factor eIF2B. Site-specific eIF2 phosphorylation on its α-subunit (S51) by either of four different cellular eIF2α-kinases (see text), each of which is activated by discrete stress, prevents eIF2 recycling. Phosphorylated eIF2 (bottom) binds tightly to and inhibits eIF2B, blocking translation initiation. The host protein phosphatase 1 catalytic (PP1c) subunit can dephosphorylate eIF2 when partnered with either an inducible (GADD34) or constitutively active (CReP) regulatory component. Virus-encoded factors that antagonize (red, to the left) specific host eIF2α kinases are indicated to the left. Viral PKR antagonists have been subdivided according to their mechanisms of action (see text; dsRNA BPs; double-stranded RNA binding proteins). Virus-encoded factors that activate cellular phosphatases to dephosphorylate eIF2α, or allow translation to proceed without eIF2 or in the presence of phosphorylated eIF2α, are shown (green, to the right).
act directly on eIF2 or other eIF2α kinases. Viral functions that hinder eIF2α phosphorylation are key components of viral pathogenesis, and mutations that compromise these functions often result in attenuated variants. Adaptive evolutionary changes in PKR, under pressure to avoid viral substrate mimicry while maintaining natural substrate (eIF2α) recognition, emphasizes the ongoing nature of this struggle between host defenses and viral countermeasures for control over eIF2 (Elde et al. 2009; Rothenburg et al. 2009). eIF2 itself is regulated by IFN-stimulated genes (ISGs) 54 and 56, which antagonize ribosome binding to eIF4F and TC loading by binding to eIF3e and eIF3c (Guo et al. 2000; Hui et al. 2003, 2005; Terenzi et al. 2006). Viral ISG54 and 56 antagonists, however, have not been reported.

Viral Inhibitors of eIF2α Phosphorylation

Perhaps the most common strategy for preventing PKR activation and safeguarding eIF2 in virus-infected cells involves virus-encoded dsRNA-binding proteins that sequester dsRNA, preventing PKR from recognizing its activating ligand. In addition to dsRNA binding, many of these proteins also associate with and inhibit PKR, and prevent OAS activation (for review, see Walsh and Mohr 2011). A variation on this theme uses a structured, non-coding RNA lure to inhibit PKR activation, such as Ad VA RNA2, HIV-1 TAR, and EBV EBER. VacV also encodes a pseudosubstrate, K3L, that effectively deflects PKR and PERK away from its substrate, eIF2α. The host molecular chaperone p58IPK, a PKR/PERK inhibitor, is recruited to prevent eIF2α phosphorylation in cells infected with influenza virus, TMV, or TEV (Yan et al. 2002; Bilgin et al. 2003; Goodman et al. 2007, 2009). Finally, eIF2α itself can be targeted for dephosphorylation by viral functions. The ASFV DP17L-, HPV E6-, and HSV1 γ34.5-encoded phosphatase regulatory subunits target cellular catalytic PP1 subunits to phosphorylated eIF2α (He et al. 1997; Kazemi et al. 2004; Zhang et al. 2010; Li et al. 2011). Recruiting a phosphatase to dephosphorylate eIF2α is advantageous, conferring resistance to any cellular eIF2α kinase, not just PKR.

Combinatorial Strategies to Prevent eIF2α Phosphorylation

Some viruses use multiple, independent strategies to prevent eIF2α phosphorylation. VacV, for example, combines the dsRNA-binding protein/PKR inhibitor E3L with the PERK and PKR pseudosubstrate K3L (Chang et al. 1992; Davies et al. 1992, 1993; Kawagishi-Kobayashi et al. 1997; Sood et al. 2000; Ramelot et al. 2002; Pavio et al. 2003; Seo et al. 2008; Rothenburg et al. 2011). HSV-1, on the other hand, relies on the Us11 dsRNA-binding/PKR antagonist (Mulvey et al. 1999), the γ34.5 eIF2α phosphatase subunit, and a viral glycoprotein B (gB) PERK antagonist that prevents ER stress-induced eIF2α phosphorylation (Mulvey et al. 2003, 2007). Genomic elements can also play a role in inhibiting PKR. Although HCV E2 is a PKR and PERK pseudosubstrate (Taylor et al. 1999, 2001; Pavio et al. 2003), both the HCV NS5A protein (Gale et al. 1998; Gale and Foy 2005) and the HCV IRES itself (Vyas et al. 2003) directly inhibit PKR. Additionally, HIV-1 Tat and the cellular TAR RNA-binding protein (TRBP) bind the viral TAR element, and TRBP inhibits PKR (Gunnery et al. 1992).

