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CHAPTER 3

Virus Versus Host Cell Translation: Love and Hate Stories

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Contents

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Abstract Regulation of protein synthesis by viruses occurs at all levels of translation. Even prior to protein synthesis itself, the accessibility of the various open reading frames contained in the viral genome is precisely controlled. Eukaryotic viruses resort to a vast array of strategies to divert the translation machinery in their favor, in particular, at initiation of translation. These strategies are not only designed to circumvent strategies common to cell protein synthesis in eukaryotes, but as revealed more recently, they also aim at modifying or damaging cell factors, the virus having the capacity to multiply in the absence of these factors. In addition to unraveling mechanisms that may constitute new targets in view of controlling virus diseases, viruses constitute incomparably useful tools to gain in-depth knowledge on a multitude of cell pathways.

ABBREVIATIONS OF VIRUS NAMES

AAV-2	Adeno-associated virus type 2
AMCV	Artichoke mottled crinkle virus
APV	Achritosiphon pisum virus
ASLV	Avian sarcoma leukemia virus
BDV	Borna disease virus
BLV	Bovine leukemia virus
BNYVV	Beet necrotic yellow vein virus
BSBV	Beet soil-borne virus
BSMV	Barley stripe mosaic virus
BVQ	Beet virus Q
BWYV	Beet western yellows virus
BYDV	Barley yellow dwarf virus
BYV	Beet yellows virus
CaMV	Cauliflower mosaic virus
CarMV	Carnation mottle virus
CCFV	Cardamine chlorotic fleck virus
CCSV	Cucumber chlorotic spot virus
CoMV	Cocksfoot mottle virus
CNV	Cucumber necrosis virus
CPMV	Cowpea mosaic virus
CrPV	Cricket paralysis virus
CRSV	Carnation ringspot virus
CTV	Citrus tristeza virus

CVB	Coxsackie virus B
CyRSV	Cymbidium ringspot virus
DmeGypV	*Drosophila melanogaster* gypsy virus
EAV	Equine arterivirus
EBV	Epstein–Barr virus
EIAV	Equine infectious anemia virus
EMCV	Encephalomyocarditis virus
EqTV	Equine torovirus
FCV	Feline calicivirus
FMDV	Foot-and-mouth disease virus
HAstV	Human astrovirus
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCMV	Human cytomegalovirus
HCV	Hepatitis C virus
HDV	Hepatitis delta virus
HIV-1	Human immunodeficiency virus 1
HPIV-1	Human parainfluenza virus 1
HPV	Human papillomavirus
HRV	Human rhinovirus
HSV-1	Herpes simplex virus 1
HTLV-1	Human T-lymphotropic virus 1
IBV	Infectious bronchitis virus
LIYV	Lettuce infectious yellows virus
LRV1-1	Leishmania RNA virus 1-1
MCMV	Maize chlorotic mottle virus
MHV	Murine hepatitis virus
MLV	Murine leukemia virus
MMTV	Mouse mammary tumor virus
MNSV	Melon necrotic spot virus
MoMLV	Moloney murine leukaemia virus
NV	Norwalk virus
OCSV	Oat chlorotic stunt virus
PCMV	Peach chlorotic mottle virus
PCV	Peanut clump virus
PEBV	Pea early-browning virus
PEMV	Pea enation mosaic virus
PLRV	Potato leafroll virus
PPV	Plum pox virus
PSIV	Plautia stali intestine virus
PVM	Potato virus M
RCNMV	Red clover necrotic mottle virus
RhPV	Rhodopalosiphum padi virus

RTBV	Rice tungro bacilliform virus
SARS-CoV	Severe acute respiratory syndrome coronavirus
SbDV	Soybean dwarf virus
SBWMV	Soil-borne wheat mosaic virus
SceTy1V	Saccharomyces cerevisiae Ty1 virus
SceTy3V	Saccharomyces cerevisiae Ty3 virus
SCNMV	Sweet clover necrotic mottle virus
ScV-L-A	Saccharomyces cerevisiae virus L-A
SFV	Semliki Forest virus
SINV	Sindbis virus
STNV	Satellite tobacco necrosis virus
SV40	Simian virus 40
TBSV	Tomato bushy stunt virus
TCV	Turnip crinkle virus
TEV	Tobacco etch virus
TMEV	Theiler's murine encephalomyelitis virus
TMV	Tobacco mosaic virus
TNV	Tobacco necrosis virus
TRV	Tobacco rattle virus
TuMV	Turnip mosaic virus
VSV	Vesicular stomatitis virus
WDSV	Walleye dermal sarcoma virus

OTHER ABBREVIATIONS

aa	amino acid
CAT	chloramphenicol acetyltransferase
3′-CITE	3′-cap-independent translation element
CP	coat protein
eEF	eukaryotic elongation factor
eIF	eukaryotic initiation factor
eRF	eukaryotic release factor
4E-BP	eIF4E-binding protein
GCN2	general control nonderepressible-2
GP	glycoprotein
IGR	intergenic region
IRES	internal ribosome entry site
ITAF	IRES *trans*-acting factor
nt	nucleotide
ORF	open reading frame
P	phosphoprotein
PABP	poly(A) binding protein
Paip1	PABP-interacting protein 1

PCBP	poly(rC) binding protein
PERK	PKR-like endoplasmic reticulum kinase
PKR	protein kinase RNA
PTB	pyrimidine tract binding protein
RdRp	RNA-dependent RNA polymerase
sORF	short ORF
sg	subgenomic
TAV	transactivator
TC	ternary complex (eIF2-GTP-Met-tRNAi^{Met})
TE	translation enhancer
TLS	tRNA-like structure
unr	upstream of N-ras
uORF2	upstream ORF2
UTR	untranslated region
VPg	viral protein genome linked

I. INTRODUCTION

Because of the small size of their genomes and hence of their limited coding capacity, viruses have evolved a cohort of strategies to synthesize a few—and borrow from their host many—of the numerous elements required for their multiplication. The sophistication of the strategies elaborated by viruses is unsurpassed, and many of these strategies are common among viruses, but are rare or even nonexistent in uninfected cells. Many were first demonstrated in viral systems before being described in cell systems (reviewed in Bernardi and Haenni, 1998). The genome of viruses is compact and used to its limits: overlapping open reading frames (ORFs) are frequent, intergenic regions (IGRs) are usually short, and noncoding as well as coding regions are often involved in regulation of replication, transcription, and/or translation.

This chapter presents an overview of the strategies used by viruses of eukaryotes to regulate the expression of their viral genomes, ranging from the production of the RNA templates to translation of the encoded proteins. Emphasis is placed on RNA viruses, in which most of the strategies were originally described; moreover, only a few examples are taken from retroviruses, since the strategies used by these viruses have been discussed at length in several recent review articles (Balvay *et al.*, 2007; Brierley and Dos Ramos, 2006; Goff, 2004; Yilmaz *et al.*, 2006). For further information dealing with certain aspects of translation regulation mechanisms used by viruses, the reader may wish to turn to other reviews (Bushell and Sarnow, 2002; Gale *et al.*, 2000; Mohr *et al.*, 2007; Ryabova *et al.*, 2002).

II. REGULATION PRIOR TO TRANSLATION

Viruses use several regulation strategies prior to translation to obtain maximum protein diversity from their small genomes. Prior to initiation of translation, the viral RNA, due to serve as template for protein synthesis, can be modified so as to favor synthesis of certain viral proteins, sometimes to the detriment of cell proteins. This can be achieved by various mechanisms such as editing, splicing, and the production of subgenomic (sg) RNAs including cap-snatching. The importance of regulation at this level has, moreover, been highlighted in recent publications showing that viral translation and transcription are coupled (Barr, 2007; Katsafanas and Moss, 2007; Sanz *et al.*, 2007).

A. Editing

Editing is a mechanism in which an RNA-encoded nucleotide (nt) is modified, or one, two, or more pseudotemplated nts are inserted at the editing site; various forms of editing have been described (Weissmann *et al.*, 1990). Viruses resort to editing by nt modification in the case of Hepatitis delta virus (HDV; genus Deltavirus), and by the addition of one or more nts in paramyxoviruses.

1. Editing by nucleotide modification

HDV is a highly pathogenic subviral particle totally dependent on the DNA virus Hepatitis B virus (HBV; family Hepadnaviridae) for its propagation (reviewed in Taylor, 2006); it requires the HBV envelope proteins to assemble into HDV particles. The genome of HDV is a (−) sense, closed circular, and highly structured single-stranded RNA (of ∼1680 nts in HDV genotype III) referred to as the genomic RNA (Fig. 1); it is devoid of coding capacity (i.e., devoid of ORF). However, the complementary antigenomic RNA contains a unique ORF for the short surface antigen HDAg-S of 195 amino acids (aa); HDAg-S is produced from an 800-nt long linear sg mRNA that is both capped and polyadenylated (Gudima *et al.*, 2000). The protein is produced throughout infection and is required for HDV replication. At late times in infection, editing of the antigenomic RNA occurs by deamination of the A residue (position 1012) of the UAG codon that ends the HDAg-S ORF; editing does not occur on the HDAg-S mRNA. Hence the antigenome, which is the template for editing, must be replicated to yield the edited genomic RNA prior to being transcribed to produce the edited sg mRNA that is also capped and polyadenylated. Editing also requires previous refolding of the antigenome, from a rod-like to a branched double-hairpin structure in HDV genotype III, or to a highly conserved base-paired structure in HDV genotype I (Casey, 2002; Cheng *et al.*, 2003).

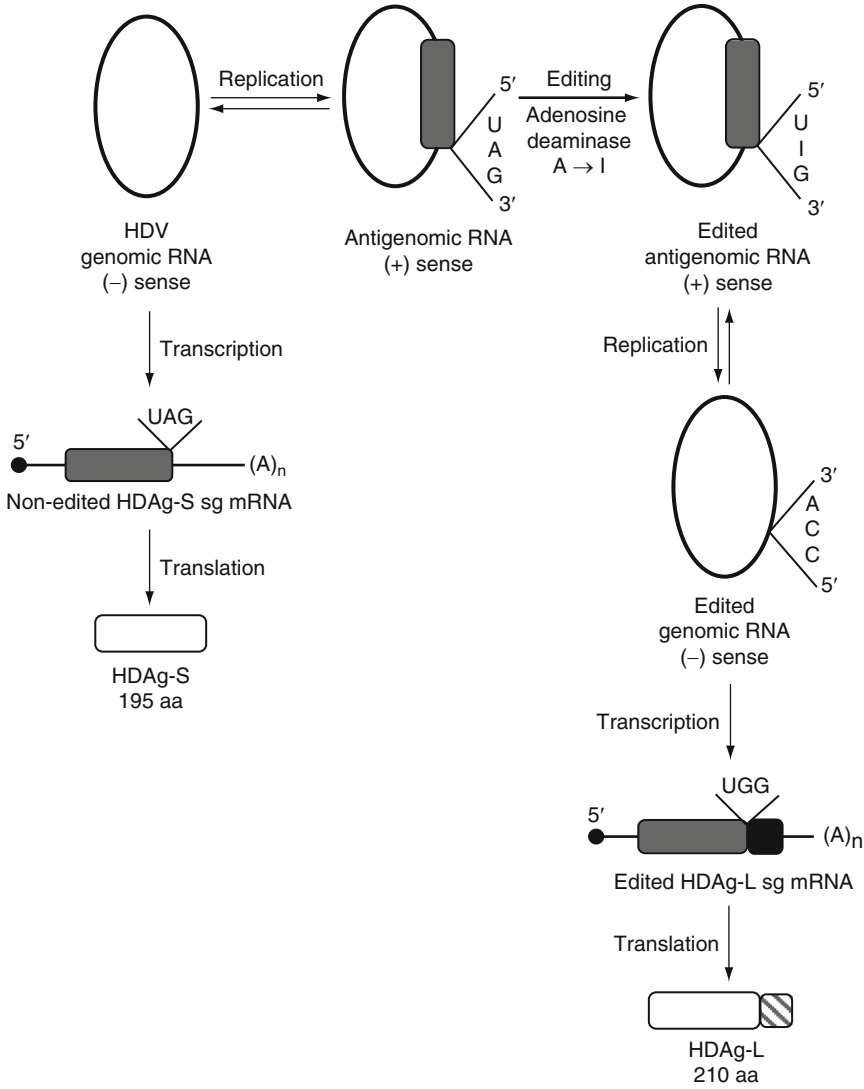


FIGURE 1 RNA editing of the antigenomic RNA during HDV replication. Editing allows the virus to express two proteins HDAg-S and HDAg-L from one coding sequence. The black circle represents the 5′-capped terminus of the mRNA. $(A)_n$ represents a poly(A) tail. Gray rectangles represent ORFs, the black rectangle represents the edited ORF region, the white rectangles represent the HDAg protein, and the gray slashed rectangle represents the extended C-terminal region in the edited protein.