Exploiting eIF2α Phosphorylation and Bypassing eIF2

Instead of preventing eIF2α phosphorylation, some RNA viruses induce eIF2α phosphorylation (O’Malley et al. 1989; Jordan et al. 2002; Gorchakov et al. 2004; McInerney et al. 2005; Smith et al. 2006; Montero et al. 2008; Garrey et al. 2010; White et al. 2010). Although stimulating the phosphorylation of eIF2α facilitates the host antiviral response by globally inhibiting protein synthesis in infected cells, some viruses use an alternative mode of translation initiation that does not absolutely require eIF2. These viruses derive benefit from eIF2α phosphorylation, which can effectively cause host shut-off and prevent IFN synthesis. Classical swine fever virus (CSFV) uses both eIF2α-dependent and -independent modes of translation initiation (Pestova et al. 2008). In SINV-infected cells, a stem–loop structure in the late 26S
mRNA stalls the ribosome at the initiation site and requires eIF2A to initiate translation in the presence of phosphorylated eIF2α (Ventoso et al. 2006). As noted above, the CrPV IRES loads ribosomes and initiates translation without eIF2, other eIFs, or initiator tRNA. With high magnesium concentrations in vitro, the HCV IRES also directs eIF2-independent initiation (Lancaster et al. 2006), whereas, it can use eIF2A-mediated Met-tRNAi delivery under stress conditions (Kim et al. 2011). However, although eIF2α phosphorylation is induced during infection (Garaigorta and Chisari 2009; Kang et al. 2009; Arnaud et al. 2010), the HCV IRES has been suggested to compete efficiently for eIF2 and Met-tRNAi under limiting conditions (Roberto et al. 2006). Furthermore, as discussed above, HCV encodes three distinct functions to inhibit PKR and eIF2α phosphorylation. As with Ad (O’Malley et al. 1989), one possible explanation posits that HCV prevents eIF2 phosphorylation specifically at intracellular viral replication sites while allowing eIF2α phosphorylation to occur in the cytoplasm to impair host protein synthesis.

eIF2α is also phosphorylated as poliovirus infection progresses, and this correlates with declining viral protein synthesis (O’Neill and Racaniello 1989). Although poliovirus mRNA translation is sensitive to eIF2α phosphorylation in vitro, viral mRNA translation late in infection is partially resistant to stress-induced eIF2α phosphorylation (Redondo et al. 2011; Welnowska et al. 2011; White et al. 2011). The underlying mechanism is unknown but may involve cleavage of eIF5B (de Breyne et al. 2008a; White et al. 2011) and local control of active eIF2 pools or cellular factors. Indeed, host factors such as ligatin (eIF2D) and MCT1-DENR can recruit Met-tRNAi to ribosomes and function when the AUG start codon is directly positioned in the P-site (Dmitriev et al. 2010; Skabkin et al. 2010), potentially explaining eIF2-independent initiation mechanisms used by HCV and SINV.

eIF2α phosphorylation is also implicated in the formation of stress granules (SGs), stress-induced cytoplasmic sites of translationally inactive mRNA accumulation. Many viruses disrupt SG formation to evade translational inhibition (Emara and Brinton 2007; White et al. 2007; Montero et al. 2008; Khong and Jan 2011; Simpson-Holley et al. 2011), whereas others induce their formation to impair host translation or even facilitate virus assembly (McInerney et al. 2005; Raaben et al. 2007; Qin et al. 2009; Lindquist et al. 2010; Piotrowska et al. 2010). Notably, mammalian orthoreovirus escapes translational suppression by disrupting SGs, but does so independently of the status of eIF2α phosphorylation or PKR (Qin et al. 2011).

**REGULATED TERMINATION AND REINITIATION: TRANSLATIONAL STRATEGIES FOR MAXIMIZING GENOME CODING CAPACITY**

The small genome size of many RNA viruses constrains their coding capacity. Consequently, many viral mRNAs contain overlapping ORFs regulated by frameshifting or multiple ORFs regulated by termination and reinitiation events. Thus, translational control of ORF decoding plays an indispensable role in regulating viral protein production from polycistronic mRNAs. Influenza and feline calicivirus (FCV) use 45- to 87-nucleotide stretches termed TURBS (termination upstream ribosome binding site) that base-pair with terminating ribosomes to promote reinitiation at nearby downstream ORFs encoding viral BM2 and VP2 proteins, respectively (Horvath et al. 1990; Luttermann and Meyers 2009; Powell et al. 2011), as well as binding the ribosome and eIF3 for FCV VP1 reinitiation (Poyry et al. 2007). Murine norovirus VP2 is also translated by a coupled termination and reinitiation process (Napthine et al. 2009).