Deamination of the A residue in UAG leading to an I (inosine) residue and producing the triplet UIG (Fig. 1) is triggered by a host adenosine deaminase that acts on RNA substrates. Upon replication of the edited

antigenome, the I residue recognized as G leads to ACC in the edited genomic RNA that is then transcribed as UGG coding for tryptophane in the edited mRNA. As a consequence, the edited sg mRNA presents an extended ORF and produces HDAg-L of 210 aa. The two viral proteins share the same N-terminal region, the longer protein bearing an extended C-terminal region; they are responsible for two distinct functions in the HDV-infected cell. The longer protein inhibits replication and editing and is necessary for virus assembly, whereas the shorter protein is required for replication (Cheng *et al.*, 2003). Editing is, therefore, a vital process for HDV propagation, and an exquisite balance between the nonedited and edited mRNAs, and between replication and virus production is a major factor in maintaining optimum virus production. How this equilibrium is reached remains largely speculative, although editing is known to involve specific structural elements that depend on the HDV genotype considered (Casey, 2002; Cheng *et al.*, 2003).

2. Editing by nucleotide addition

In a coding RNA, the introduction of nontemplated nts leads to the production of a new edited mRNA. In such an mRNA, a change in reading frame at the point of editing has occurred, resulting in the synthesis of a new protein. The new ''edited'' protein is identical to the ''original'' protein resulting from the nonedited mRNA, from the 5′ terminus to the editing site, but different thereafter. The protein resulting from editing is usually endowed with properties and/or activities that are absent from the original protein.

Paramyxoviruses are animal viruses that belong to the order Mononegavirales. They possess a nonsegmented (also known as monopartite) (−) strand RNA genome of 15–16 kb (reviewed in Nagai, 1999). Their genome encodes a minimum of six structural proteins that are produced from six capped and polyadenylated mRNAs. In the complementary antigenomic RNA, the ORFs are separated by conserved sequences that dictate initiation and termination of the six transcripts. Except for the phosphoprotein (P) mRNA, each mRNA expresses a single protein from a single ORF. The P gene is more complex. In most members of the subfamily Paramyxovirinae (family Paramyxoviridae), editing of the P mRNA results in the insertion of 1–5 nontemplated G residues within a run of Gs at the level of a conserved A_nG_n editing sequence (Cattaneo *et al.*, 1989; Mahapatra *et al.*, 2003; Steward *et al.*, 1993; reviewed in Strauss and Strauss, 1991), presumably as a result of a stuttering process (Vidal *et al.*, 1990). This causes a shift within the P ORF and may lead to the synthesis of up to six nonstructural proteins from edited and nonedited mRNAs depending on the virus. In Sendai virus, two mRNAs can be produced by editing of the P/C (also known as P) mRNA, the V mRNA (insertion of 1 G), and the W mRNA (insertion of 2 or 5 Gs) (Fig. 2A)

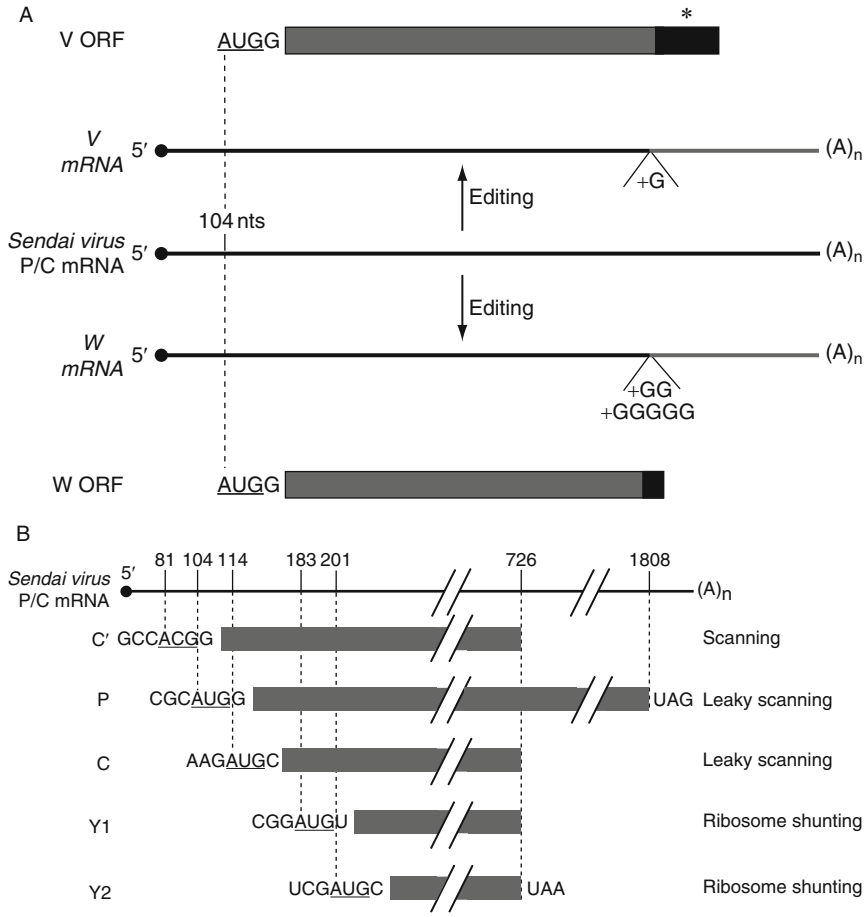


FIGURE 2 Schematic representation of the Sendai virus P/C mRNA expression. (A) Regulation prior to translation: editing of P/C mRNA. *, Cysteine-rich coding region. Initiation codon is underlined. (B) Regulation at initiation of translation of P/C mRNA. Initiation codons of each ORF are underlined and the sequence contexts are presented; termination codons are shown. Other indications are as in legend of Fig. 1.

(Curran *et al.*, 1991). The V protein, a cysteine-rich protein, binds Zn^{+2}, a characteristic related to virus pathogenicity in mice. Indeed, mutation of the cysteine residues in the corresponding V protein in the Sendai virus genome reduces Zn^{+2} binding and pathogenicity (Fukuhara *et al.*, 2002).

Editing is also observed for the synthesis of the structural glycoproteins (GPs) of Ebola virus (family Filoviridae, order Mononegavirales), whose monopartite (−) strand RNA genome contains seven genes. Two GPs are produced from the GP gene, a short and a long form that make up

80% and 20% of the total GP protein synthesized, respectively; they differ in their C-terminal region. The short form of GP is produced by the unedited transcript, whereas the long form results from an edited transcript that has acquired an additional nontemplated A residue within a stretch of seven conserved A residues in the GP ORF. The long form possesses a transmembrane anchor sequence absent from the short form (Sanchez *et al.*, 1996; Volchkov *et al.*, 1995).

B. Splicing

Splicing is a strategy used by DNA viruses such as those of the family Adenoviridae and Polyomaviridae (reviewed in Ziff, 1980, 1985), the Caulimoviridae (reviewed in Ryabova *et al.*, 2006), the Baculoviridae (Chisholm and Henner, 1988; Kovacs *et al.*, 1991), and of the genus Mastrevirus, family Geminiviridae (Schalk *et al.*, 1989). It is less frequently encountered among RNA viruses, although it is observed in certain RNA viruses that replicate in the nucleus. This is the case of retroviruses whose mRNAs undergo a complicated cascade of splicing and alternative splicing events. The splicing mechanisms used by these viruses will not be developed here, having received considerable attention in several review articles (Cullen, 1998; Stoltzfus and Madsen, 2006). Examples of nonretroviruses whose RNA genomes multiply in the nucleus and employ splicing are briefly presented here; they are Borna disease virus (BDV) and Influenza virus.

BDV (family Bornaviridae) belongs to the order Mononegavirales. However, it differs from the other members of this order by several unique features (reviewed in de la Torre, 2002; Tomonaga *et al.*, 2002). As opposed to the other members of this order whose life cycle occurs entirely in the cytoplasm, BDV is replicated and transcribed in the nucleus of the infected cell and employs the cellular RNA splicing machinery. The two splice donor and three splice acceptor sites follow the general mammalian splice site consensus (Fig. 3). The six ORFs contained in the antigenome are not separated by conserved IGRs as in other mononegavirales. Rather, the six proteins of BDV are translated from capped and polyadenylated transcripts that are initiated at only three sites (S1–S3) and terminate at five possible sites (T1–T4, t6). The nucleoprotein (known as N) is produced from a transcript initiated at S1, and the X protein and P from a transcript initiated at S2. The matrix (M), glycoprotein (G), and polymerase (L) are all produced from transcripts initiated at S3, and resort to alternative splicing for the production of the transcripts required. Splicing of intron I that overlaps the M ORF abolishes synthesis of the corresponding protein and produces protein G, while splicing of introns I and II (the latter corresponds to most of the G ORF) leads to the synthesis of the L protein. Additionally,

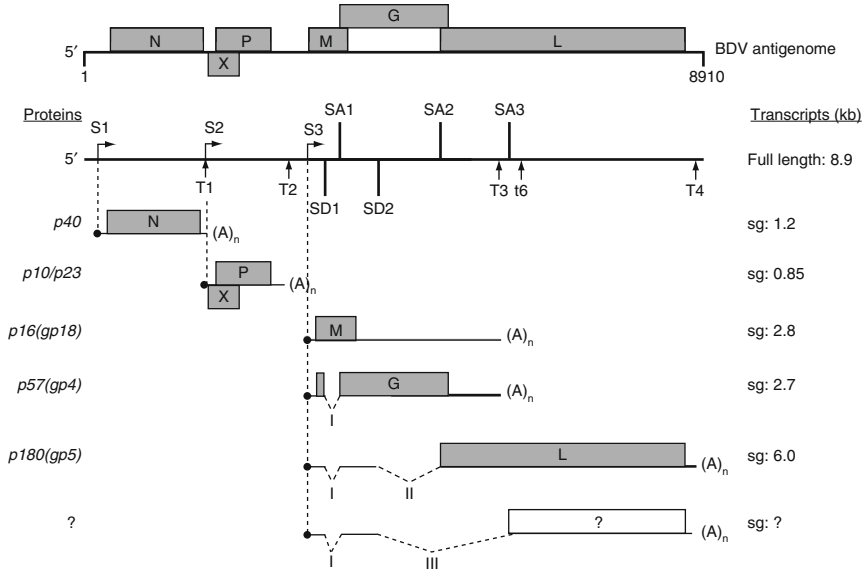


FIGURE 3 Regulation prior to translation by splicing in BDV. S1–S3, transcription initiation sites; T1–T4 and t6, polyadenylation/termination sites; SA1–SA3, splice acceptor sites; SD1 and SD2, splice donor sites. I, II, and III are introns. N, nucleoprotein; P, phosphoprotein; M, matrix; G, glycoprotein; and L, polymerase. The open rectangle corresponds to the ORF of a putative protein. Other indications are as in legend of Fig. 1.

splicing of intron III that uses the same 5′ splice donor site as intron II but another 3′ splice acceptor site also eliminates most of the G ORF as well as the 5′ region of the L ORF. This could lead to the production of yet another BDV protein; this putative protein has so far not been identified (reviewed in Jordan and Lipkin, 2001). Although translation of M is prevented by splicing of intron I, this leaves a minicistron corresponding to the N-terminal region of M which enhances translation of G, presumably by promoting ribosomal reinitiation. However, mutation experiments using the unspliced transcript, suggest that leaky scanning is also a mechanism that could lead to the synthesis of G from the unspliced transcript (Schneider *et al.*, 1997).

Influenza viruses (family Orthomyxoviridae) are enveloped viruses with a segmented (−) strand RNA genome; they are replicated and transcribed in the nucleus by the viral RNA-dependent RNA polymerase (RdRp) complex composed of PB1, PB2, and PA. In the nucleus of infected cells, transcription of the viral RNAs into mRNAs by the RdRp requires cooperation with ongoing transcription by the cellular RNA polymerase II, since the RdRp initiates synthesis of viral mRNAs via cap-snatching using capped cellular mRNAs (see below; reviewed in

Lamb and Krug, 2001; Rao *et al.*, 2003). Influenza A virus and Influenza B virus are composed of eight RNA segments. Alternative splicing leads to the synthesis of two proteins from segments seven and eight of Influenza A virus. Regulation of the choice of the 5′ or 3′ splice sites is finely controlled. Although alternative splicing occurs in many viruses, only in a few cases have viral proteins been shown to be involved in this mechanism. In segment seven of Influenza A virus, two alternative 5′ splice sites control the production of the shorter ($mRNA_3$: 111 nts) and the longer (M2 mRNA: 151 nts) spliced mRNAs from the pre-mRNA known as M1 mRNA. Both spliced RNAs use the same 3′ splice site. At early times after infection, the more favorable upstream 5′ splice site is used, leading to the synthesis of $mRNA_3$ that potentially codes for a 9-aa peptide (as yet undetected). At later times after infection, the RdRp complex now produced in sufficient amounts binds to and blocks the upstream 5′ splice site, forcing the cell splicing machinery to switch to the less favorable downstream 5′ splice site. As a consequence, M2 mRNA is synthesized as is also its encoded M2 ion channel protein of 97 aa (Shih *et al.*, 1995).

C. Subgenomic RNA synthesis

Contrary to mRNAs of eukaryotic cells that are largely monocistronic, the RNA genomes of many eukaryotic viruses contain multiple ORFs of which generally only the 5′-proximal ORF is accessible for translation. Thus, viruses have evolved several strategies to synthesize the proteins corresponding to 5′-distal ORFs (reviewed in Miller and Koev, 2000; White, 2002). One of the most common mechanisms is the production of 3′-coterminal sgRNAs. In such templates, the internally positioned and the 3′-proximal ORFs in the genome of (+) strand RNA viruses are accessed by sgRNAs in which these ORFs become 5′-proximal and serve as mRNAs. sgRNAs are generally synthesized by internal initiation of RNA synthesis on the complementary (−) RNA strand. They are 5′-truncated versions of the genomic RNA and therefore perfect copies of the region of the genome from which they derive.

A particular mechanism of sgRNA production is used by RNA viruses whose genome segments are ambisense or of (−) polarity and resort to cap-snatching. This mechanism was first described for the synthesis of the mRNAs of *Influenza virus* (Bouloy *et al.*, 1978; Krug *et al.*, 1979). The endonuclease activity of the viral RdRp cleaves nuclear cellular capped RNAs to generate capped primers of up to about 20 nts in length for viral mRNA synthesis. As a result, the viral mRNAs contain capped nonviral oligonucleotides at their 5′ end. Several plant (members of the family *Bunyaviridae* and of the genus *Tenuivirus*) and animal (members of the family *Bunyaviridae*) viruses with (−) strand or ambisense RNA genomes also use this transcription initiation mechanism. Since these viruses

multiply in the cytoplasm, they use cytoplasmic rather than nuclear cellular capped RNAs as primers (Garcin and Kolakofsky, 1990; Garcin *et al.*, 1995; Huiet *et al.*, 1993; Raju *et al.*, 1990; Ramírez *et al.*, 1995; Vialat and Bouloy, 1992).

III. INITIATION OF TRANSLATION

A. Cap-dependent initiation

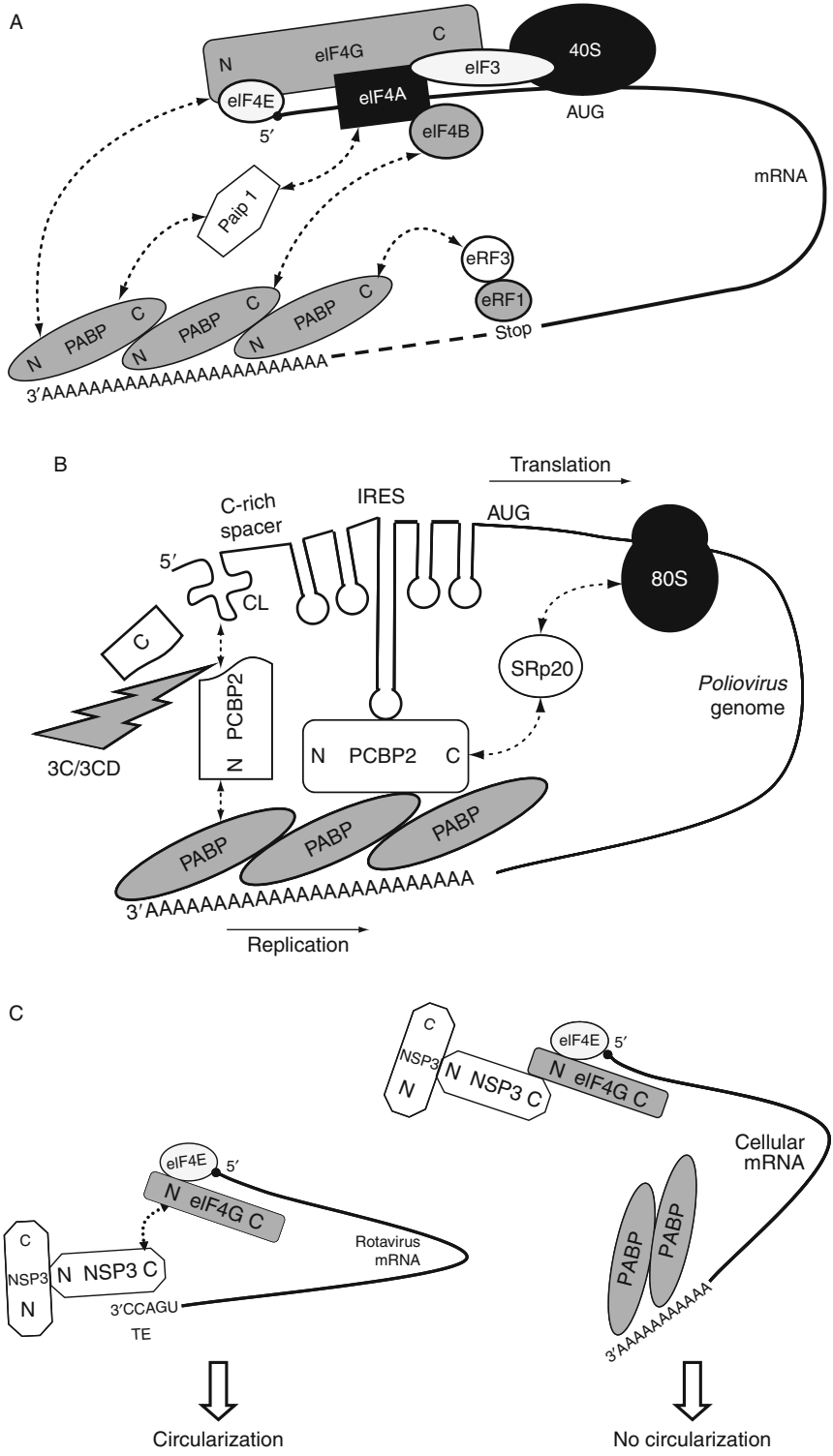
The most common strategy of translation initiation encountered among eukaryotes is cap-dependent translation (reviewed in Jackson and Kaminski, 1995; Pestova *et al.*, 2007). This occurs in capped, generally monocistronic mRNAs, whose initiation codon lies close to the 5′ cap structure, and whose leader sequence also called 5′ untranslated region (UTR) possesses varying degrees of secondary structure. A number of complex steps lead to binding of the small 40S ribosomal subunit to the mRNA. The assembly of the eukaryotic initiation factor (eIF) 2, GTP, and Met-tRNAi^{Met} forms the ternary complex (TC). Interaction of the TC with the 40S ribosomal subunit, facilitated by eIF1, eIF1A, and eIF3, leads to the formation of the 43S preinitiation complex. eIF3 is composed of 13 subunits (eIF3a–eIF3m) (Hinnebusch, 2006). The cap structure is recognized by the heterotrimer eIF4F composed of eIF4G (multivalent scaffolding protein), eIF4E (cap-binding protein), and eIF4A (ATP-dependent helicase). The 43S preinitiation complex binds to the 5′ end of the mRNA with the help of eIF4F in the presence of eIF4B, and the complex scans the mRNA leader sequence until it reaches the initiation codon to form the 48S initiation complex (Kozak and Shatkin, 1978). The initiation codon is usually the first AUG codon encountered; it is recognized by base-pairing with the anticodon of Met-tRNAi^{Met} and the efficiency of recognition depends on the sequence context surrounding the initiation codon. The most favorable context in mammals is RCCAUGG with purine (R) at position −3 (Kozak, 1986, 1991), and in plants it is ACAAUGG (Fütterer and Hohn, 1996). At this step the 48S initiation complex is joined by the large 60S ribosomal subunit to form the 80S ribosome. Joining requires two additional factors: eIF5 and eIF5B. Hydrolysis of eIF2-bound GTP induced by eIF5 leads to reduction in the affinity of eIF2 for Met-tRNAi^{Met}. In turn, the essential ribosome-dependent GTPase activity of eIF5B leads to displacement of the eIF2-bound GDP and other initiation factors from the 40S subunit (reviewed in Pestova *et al.*, 2007). The assembled 80S ribosome contains the initiator Met-tRNAi^{Met} in the ribosomal P (peptidyl) site and another aa-tRNA in the ribosomal A (aminoacyl) site. The delivery of the aa-tRNA is mediated by the eukaryotic elongation factor (eEF) 1A–GTP complex. After peptide bond formation (triggered

by the peptidyl transferase in the ribosome) eEF2 binding and subsequent GTP hydrolysis catalyze ribosomal translocation, and the elongation cycle begins (Frank *et al.*, 2007). This general strategy is also adopted by a large number of eukaryotic viruses. Yet the RNA genome of certain viruses lacks a cap structure; the 5′ end of such RNA genomes can carry a covalently bound viral protein designated viral protein genome-linked (VPg), or begin with a di- (or a mono-) phosphate. In other cases, the 5′ UTR of the viral RNA contains an internal ribosome entry site (IRES) responsible for initiation of translation.