Viral proteins also regulate reinitiation; the retroviral Gag protein of Moloney murine leukemia virus (M-MuLV) binds eRF1 to enhance reinitiation or translational readthrough to synthesize the Gag-Pol precursor protein (Orlova et al. 2003). Reinitiation frequency is fine-tuned by pH-dependent conformational changes in the M-MuLV recoding signal sequence to ensure the balance of gag versus gag-pol fusion protein synthesis (Houck-Loomis et al. 2011). Re-initiation also protects HIV-1 retrovirus mRNA from nonsense-mediated decay (Hogg and Goff...
In an intricate regulatory mechanism, Borna virus X and P proteins are encoded by an mRNA that contains an additional uORF. X translation is regulated by a coupled termination and reinitiation event at the uORF, and the efficiency of reinitiation on the X ORF is enhanced by P through interactions with a host helicase, DDX21 (Watanabe et al. 2009).

Reinitiation on cauliflower mosaic virus (CaMV) polycistronic mRNA involves viral and host factors that manipulate eIF3. The viral transactivator viroplasmin (TAV) associates with the plant protein RISP, which supports reinitiation, and subsequently binds to eIF3g (Thiebeauld et al. 2009). Interestingly, eIF4B and TAV-bound RISP bind to the same eIF3g site. RISP associates with eIF3a, eIF3c, and ribosomal protein L24 to link TAV with 40S and eIF3-bound 40S subunits. TAV also recruits the plant cell TOR, which phosphorylates RISP, promoting reinitiation and viral replication (Schepetilnikov et al. 2011).

Most mRNAs encoded by large DNA viruses are not polycistronic, limiting the need for termination/reinitiation strategies. Nevertheless, termination within a small HCMV uORF plays a regulatory role restricting reinitiation at downstream cistrons. Sequence-dependent ribosomal stalling induced by the uORF2 peptide prevents scanning ribosomes from reaching the downstream UL4 ORF (Janzen et al. 2002). By binding eRF1, the uORF2 peptide inhibits translation at its own stop codon, and the stalled ribosome disengages the mRNA. Cryo-EM reconstruction showed uORF2 stabilized at the ribosomal exit tunnel constriction, where it directly interacts with ribosomal proteins L4 and L17. Peptide-induced conformational changes in the peptidyl transfer center were also observed, potentially contributing to translational stalling (Bhushan et al. 2010).

CONCLUDING REMARKS

Because of their reliance on the host for protein synthesis, the intimate relationship between viral genomes and their mRNAs, and the exigencies imposed by host defense mechanisms, viruses have evolved a vast array of strategies for exploiting and dominating the cellular translation machinery. Studies of translational regulation during virus infection have illuminated many features of the cellular translation system. They have also led to the discovery of translation mechanisms that figure prominently in virus-infected cells, and some that may even be virus specific. Notwithstanding the wealth of detail already amassed, there are many open questions, some of them noted above, and there is every reason to believe that we have only scratched the surface.

One prediction is that new principles will continue to emerge as the exploration of
Translation during Virus Infection

virus–host cell interactions expands in breadth and depth. For example, the control of translation in virus-infected cells shares notable similarities with stress-induced translational control mechanisms operative in uninfected cells. To prevent the accumulation of phosphorylated eIF2α, HSV1 encodes a phosphatase regulatory subunit similar to the ER stress-induced GADD34 (He et al. 1997). Cap-dependent translation is impaired in heat-shocked cells, necessitating a mechanism for heat shock protein synthesis much in the same way that viral translation proceeds in infected cells (Yueh and Schneider 1996, 2000). Indeed, both Ad late RNA and HSP70 mRNA contain a ribosome shunt to enable translation when eIF4F is limiting. Many of the key integrators controlling translation in response to nutrient availability, growth factors, and energy supplies are hijacked in infected cells to ensure high-level synthesis of viral proteins.

Another strong prediction is that the intensive analysis of virus–host interactions will have practical value, leading to therapeutics. Idiosyncratic mechanisms evolved by viruses, as well as the interplay between the virus and its host’s translation system, represent potentially exploitable weaknesses. Remarkably, most, if not all, recessive virus resistance alleles in plants map to eIF4E or eIF4G, highlighting the importance of translation factors in the biology of plant RNA viruses (Nieto et al. 2007; Yeam et al. 2007; Truniger and Aranda 2009). As a potential host defense mechanism, pokeweed antiviral protein associates with eIF4G to access the cap-binding translation initiation factor (eIF4E) and eIF4G. Many of the key integrators controlling translation in response to nutrient availability, growth factors, and energy supplies are hijacked in infected cells to ensure high-level synthesis of viral proteins.

Yet another prediction is that viral proteins contribute to the evolution of plant RNA viruses (Nieto et al. 2007; Yeam et al. 2007; Truniger and Aranda 2009). As a potential host defense mechanism, pokeweed antiviral protein associates with eIF4G to access the cap-binding translation initiation factor (eIF4E) and eIF4G. Many of the key integrators controlling translation in response to nutrient availability, growth factors, and energy supplies are hijacked in infected cells to ensure high-level synthesis of viral proteins.

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Tinkering with Translation: Protein Synthesis in Virus-Infected Cells

Derek Walsh, Michael B. Mathews and Ian Mohr

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