B. Closed-loop model or circularization

In most eukaryotic mRNAs, the 5′ cap structure and the 3′ poly(A) tail appear to work together leading to efficient translation initiation. This is believed to occur when the 5′ and 3′ ends are brought in close proximity, referred to as the mRNA circularization or closed-loop model. The existence of cellular polyribosomes arranged in a circle was visualized using electron microscopy (Christensen *et al.*, 1987). Circularization is brought about by binding of the initiation factor eIF4E to the 5′ cap and to eIF4G. In turn, eIF4G binds to the poly(A)-binding protein (PABP) bound to the 3′ poly(A) tail (Fig. 4A). PABP contains four conserved RNA recognition motifs in its N-terminal domain that are involved in RNA and eIF4G interactions, and a C-terminal domain that binds to several proteins, including eIF4B, the eukaryotic release factor (eRF) 3 and the PABP-interacting protein 1 (Paip1). Therefore, PABP promotes the formation of the closed-loop complex by binding directly to eIF4G (Gale *et al.*, 2000; Gallie, 1998; Imataka *et al.*, 1998; reviewed in Dreher and Miller, 2006) or through Paip1 binding to eIF4A (Craig *et al.*, 1998) or by PABP interaction with eIF4B (Bushell *et al.*, 2001; Le *et al.*, 1997) (Fig. 4A). Circularization thus appears to be mediated by RNA–protein and protein–protein interactions. Increasing evidence has been provided for the involvement of both 5′ and 3′ UTRs of eukaryotic mRNAs and viral mRNAs in initiation of translation (reviewed in Edgil and Harris, 2006; Hentze *et al.*, 2007; Komarova *et al.*, 2006; Mazumder *et al.*, 2003; Wilkie *et al.*, 2003). In addition to contributing to mRNA stabilization, circularization probably facilitates ribosome recruiting from the 3′ end of the mRNA after a terminated round of translation, to the 5′ region for initiation of a second round. This could be achieved via interaction of PABP with eRF3 that by interacting with eRF1, would result in the formation of a closed loop by way of the 5′ cap—eIF4E–eIF4G–PABP–eRF3–eRF1—termination codon (Fig. 4A) (Uchida *et al.*, 2002).

Certain viral mRNAs are devoid of 5′ cap structure or VPg, and some of them are devoid of 3′ poly(A) tail. Nevertheless, such mRNAs are highly efficient, and circularization presumably required for efficient


A
N
eIF4G
C
eIF4E
5′
eIF4A
eIF3
40S
AUG
eIF4B
mRNA
Paip 1
eRF3
eRF1
Stop
N PABP C
N PABP C
N PABP C
3′AAAAAAAAAAAAAAAAAAAAAAA
B
Translation
C-rich
spacer
IRES
AUG
5′
CL
80S
C
SRp20
Poliovirus
genome
3C/3CD
N PCBP2
N PCBP2 C
PABP
PABP
PABP
3′AAAAAAAAAAAAAAAAAAAAAAA
Replication
C
eIF4E
5′
C
NSP3
N
N NSP3 C
N eIF4G C
Cellular
mRNA
eIF4E
5′
N eIF4G C
C
NSP3
N
N NSP3 C
Rotavirus
mRNA
3′CCAGU
TE
PABP
PABP
3′AAAAAAAAAA
Circularization
No circularization

translation is achieved via various mechanisms. In the case of viral RNAs with a poly(A) tail, circularization has been investigated by looking for viral and/or host proteins that participate in circularization. For instance, in Poliovirus (family Picornaviridae) RNA whose VPg is removed soon after entry of the virus into the cell, the long 5′ UTR of its genomic RNA contains an IRES preceded by a cloverleaf structure (Fig. 4B). PABP interacts with the poly(A) tail of the viral RNA. It also binds to the poly (rC)-binding protein 2 (PCBP2) that binds to the IRES structure to circularize the viral mRNA for translation (Blyn *et al.*, 1997; Silvera *et al.*, 1999; Walter *et al.*, 2002). Binding of PCBP2 to PABP leads to circularization of the viral RNA with the formation of an RNA–protein–protein–RNA bridge. In addition, the cellular protein SRp20 that is involved in cellular mRNA splicing and nucleocytoplasmic trafficking and also cofractionates with ribosomal subunits, interacts with PCBP2, and promotes *Poliovirus* IRES-driven translation (Bedard *et al.*, 2007).

Circularization can also be achieved by direct base pairing between a region in the 5′ UTR and a region in the 3′ UTR of an mRNA; it is used in particular by viral mRNAs that possess neither cap (or VPg) nor poly(A) tail. In several instances, specific interactions have been detected and their functional significance investigated by phylogenetic studies of conserved regions within the ends of viral RNAs, and by mutation analyses of the base-paired regions presumably involved (reviewed in Miller and White, 2006). Among plant RNA viruses, the region of the 3′ UTR required for translation is frequently referred to as 3′-cap-independent translation element (3′-CITE). Several classes of 3′-CITEs have been described (reviewed in Miller *et al.*, 2007). They presumably operate by long-distance base pairing between the 3′ UTR and a complementary region in the 5′ UTR, leading to interactions known as kissing stem–loop interactions. Some of the well-studied cases are those of Tobacco necrosis virus (TNV; family Tombusviridae; Meulewaeter *et al.*, 2004; Shen and Miller, 2004), Satellite tobacco necrosis virus (STNV; Guo *et al.*, 2001; Meulewaeter *et al.*, 1998) Tomato bushy stunt virus (TBSV; family Tombusviridae; Fabian and White, 2004, 2006), Barley yellow dwarf virus (BYDV; family Luteoviridae; Guo et al., 2000, 2001), and Maize necrotic streak virus (family Tombusviridae; Scheets and Redinbaugh, 2006).

FIGURE 4 Possible models of circularization. (A) Closed-loop model or circularization of cellular mRNAs. eIF4E+eIF4G+eIF4A, eIF4F complex; Stop, termination codon. (B) Models of circularization of Poliovirus genome. CL, cloverleaf structure; 3C and 3CD, viral proteases. (C) Role of rotavirus NSP3 in mRNA circularization. NSP3 mediates viral mRNA circularization (left) and inhibits cellular mRNA circularization (right). N and C, N- and C-terminal regions of proteins; TE, translation enhancer. Dashed arrows indicate interactions between proteins. Other indications are as in legend of Fig. 1.

An interesting outcome of these studies has been the observation that in certain cases, part of the 3′ UTR can function by recruiting initiation factors required for initiation of translation. This seems to be the case of STNV in which a 3′ translation enhancer (TE) mimics a 5′ cap structure (Gazo *et al.*, 2004) by binding to eIF4E and this binding is enhanced by eIF4G (or eIFiso4E and eIFiso4G of eIFiso4F, isoforms only found in plants). Moreover, the 3′ UTR of STNV RNA contains a region that has been reported to be complementary of the 3′ end of the ribosomal 18S RNA (Danthinne *et al.*, 1993). Thus, long-distance RNA–RNA interaction between the 5′ and 3′ UTRs might bring eIF4F and the 40S subunit positioned on 3′ UTR close to the initiation codon, favoring initiation of translation. Phylogenetic studies suggest that similar mechanisms may be involved in stimulating translation of other viral mRNAs devoid of cap and poly(A) tail (Gazo *et al.*, 2004; Miller *et al.*, 2007; Shen and Miller, 2004; Treder *et al.*, 2008).

Rotaviruses (family Reoviridae) contain 11 double-stranded generally monocistronic RNAs; they are capped, and most of them contain a short conserved sequence (UGACC) at their 3′ end. This sequence serves as 3′ TE. Enhanced gene expression by the 3′ TE requires the viral nonstructural protein NSP3 (Fig. 4C). This protein binds not only to the 3′ TE but also to eIF4G, suggesting that it behaves as a functional homolog of PABP, leading to circularization of the mRNA (Piron *et al.*, 1998). Moreover, upstream of the common UGACC sequence in its 3′ UTR, the mRNA of gene 6 coding for the structural protein VP6 possesses a unique gene-specific TE that does not require NSP3 for activity (Yang *et al.*, 2004).

Finally, in the tripartite (+) strand RNA virus Alfalfa mosaic virus (family Bromoviridae), whose RNAs are capped but lack a poly(A) tail, a few molecules of coat (also known as capsid) protein (CP) appear to replace PABP in promoting translation: the CP binds strongly to specific regions in the 3′ UTR and also to eIF4G (or eIFiso4G; Krab *et al.*, 2005; reviewed in Bol, 2005). When an artificial poly(A) tail is tagged to the 3′ UTR, CP molecules are no longer required for translation (Neeleman *et al.*, 2001).

C. VPg and initiation

The presence of a VPg linked covalently to the 5′ end of an RNA is characteristic of members of various virus families such as the Birnaviridae, Caliciviridae, Picornaviridae, Potyviridae, Comoviridae, and Luteoviridae (reviewed in Sadowy *et al.*, 2001). The size of the VPg varies from 3 kDa (members of the Picornaviridae family) to 90 kDa (members of the Birnaviridae family). Binding of VPg to eIF3 and eIF4E suggests that an initiation complex is formed and recruited to the viral mRNA, a complex in which VPg would behave as a cap substitute. VPg may therefore interfere

with translation by interacting with initiation factors that are required for initiation of both cap-dependent and IRES-containing mRNA translation.

In Poliovirus, whose genome contains a VPg and an IRES in its 5′ UTR, the VPg is removed from the genomic RNA early in infection and the viral mRNA lacks a VPg. Therefore, VPg does not regulate initiation of translation in this virus and probably in other members of the *Picornaviridae* family.

The genome of Turnip mosaic virus (TuMV, family Potyviridae) is devoid of IRES and cap structure. Its VPg in the precursor form 6K-VPg-Pro appears to favor translation of viral proteins by interacting with eIFiso4E (Leonard *et al.*, 2004; Wittmann *et al.*, 1997). TuMV and Tobacco etch virus (TEV; family, Potyviridae) can interfere *in vitro* with the formation of a translation initiation complex on host plant cellular mRNA by sequestering eIFiso4E, since the binding affinity of VPg for eIFiso4E is stronger than that of capped RNA. VPg enhances uncapped viral mRNA translation and inhibits capped mRNA translation. Moreover, it appears to function as an alternative cap-like structure by forming a complex with eIFiso4E and eIFiso4G (Khan *et al.*, 2008; Miyoshi *et al.*, 2006).

Furthermore, for viruses such as those of the family Caliciviridae that are also devoid of cap or IRES, evidence for the involvement of the VPg in translation initiation has been documented: in addition to binding to the eIF3 complex (in particular to its eIF3d subunit), the Norwalk virus (NV) VPg inhibits translation of cap-dependent and of IRES-containing reporter mRNAs *in vitro* (Daughenbaugh *et al.*, 2003). In Feline calicivirus (FCV), the VPg directly interacts with eIF4E *in vitro* (Goodfellow *et al.*, 2005) and removal of the VPg from the FCV RNA results in dramatic reduction of viral protein synthesis (Herbert *et al.*, 1997).

D. IRES-directed initiation

Initiation of translation of the genome of numerous RNA viruses does not comply with the general cap-dependent scanning mechanism of eukaryotic protein synthesis (reviewed in Doudna and Sarnow, 2007; Kneller *et al.*, 2006). Rather, initiation can occur downstream of a (usually) long GC-rich 5′ UTR known as IRES that in contrast to classical cap-dependent initiation of translation, plays an active role in 40S ribosomal subunit recruitment. These viral 5′ UTRs are generally highly structured, thereby hindering movement of the scanning ribosomes. Animal viruses that resort to this strategy are picornaviruses (reviewed in Belsham and Jackson, 2000; Martínez-Salas and Fernández-Miragall, 2004; Martínez-Salas *et al.*, 2001; Pestova *et al.*, 2001) and pestiviruses (Pisarev *et al.*, 2005).

Ribosomal entry directly to an internal AUG initiation codon on an mRNA devoid of cap structure was demonstrated by placing an IRES between two mRNA cistrons in a dicistronic construct. The presence of

the IRES allowed the expression of the downstream cistron independently of the upstream cistron (Jang *et al.*, 1988; Pelletier and Sonenberg, 1988). Hence, *cis*-acting elements in the IRES appear to cap independently recruit ribosomes to the initiation codon, and the 5′ UTR can be considered an IRES if it drives initiation of translation of the downstream cistron.

Considerable work has been directed toward deciphering the sequence elements involved in IRES-mediated initiation, and the protein factors participating in this step of translation. Translation by an IRES obviates the need of certain host eIFs (that differ for different groups of IRESs), and often requires additional host proteins, the IRES *trans*-acting factors (ITAFs). These are mRNA-binding proteins such as the pyrimidine tract-binding protein (PTB), ITAF45, PCBP2, the cellular cytoplasmic RNA-binding protein designated upstream of N-ras (unr), and the La autoantigen. The IRESs involved in initiation are part of the 5′ UTR or of the IGR, and their integrity is required for full activity. They sometimes include 5′ nts of the ORF following the IRES (Rijnbrand *et al.*, 2001). Based on their sequence and structure, the IRESs of members of the Picornaviridae family can be divided into three major groups; (1) Enterovirus (Poliovirus) and Rhinovirus (Human rhinovirus, HRV), (2) Cardiovirus (Encephalomyocarditis virus, EMCV and Theiler's murine encephalomyelitis virus, TMEV) and Aphthovirus (Foot-and-mouth disease virus, FMDV), and (3) Hepatovirus (Hepatitis A virus, HAV) (reviewed in Belsham and Jackson, 2000; Kean *et al.*, 2001; Martínez-Salas and Fernández-Miragall, 2004).

Studies *in vitro* showed that the EMCV IRES-mediated initiation of translation is ATP dependent and requires eIF2, eIF3, eIF4A, and eIF4B as well as the central region of eIF4G to which eIF4A binds. eIF4E is not required, and therefore cleavage of eIF4G as well as the absence of eIF1 which is important for 40S ribosomal subunit scanning do not abolish EMCV IRES function. The same applies to the FMDV IRES-mediated translation from the first initiator AUG (reviewed in Pestova *et al.*, 2001). PTB, an auxiliary cellular 57-kDa protein with four RNA recognition motifs, strongly stimulates initiation of translation of all group 1 and 2 IRESs (Andreev *et al.*, 2007; Borovjagin *et al.*, 1994; Gosert *et al.*, 2000; Hunt and Jackson, 1999; Pilipenko *et al.*, 2000). ITAF45 is additionally required for FMDV IRES-mediated translation, and PCBP2 as well as unr for Poliovirus and Rhinovirus IRESs (Andreev *et al.*, 2007; Blyn *et al.*, 1997; Boussadia *et al.*, 2003; Pilipenko *et al.*, 2000). The La autoantigen stimulates PV IRES-mediated translation (Costa-Mattioli *et al.*, 2004).

The 5′ UTR of hepatovirus RNAs such as Hepatitis C virus (HCV; family Flaviviridae) are 342–385 nts long. Initiation at their IRES differs from initiation in picornavirus IRESs *in vitro*: binding of the 40S ribosomal subunit to the HCV IRES occurs directly, without requirement for the translation initiation factors eIF4F and eIF4B (reviewed in

Pestova *et al.*, 2001). Thus, the IRES functionally replaces eIF4F on the 40S ribosomal subunit (Siridechadilok *et al.*, 2005). Lack of eIF4F is compensated by conformational modifications in the 40S ribosomal subunit (Spahn *et al.*, 2001). Moreover, the activity of HCV-like IRESs is also affected by the coding sequence immediately downstream of the initiation codon. Not only flaviviruses but also RNA genomes of some picornaviruses such as Porcine Teschovirus carry HCV-like IRES elements within their 5′ UTR (Pisarev *et al.*, 2004).

An interesting variant of IRESs exists in viruses of the *Dicistroviridae* family such as Cricket paralysis virus (CrPV), viruses originally believed to be the insect counterpart of mammalian picornaviruses (reviewed in Doudna and Sarnow, 2007; Jan, 2006). The monopartite RNA genome of CrPV harbors a 5′ VPg and a 3′ poly(A) tail. It contains two nonoverlapping ORFs separated by an IGR (as opposed to picornaviruses that have only one ORF); the expression of the two ORFs is triggered by two distinct IRESs, one in the 5′ UTR and the other in the IGR (Jan *et al.*, 2003; Sasaki and Nakashima, 1999, 2000; Wilson *et al.*, 2000b). As shown using the long (580 nts) 5′ IRES contained in the Rhopalosiphum padi virus (RhPV) RNA, the 5′ UTR initiates translation of a nonstuctural polyprotein at the expected AUG codon. No specific boundaries of this IRES can be defined, suggesting that the IRES contains multiple domains capable of recruiting ribosomes for translation (Terenin *et al.*, 2005). The IGR of 175–533 nts separating the two ORFs contains the second IRES ($\sim$180 nts) that initiates synthesis of a structural polyprotein on a non-AUG codon and requires neither initiation factors nor Met-tRNAi^{Met} but a small domain (domain 3) downstream of the IGR IRES that docks into the 40S ribosomal P site mimicking the tRNA anticodon-loop structure during translation initiation (Costantino *et al.*, 2008; Jan and Sarnow, 2002; Wilson *et al.*, 2000a). In most cases, initiation from the second IRES begins at a GCU, GCA, or GCC triplet coding for alanine or at a CAA triplet coding for glutamine (reviewed in Pisarev *et al.*, 2005). In the model proposed for the initiation of the second IRES, domain 3 within the IGR occupies the ribosomal P site, the ribosomal A site remaining accessible for the Ala-tRNA or the Gln-tRNA, and translocation occurs on the ribosome without peptide bond formation (designated as the elongation-competent assembly of ribosome). As in the case of the HCV IRES, binding of the CrPV IGR to the 40S ribosomal subunit induces conformational changes on the ribosome (Costantino *et al.*, 2008; Pfingsten *et al.*, 2006; Spahn *et al.*, 2004).

The rates of cap- and IRES-dependent initiation pathways *in vitro* are different: using FMDV RNA as template it was shown that cap-dependent assembly of the 48S ribosomal complex occurs faster than IRES-mediated assembly (Andreev *et al.*, 2007). Moreover, some viruses have evolved sequences that prevent their IRESs from functioning. For example, the HCV IRES possesses a conserved stem–loop structure

containing the initiation codon and this structure has been shown to decrease IRES efficiency (Honda *et al.*, 1996). One possible explanation is that for successful viral infection, IRESs should work at a very specific level of efficiency, which does not necessarily correspond to maximum efficiency.

As opposed to animal virus IRESs, plant virus IRES elements are shorter and less structured. Moreover, such elements are not confined to the 5′ UTRs on the genome of plant RNA viruses, and they are then at times referred to as TEs. Depending on the plant viral genome, the IRES is located (1) in the 5′ UTR such as in the picorna-like virus Potato virus Y (family Potyviridae; Levis and Astier-Manifacier, 1993), (2) within or between ORFs such as in a crucifer-infecting Tobacco mosaic virus (TMV, genus Tobamovirus; Jaag *et al.*, 2003; Skulachev *et al.*, 1999; Zvereva *et al.*, 2004) and in Potato leafroll virus (PLRV, family Luteoviridae; Jaag *et al.*, 2003), or (3) in the 3′ UTRs of viruses such as in BYDV (Guo *et al.*, 2001; Wang *et al.*, 1997). In the Hibiscus chlorotic ringspot virus (family Tombusviridae) genome, the activity of the 5′-located IRES is enhanced by the presence of a TE (also known as CITE) located in the 3′ UTR (Koh et al., 2002, 2003). The possible mechanisms of action of 3′ TEs has in recent years revealed the immense variety of strategies used in translation initiation by plant RNA viruses (reviewed in Miller and White, 2006).

E. Non-AUG initiation codons

In some cases in eukaryotes as also in prokaryotes, initiation of translation of cellular and viral mRNAs occurs on a non-AUG codon. Table I summarizes the situation for viruses that initiate some of their proteins on non-AUG codons.

In addition to containing the P ORF, the *Sendai virus* P mRNA harbors the C ORF in another reading frame that leads to the synthesis of a nested set of C-coterminal proteins (proteins C′, C, Y1, and Y2) known jointly as the C proteins (Fig. 2B). Except for C′ that is initiated upstream of the P protein on the mRNA, the other C proteins are entirely contained within the P ORF. C′ is initiated on an ACG codon in an optimum sequence context, and nts +5 and +6 also appear to be important for initiation at such non-AUG codons. The other C proteins (C, Y1, and Y2) are initiated on downstream-located AUG codons in suboptimal contexts and are presumably synthesized by leaky scanning or ribosome shunting (Curran and Kolakofsky, 1988; Gupta and Patwardhan, 1988; Kato *et al.*, 2004). Use of ACG as initiation codon has been described in the neurovirulent strains of TMEV (van Eyll and Michiels, 2002).

The initiation codon in *Human parainfluenza virus 1* (HPIV-1, family *Paramyxoviridae*) for the synthesis of C′ is a GUG codon. *In vivo*, GUG appears nearly as efficient as AUG in initiating C′ expression in the same context (Boeck *et al.*, 1992).

TABLE I Viruses shown or postulated to use non-AUG codons as initiators of protein synthesis

Family/genus	RNA[a]	Initiation codon	Protein	References
Plant viruses				
Caulimoviridae				
Tungrovirus				
RTBV	1	AUU	ORF1	Fütterer *et al.* (1996)
Furovirus				
SBWMV	2	CUG	28K[b]	Shirako (1998)
(**Flexiviridae**)				
(Foveavirus)				
PCMV	1	AUC	ORF1	James *et al.* (2007)
	1	AUA	ORF 5[b]	James *et al.* (2007)
Animal viruses				
Parvoviridae				
Dependovirus				
AAV-2	1	ACG	B	Becerra *et al.* (1985)
Retroviridae				
Lentivirus				
EIAV	1	CUG	Tat	Carroll and Derse (1993)
Gammaretrovirus				
MoMLV	1	CUG	$Pr75^{gag}$	Prats *et al.* (1989)
Deltaretrovirus				
HTLV-1	1	GUG	Rex	Corcelette *et al.* (2000)
		CUG	Tax	Corcelette *et al.* (2000)

Paramyxoviridae				
Respirovirus				
Sendai virus	1	ACG	C′	Boeck and Kolakofsky (1994), Curran and Kolakofsky (1988), and Gupta and Patwardhan (1988)
HPIV-1	1	GUG	C′	Boeck *et al.* (1992)
Picornaviridae				
Cardiovirus				
TMEV	1	AUG/ACG[c]	L*	van Eyll and Michiels (2002)
Flaviviridae				
Flavivirus				
HCV	1	GUG/GCG[c]	F	Baril and Brakier-Gingras (2005)
Dicistroviridae				
Cripavirus				
CrPV	1	GCU[d]	ORF 2	Wilson *et al.* (2000a)
PSIV	1	CAA[e]	ORF 2	Sasaki and Nakashima (2000) and Yamamoto *et al.* (2007)
RhPV	1	GCA[d]	ORF 2	Domier *et al.* (2000)

For each virus, the RNA segment whose protein is initiated at a non-AUG codon is indicated as also the initiation codon used, and the designation of the resulting protein. The brackets surrounding Flexiviridae and Foveavirus indicate that PCMV is presumed to belong to this family and genus.

[a] RTBV contains a double-stranded DNA; AAV-2 contains a single-stranded DNA.

[b] CP ORF.

[c] Depending on the variant.

[d] Ala as initiator.

[e] Gln as initiator.

The Moloney murine leukemia virus (MoMLV, family Retroviridae) genomic RNA codes for two in-phase precursor proteins $Pr65^{gag}$ and $Pr75^{gag}$. It uses an upstream CUG as translation initiation codon for the synthesis of $Pr75^{gag}$ that migrates to the cell surface and is involved in virus spread (Prats *et al.*, 1989).

Among plant viruses, a non-AUG initiation codon exists in the polycistronic mRNA of the pararetrovirus Rice tungro bacilliform virus (RTBV; family Caulimoviridae). ORF I of the mRNA (harboring ORFs I–III) is accessed by reinitiation after translation of a short ORF (sORF). Following a long 5′ leader sequence harboring several sORFs that are bypassed by ribosome shunting, synthesis is initiated on an AUU codon at ORF I (Fütterer and Hohn, 1996). Only 10% of the ribosomes initiate at ORF I; the remaining 90% reach ORFs II and III and initiate on an AUG codon (reviewed in Ryabova *et al.*, 2006). A similar situation occurs in other pararetroviruses. RNA 2 of the bipartite (+) sense single-stranded RNA genome of Soil-borne wheat mosaic virus (SBWMV, genus Furovirus) codes for two proteins; the shorter (19K) CP is produced via conventional AUG initiation, whereas the N-terminally extended 28K protein is initiated at a CUG codon upstream of the CP ORF (Shirako, 1998). Under certain conditions, AUU codons located in the 5′ UTR of the TMV RNA can serve as initiation codons (Schmitz *et al.*, 1996).

In the cases presented earlier, the non-AUG codons allow initiation with a methionine residue. There is however an interesting situation of methionine-independent translation initiation (reviewed in Pisarev *et al.*, 2005; Touriol *et al.*, 2003). This is the case of the IRES-dependent initiation of translation of members of the Dicistroviridae family whose structural protein encoded by ORF 2 lacks an AUG initiation codon and translation initiation occurs at a CAA (coding for Gln) or GCU or GCA (coding for Ala) codon, depending on the virus (Table I).

F. Multiple reading frames

Whereas eukaryotic cell mRNAs are usually monocistronic, the mRNAs of eukaryotic viruses frequently contain several ORFs, the AUG positioned close to the 5′ end of the RNA generally constituting the initiation codon. To reach downstream initiation codons that correspond to internal ORFs on polycistronic RNAs lacking an IRES, viruses resort to either leaky scanning, reinitiation, or shunting.

1. Leaky scanning

A mechanism commonly used by viruses to express polycistronic RNAs is leaky scanning (reviewed in Ryabova *et al.*, 2006), in which when the initiation codon lies within less than 10 nts from the cap structure, or when it is embedded in a poor context for initiation, some of the scanning

ribosomes bypass this first initiation codon and start translation on a downstream-located initiation codon whose context is more appropriate for initiation (Fig. 2B). Leaky scanning also occurs when initiation is at a non-AUG codon in an optimal context followed by an AUG codon. Two possible situations can arise: in-frame initiation or overlapping ORFs.

a. In-frame initiation This occurs when an ORF harbors more than one potential in-frame initiation codon; it is codon context-dependent. The outcome of in-frame initiation is the production of two proteins that are identical over the total length of the shorter protein. Table II lists the cases of in-frame initiation reported. In FMDV and Plum pox potyvirus (PPV, family Potyviridae), in-frame initiation is cap independent (Andreev *et al.*, 2007; Simon-Buela *et al.*, 1997).

b. Overlapping ORFs This strategy is extremely common among viruses and is generally also codon context-dependent. The result of this strategy is the synthesis of two different proteins. A situation common to plant

TABLE II In-frame initiation

Family/genus	Genome segment	Protein	References
Comoviridae			
Comovirus			
CPMV	RNA M	Movement protein	Verver *et al.* (1991)
Hordevirus			
BSMV	RNA β	Movement protein	Petty and Jackson (1990)
Furovirus			
SBWMV	RNA 2	Coat protein	Shirako (1998)
Potyviridae			
Potyvirus			
PPV	RNA	Polyprotein	Simon-Buela *et al.* (1997)
Bornaviridae			
Bornavirus			
BDV	RNA P	24- and 16-kDa phosphoproteins	Kobayashi *et al.* (2000)
Picornaviridae			
Aphthovirus			
FMDV	RNA	Polyprotein	Andreev *et al.* (2007)

For each virus the genome segment that undergoes in-frame initiation is indicated.

viruses belonging to several genera such as the carlaviruses and potexviruses (family Flexiviridae), and the viruses of the genera Furovirus and Hordeivirus is the presence within their (+) sense single-stranded RNA genome of a group of three ORFs known as the triple gene block whose expression leads to three proteins involved in movement of the virus within the plant. Synthesis of these proteins requires the production of two sgRNAs. The 5′-proximal ORF is translated from a functionally monocistronic sgRNA, whereas the two subsequent ORFs are translated from the second sgRNA. Expression of the third ORF, which overlaps the second ORF, occurs by leaky scanning and is codon context-dependent (Verchot *et al.*, 1998; Zhou and Jackson, 1996).

Peanut clump virus (PCV, genus Pecluvirus) contains a bipartite (+) sense single-stranded strand RNA genome. In RNA2, the first of two ORFs that codes for the virus CP terminates with a UGA codon that overlaps the AUG codon initiating the second ORF: AUGA. About one-third of the ribosomes fail to initiate translation of the CP and scan the template initiating translation of the second ORF, more than 100 residues downstream of the first ORF (Herzog *et al.*, 1995). RTBV contains a closed-circular double-stranded DNA genome that is transcribed yielding two mRNAs. The longer polycistronic mRNA (known as pregenomic RNA) encodes three ORFs (I, II, and III) that are linked by AUGA, the termination codon of the upstream ORF overlapping the initiation codon of the downstream ORF (Fütterer *et al.*, 1997). ORF I is initiated at an AUU codon, preceded by a long 5′ UTR with several sORFs that are bypassed by ribosome shunting. On the other hand, ORFs II and III initiate at a conventional AUG codon. However, the AUG initiating ORF II is in a poor context, and the majority of the ribosomes bypass this AUG to reach the downstream more favorable AUG of ORF III. Leaky scanning therefore accounts for initiation of translation of ORFs II and III.

Turnip yellow mosaic virus (family Tymoviridae) is a monopartite (+) sense single-stranded RNA virus that bears a cap structure, and harbors a tRNA-like structure (TLS) at its 3′end that can be valylated *in vitro* and *in vivo*. Its first two 5′-proximal and largely overlapping ORFs code for the movement protein (ORF1), and the replicase polyprotein (ORF2) in a different reading frame. It has been reported that the valylated viral RNA serves as bait for ribosomes directing them to initiate synthesis of ORF2, and donating its valine residue for the N-terminus of the polyprotein in a cap- and initiator-independent manner (Barends *et al.*, 2003); interaction between the 3′ TLS and the initiation codon of ORF2 would lead to circularization of the RNA. However, recent studies suggest that initiation of translation of the polyprotein is cap and context dependent, the TLS having only a positive effect on translation of ORF2 without being indispensable (Matsuda and Dreher, 2007). This mechanism allows dicistronic expression from initiation codons that are closely spaced.

2. Reinitiation

Another possibility for initiation at an internal start codon in a polycistronic mRNA is reinitiation of translation of downstream ORFs following expression of a 5′-proximal ORF (of 30 codons or less; reviewed in Ryabova *et al.*, 2006). Reinitiation requires that the 40S ribosomal subunit remain on the mRNA after terminating synthesis of the 5′-proximal ORF. Efficiency of reinitiation decreases with increasing length of the IGR between the 5′-proximal and the next ORF.

Among eukaryotic viruses, polycistronic mRNAs have been the most thoroughly examined in viruses of the family Caulimoviridae, in particular in the double-strand DNA virus Cauliflower mosaic virus (CaMV). The large 35S mRNA of CaMV and related viruses contains up to seven ORFs (Fig. 5), and for some of them recurrent translation depends on reinitiation activated by the transactivator (TAV). The TAV protein is encoded by ORF VI contained in the pregenomic (or polycistronic) 35S mRNA; it is expressed by the 19S sgRNA in which it is the only ORF (Pooggin *et al.*, 2001). In dicistronic constructs harboring the CaMV ORF VII followed by ORF I (or by ORFs II, III, IV, V, or an artificial ORF) fused to the chloramphenicol acetyltransferase (CAT) gene, very low levels of CAT activity were obtained in plant protoplasts; however, when the

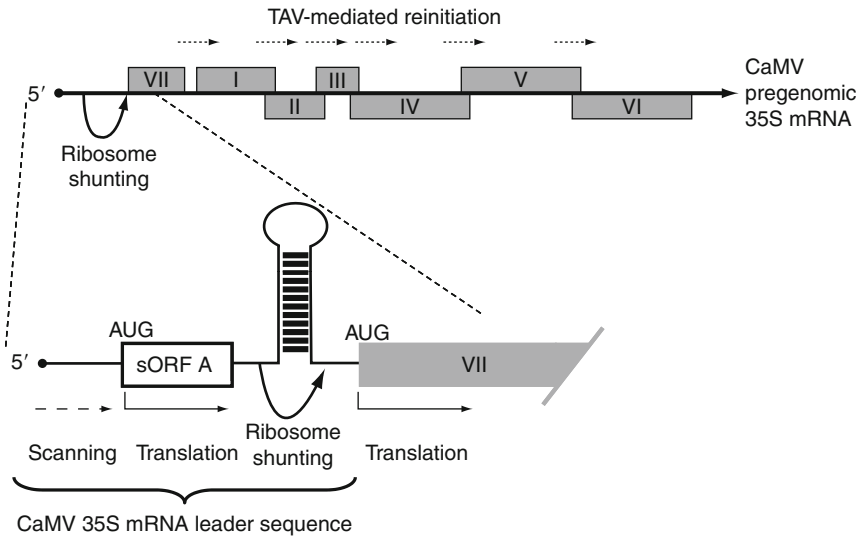


FIGURE 5 Schematic representation of the organization of the CaMV pregenomic 35S mRNA and strategies of translation initiation. I–VII are ORFs. TAV, transactivator. Arrows show migration of ribosomes by reinitiation (dotted), scanning (dashed), and shunting (curved). Translation is represented by a bent arrow. Other indications are as in legend of Fig. 1.

product of ORF VI was included, considerably higher levels of CAT activity were observed (Bonneville *et al.*, 1989; Fütterer and Hohn, 1991). The second ORF of the dicistronic construct is synthesized by reinitiation and not by an IRES, since a stem structure positioned at various sites upstream of this ORF hinders its translation (Fütterer and Hohn, 1991). TAV-stimulated initiation of the second ORF does not depend on the distance separating the two ORFs, since the distance can be abolished as in a quadruplet AUGA, or the ORFs can be separated by as many as 700 nts, and even limited overlap between the ORFs is possible. TAV directly binds to the eIF3g subunit of eIF3 and associates with the L18 and L24 proteins of the 60S ribosomal subunit (Leh *et al.*, 2000; Park *et al.*, 2001). These interactions result in TAV–eIF3 complex association with the translocating ribosome during translation, favoring reinitiation of downstream ORFs. On the other hand, eIF4B can compete with TAV for binding to eIF3g, since the binding sites of these two proteins on eIF3g overlap. Overexpression of eIF4B inhibits TAV-mediated reinitiation of a second ORF, probably by inhibiting TAV–eIF3g-40S complex formation (Park *et al.*, 2004).

The members of the *Calicivirus* family contain a (+) sense single-stranded RNA carrying a VPg. The sgRNAs of these viruses that also contain a VPg represent widely studied examples of reinitiation by mammalian ribosomes after translation of a long ORF. The Rabbit hemorrhagic disease virus genomic RNA codes for a large polyprotein ORF1 that is subsequently processed producing the viral nonstructural proteins and the 3′ terminally located major CP VP60, as well as a small 3′ terminally located ORF2 in another reading frame. The 3′-terminal part of ORF1 overlaps the 5′ region of ORF2. Expression of ORF2 yields the minor CP VP10 and is produced from a sgRNA that also contains the region of ORF1 expressing VP60. Thus, the sgRNA codes for the major VP60 encoded by the 3′-terminal part of ORF1, and for the minor VP10 produced by ORF2. The two ORFs overlap by AUGUCUGA such that the termination codon (UGA) of ORF1 lies downstream of the initiation codon (AUG) of ORF2. Synthesis of VP10 occurs from the genomic as well as from the sgRNA and involves an unusual translation termination/reinitiation process. Indeed, synthesis of VP10 depends strictly on the presence of the termination codon ending ORF1 preceded by a sequence element of about 80 nts (Meyers, 2003). The sequence element contains two motifs that are essential for expression of ORF2, one of which is conserved among caliciviruses and is complementary to a sequence in the 18S ribosomal RNA. In FCV, sgORF1 and sgORF2 overlap by 4 nts (AUGA) and translation in a reticulocyte lysate of the FCV sgRNAs showed that ORF1/ORF2 termination/reinitiation does not require the eIF4F complex and that the 3′-terminal RNA sequence of ORF1 binds to the 40S ribosomal subunit and to IF3 (Luttermann and Meyers, 2007;

Meyers, 2007; Pöyry *et al.*, 2007). Thus, the termination/reinitiation process requires sequence elements that could prevent dissociation of postterminating ribosomes via RNA–RNA, RNA–protein, and/or protein–protein interactions.

3. Shunting

A ribosome shunting mechanism has been proposed to explain how initiation of translation occurs in viral polycistronic mRNAs that have a long leader sequence with generally several sORFs, a long low-energy hairpin structure and a probable packaging signal within the 5′ UTR (reviewed in Ryabova *et al.*, 2006). This is the case of CaMV (Fig. 5). The ribosomes having entered at the level of the cap structure on the 35S mRNA would scan a few nts, then skip from a ''take-off site'' over part of the leader sequence containing a structural element and sORFs, to reach a ''landing site,'' and finally scan to the downstream ORF. It has been suggested that formation of a leader hairpin between the two sites would bring these sites in close proximity, favoring shunting. It is generally assumed that shunting is more easily achieved if the upstream ORF is short, such that the initiation factors that allowed initiation of translation of the sORF may have at least partly remained on the ribosome during translation (reviewed in Jackson, 2005). In addition to the size of the sORF, the time required for scanning seems also to be important (Pöyry *et al.*, 2004), the eIF4F initiation complex remaining on the ribosome for a few seconds without interruption of sORF translation. The leader sequence of the CaMV 35S mRNA is replete with sORFs. Of these, the 5′-proximal sORF, sORF A, is indispensable for ribosome shunting and infectivity; its aa sequence is generally not important but it must be translated and should be between 2 and 10 codons long for efficient shunting. Another important *cis*-acting element for shunting includes the distance between the termination codon of sORF A and the base of the leader hairpin (reviewed in Ryabova *et al.*, 2006). Finally, it has been reported that TAV promotes expression of ORF VII (Pooggin *et al.*, 2001).

Shunting may explain translation of polycistronic mRNAs in other viruses, generally by examining the effect on translation of inserting a strong hairpin structure near the 5′ end or in the middle region of the leader sequence, or by inserting AUG codons within the leader, as done for CaMV. Shunting occurs in the case of the 200 nt-long leader, the tripartite leader, in the Adenovirus late mRNAs from the major late promoter. This highly conserved leader contains a 25–44 nt-long unstructured 5′ region, followed by highly structured hairpins devoid of sORFs. Shunting has been reported to be enhanced by complementarity between the tripartite leader and the 3′ hairpin of the 18S ribosomal RNA (Xi *et al.*, 2004; Yueh and Schneider, 2000).

In the polycistronic P/C mRNA of Sendai virus (Fig. 2B), proteins P and C are presumably initiated by leaky scanning, whereas proteins Y1 and Y2 most possibly arise by shunting. This was suggested because changing the ACG codon of C′ to AUG dramatically reduced the synthesis of the P and C proteins, but had virtually no effect on the synthesis of Y1 and Y2 (Latorre *et al.*, 1998). Yet to date, no specific sites have been detected in the mRNA to account for shunting.

G. Modification of cell factors involved in initiation

Shutoff of host protein synthesis is the process in which cell protein synthesis is inhibited during viral infection due to the use by the virus of the host metabolism (reviewed in Gale *et al.*, 2000; Randall and Goodbourn, 2008). Host shutoff reflects the competition between viral and host mRNAs for the translation machinery, and results in selective translation of viral mRNAs over endogenous host mRNAs. Early translational switch is accompanied by disaggregation of polysomes containing capped cellular mRNAs, followed by reformation of polysomes containing exclusively viral mRNAs (reviewed in Lloyd, 2006).

It is at first sight rather surprising that in plants, no infection by a plant virus has so far been conclusively demonstrated to hinder host translation *in planta* so as to favor synthesis of viral proteins. Host translational shutoff by plant viruses has been reported only in *in vitro* translation studies of the potyviruses TuMV and TEV (Cotton *et al.*, 2006; Khan *et al.*, 2008; Miyoshi *et al.*, 2006). The authors reported different causes for the inhibition of cellular mRNA translation. On one hand inhibition would be the result of competition between cellular-capped mRNAs and VPg for eIFiso4E, the binding affinity of VPg for eIFiso4E being stronger that of the capped mRNA (Khan *et al.*, 2008; Miyoshi *et al.*, 2006). On the other hand, inhibition of cell mRNA translation by TuMV would not be mediated by the interaction of VPg-Pro (precursor of VPg) with eIFiso4E but by VP-Pro-induced degradation of RNAs (Cotton *et al.*, 2006).

It has been established for several plants that variation in eIF4E and eIFiso4E is involved in natural recessive resistance against potyviruses (reviewed in Kang *et al.*, 2005; Robaglia and Caranta, 2006). Resistance and complementation assays provide evidence for coevolution between pepper eIF4E and potyviral VPg (Charron *et al.*, 2008). Some recessive plant virus resistance genes code for eIF4E with the aa substitution Gly107Arg, and this substitution was shown to abolish the ability of eIF4E to bind TEV VPg and the cap, providing resistance against TEV infection (Yeam *et al.*, 2007). Recently, a functional map of lettuce eIF4E was obtained, and the results using mutated eIF4E suggest that the function of eIF4E in the potyvirus cycle might be distinct from its

physiological function of binding the cap structure at the 5′ ends of mRNAs to initiate translation; thus eIF4E may be required for virus RNA replication or other processes of the virus cycle (German-Retana *et al.*, 2008).

1. Phosphorylation of eIF2α

The function of eIF2 in protein synthesis is the formation of the TC and its delivery to the 40S ribosomal subunit. eIF2 is a complex composed of the three subunits α, β, and γ (Fig. 6). Phosphorylation of eIF2α inhibits the exchange of GDP for GTP catalyzed by the exchange factor eIF2B, and leads to the sequestration of eIF2B in a complex with eIF2 resulting in general inhibition of protein synthesis (Sudhakar *et al.*, 2000; reviewed in Hinnebusch, 2005). The amount of eIF2B in cells is limiting as compared to eIF2. Thus, even small changes in the phosphorylation status of eIF2α have a drastic effect on translation due to eIF2B sequestration

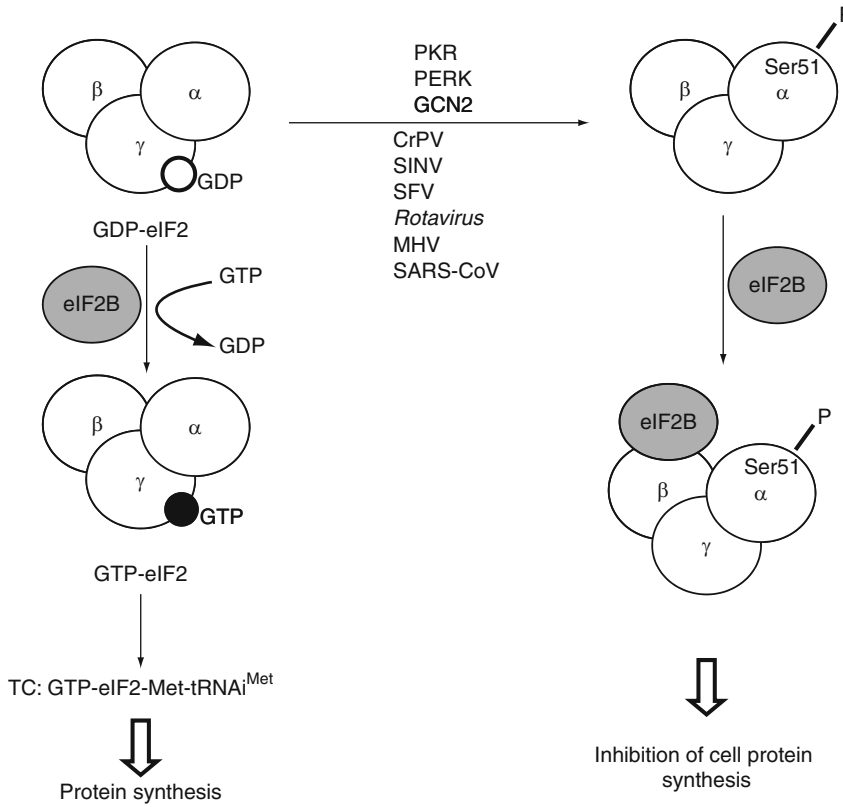


FIGURE 6 Phosphorylation of eIF2α in virus-infected cells. TC, ternary complex; P, phosphorylation. α, β, and γ are the subunits of eIF2.

(Balachandran and Barber, 2004; Krishnamoorthy *et al.*, 2001; Sudhakar *et al.*, 2000; Yang and Hinnebusch, 1996). For several mRNAs the eIF2 complex is replaced by a single polypeptide designated eIF2A that directs codon-dependent and GTP-independent Met-tRNAi^{Met} binding to the 40S ribosomal subunit and may act by favoring expression of specific proteins (Adams *et al.*, 1975; Merrick and Anderson, 1975; Zoll *et al.*, 2002).

Four cellular eIF2α kinases are known to phosphorylate the eIF2α subunit at residue Ser51. Three of the kinases—the protein kinase RNA (PKR), the PKR-like endoplasmic reticulum kinase (PERK), and the general control nonderepressible-2 (GCN2) kinase—play a prominent role in virus-infected cells (Fig. 6). PKR binds to and is activated by double-strand RNAs that are generated during replication and transcription of viral genomes. Accumulation of unfolded proteins in the endoplasmic reticulum during viral infection induces a signaling cascade from the cytoplasmic kinase domain of PERK, leading to induction of eIF2α phosphorylation. Finally, GCN2 kinase is reported to be activated upon Sindbis virus (SINV, family Togaviridae) infection (Berlanga *et al.*, 2006).

Many viruses evolved diverse strategies to prevent PKR or PERK activation in infected cells; these strategies have been discussed in detail in recent reviews (Dever *et al.*, 2007; Garcia *et al.*, 2007; Mohr, 2006; Mohr *et al.*, 2007). However, there are several examples in which viruses use eIF2α phosphorylation to switch off cell translation and direct the cell machinery to synthesize their own proteins (Fig. 6). A classical illustration of how eIF2 modification fosters translation of viral mRNAs is initiation of translation on the CrPV IRES. The IRES contained in the IGR promotes initiation of protein synthesis without the assistance of any initiation factors, including eIF2 (reviewed in Doudna and Sarnow, 2007; Pisarev *et al.*, 2005). Moreover, CrPV stimulates eIF2α phosphorylation; this inactivates host mRNA translation by decreasing the amount of preinitiation 43S ribosomal complexes formed and facilitates translation initiation on the CrPV IRES. Indeed, lowering the amounts of TC and 43S ribosomal complexes increases the efficiency of initiation on the CrPV IRES (Pestova *et al.*, 2004; Thompson *et al.*, 2001). HCV encodes proteins known to inactivate PKR (or PKR + PERK) function(s) (Garcia *et al.*, 2007). However, HCV IRES-driven translation initiation can also be maintained in the presence of activated PKR and reduced TCs (Robert *et al.*, 2006). A new pathway of eIF2- and eIF5-independent initiation of translation on the HCV IRES has been proposed recently in which assembly of the 80S complex requires only two initiation factors, eIF5B and eIF3 (Terenin *et al.*, 2008).

Infection by viruses of the genus Alphavirus (family Togaviridae) such as SINV or Semliki forest virus (SFV) activates PKR, which results in almost complete phosphorylation of eIF2α at late times postinfection. Translation of the viral sg 26S mRNA takes place efficiently during this time, whereas translation of genomic mRNA is impaired by eIF2α

phosphorylation (Molina *et al.*, 2007; Ventoso *et al.*, 2006). It was shown that a hairpin loop structure within the 26S mRNA-coding region, located downstream of the AUG initiation codon, promotes eIF2-independent translation with the help of eIF2A (Ventoso *et al.*, 2006). However, the fact that translation of the 26S mRNA must be coupled to transcription to be efficient in infected cells suggests that additional viral or cellular factors are involved in translation initiation on the 26S mRNA (Sanz *et al.*, 2007).

Early in the infection process rotaviruses take over the host translation machinery, and this is achieved via interaction of the viral NSP3 with eIF4G and phosphorylation of eIF2α (Figs. 4C and 6; Montero *et al.*, 2008; Piron *et al.*, 1998). These two mechanisms may explain the severe shutoff of cell protein synthesis observed during rotavirus infection, although it is not clear how capped viral mRNAs are efficiently translated in such eIF2α-sequestered conditions.

Murine hepatitis virus (MHV) as well as Severe acute respiratory syndrome coronavirus (SARS-CoV), both of the family Coronaviridae, induce host translational shutoff. This is achieved via different mechanisms: degradation of cell mRNAs including mRNAs encoding translation-related factors (Leong *et al.*, 2005; Raaben *et al.*, 2007), increase in eIF2α phosphorylation presumably via PERK, and formation of stress granules and processing bodies that are thus sites of mRNA stalling and degradation, respectively (Chan *et al.*, 2006; Raaben *et al.*, 2007; Versteeg *et al.*, 2006). Expression of the SARS-CoV NSP1 is involved in degradation of several host mRNAs and in host translation shutoff (Kamitani *et al.*, 2006). Surprisingly, despite eIF2α phosphorylation the SARS-CoV proteins are still efficiently synthesized even though coronaviral mRNAs are structurally equivalent to host mRNAs (Hilton *et al.*, 1986; Siddell *et al.*, 1981).

It is interesting to observe that despite considerable work performed in recent years, phosphorylation of eIF2α still represents one of the most intriguing problems in translational control during viral infection, since it is still not clear why the phosphorylation of eIF2 affects cellular protein synthesis without impairing translation initiation of many viral RNAs.

2. Modification of eIF4E and 4E-BP

eIF4E is believed to be the least abundant of all initiation factors and, therefore, to be a perfect target for regulation of protein synthesis. It interacts with the cap structure of mRNAs, with the scaffold protein eIF4G and with repressor proteins known as eIF4E-binding proteins (4E-BPs). eIF4E undergoes regulated phosphorylation on Ser209 mediated by the eIF4G-associated MAPK signal-integrating kinases, Mnk1 and Mnk2 (Fig. 7) (Pyronnet *et al.*, 1999; Raught and Gingras, 2007). Uninfected cells growing exponentially typically possess roughly equal amounts of phosphorylated and nonphosphorylated forms of eIF4E (Feigenblum and Schneider, 1993) and the ratio

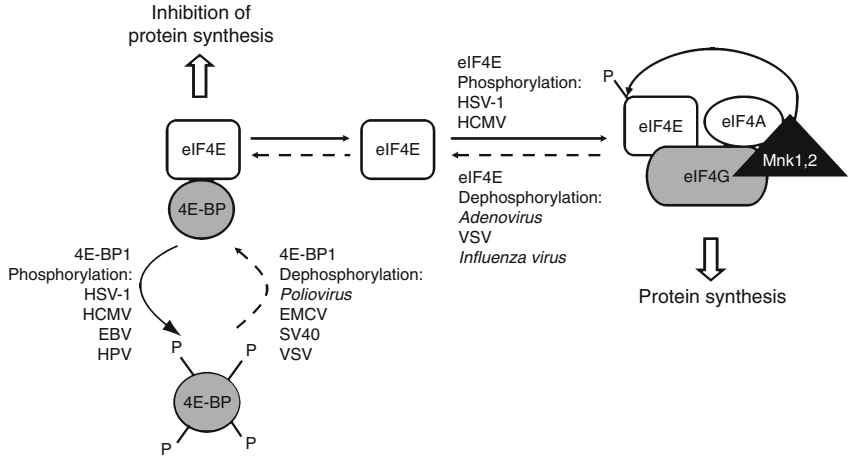


FIGURE 7 Phosphorylation and dephosphorylation of eIF4E and 4E-BP1. eIF4E+eIF4G+eIF4A form eIF4F. Other indications are as in legends of Figs. 1 and 6.

shifts toward the phosphorylated form of eIF4E following treatment of the cells with growth factors, hormones, and mitogens (Flynn and Proud, 1995; Joshi *et al.*, 1995; Makkinje *et al.*, 1995). However, the functional role of eIF4E phosphorylation remains elusive. Indeed, there is no direct link between eIF4E phosphorylation and the enhanced translation observed as a result of these stimuli, since recent studies showed that phosphorylation of eIF4E decreases the affinity of eIF4E for capped mRNA. Thus, the working hypothesis is that the nonphosphorylated form of eIF4E within the eIF4F complex (eIF4E, eIF4G, and eIF4A) binds to the cap structure on the mRNA, and that eIF4E phosphorylation accompanies initiation complex transition to elongation (reviewed in Scheper and Proud, 2002). In addition, phosphorylation could dissociate eIF4E from the cap and enable the eIF4F complex to move along the 5′ UTR and unwind the secondary structure.

4E-BP constitutes a family of translation repressors that prevent eIF4F assembly and act as negative growth regulators (Raught and Gingras, 2007). 4E-BPs are phosphoproteins, 4E-BP1 being the best studied of the three 4E-BPs known in mammals. It undergoes phosphorylation at multiple sites leading to its dissociation from eIF4E, leaving eIF4E free to bind eIF4G and to form the eIF4F complex (Fig. 7) (Lin *et al.*, 1994; Pause *et al.*, 1994). The mechanism proposed is that eIF4E possesses an eIF4G-binding site which overlaps with 4E-BP motifs; thus, 4E-BP and eIF4G binding to eIF4E would be mutually exclusive (Haghighat *et al.*, 1995; Marcotrigiano *et al.*, 1999).

a. Dephosphorylation of eIF4E and of 4E-BP1 Adenovirus (family Adenoviridae), Vesicular stomatitis virus (VSV; family Rhabdoviridae), and Influenza virus infections lead to accumulation of nonphosphorylated

eIF4E and subsequent inhibition of host protein synthesis. Adenovirus mediates the quantitative dephosphorylation of eIF4E (up to 95% of the total eIF4E) leading to suppression of cellular protein synthesis (Fig. 7) (Feigenblum and Schneider, 1993). The Adenovirus late protein designated 100K is synthesized at high levels at the onset of the late phase of infection (Bablanian and Russell, 1974; Oosterom-Dragon and Ginsberg, 1980). It interacts with the C-terminus of eIF4G (Cuesta *et al.*, 2000) and with the tripartite leader sequence of viral late mRNAs (Xi *et al.*, 2004). Binding of the 100K protein to eIF4G evicts Mnk1 from the eIF4F complex, thus impairing eIF4E phosphorylation in the initiation complex and inhibiting translation of host mRNAs (Cuesta *et al.*, 2000). On the other hand, adenoviral late mRNAs are translated efficiently via ribosome shunting (Xi et al., 2004, 2005). VSV infection causes dephosphorylation of eIF4E and 4E-BP1 thus hampering host protein synthesis (Fig. 7). The resulting changes in eIF4F do not inhibit translation of viral mRNAs, although the detailed mechanism of how VSV mRNAs that are capped and possess poly(A) tails overcome the obstacle created has not been elucidated (Connor and Lyles, 2002). Influenza virus infection results in partial (up to 70%) dephosphorylation of eIF4E and concomitant loss of eIF4F activity (Fig. 7). Thus, Influenza virus mRNAs that are capped via cap-snatching and polyadenylated (Herz *et al.*, 1981; Krug *et al.*, 1979; Luo *et al.*, 1991) are translated efficiently under conditions of partial inactivation of eIF4F (Feigenblum and Schneider, 1993) when host protein synthesis is blocked (Katze and Krug, 1990). Several studies have shown that the NS1 viral protein selectively promotes translation of viral mRNAs by increasing their rate of initiation (de la Luna *et al.*, 1995; Enami *et al.*, 1994; Katze *et al.*, 1986; Park and Katze, 1995) and interacts with PABP and eIF4GI (one of the two isoforms of eIF4G in animals) in viral mRNA translation initiation complexes (Aragón *et al.*, 2000; Burgui *et al.*, 2003). Moreover, a recent report has provided evidence that the Influenza virus RdRp substitutes for eIF4E in viral mRNA translation and binds to the translation preinitiation complex (Burgui *et al.*, 2007). One can speculate that the combination of dephosphorylation of eIF4E, hyperphosphorylation of eIF4G, and binding of RdRp to the preinitiation complex and of NS1 to eIF4GI creates an eIF4F factor more specific for Influenza virus mRNA translation.

4E-BP1 is dephosphorylated following infection with Poliovirus or EMCV (Fig. 7). This is a well-established example of viral switch from cap-dependent to IRES-mediated initiation of translation in picornavirus-infected cells (Gingras *et al.*, 1996; Svitkin *et al.*, 2005). Simian virus 40 (SV40; family Polyomaviridae) is a recent example of a virus that causes significant decrease in phosphorylation of 4E-BP1 late in lytic infection. This process is specifically mediated by the SV40 small t antigen. As in the case of Poliovirus and EMCV, dephosphorylation of 4E-BP1 and its

subsequent binding to eIF4E displaces eIF4E from the eIF4F complex. This mechanism functions as a switch in translation initiation mechanisms favoring IRES-mediated translation (Yu *et al.*, 2005). Indeed, recent studies have shown that the SV40 late 19S mRNA possesses an IRES (Yu and Alwine, 2006).

b. Phosphorylation of eIF4E and 4E-BP1 Members of the Herpesviridae family of the Alphaherpesvirinae subfamily, such as Herpes Simplex Virus 1 (HSV-1), and of the Betaherpesvirinae subfamily, such as Human cytomegalovirus (HCMV), can stimulate the assembly of eIF4F complexes in primary human cells; this is partly achieved by phosphorylation of eIF4E and 4E-BP1 early in the productive viral growth cycle (Fig. 7) (Kudchodkar *et al.*, 2006; Walsh and Mohr, 2004; Walsh *et al.*, 2005). At the same time HSV-1 infection dramatically impairs host protein synthesis (Elgadi *et al.*, 1999; Everly *et al.*, 2002; Sciabica *et al.*, 2003) whereas with HCMV the effect on host protein synthesis is weak (Stinski, 1977). Interestingly, the ratio of eIF4F over 4E-BP1 increases in cells infected with either HSV-1 or HCMV, promoting assembly of eIF4F complexes. For HSV-1 this is achieved exclusively through proteasome-mediated degradation of 4E-BP1 (Walsh and Mohr, 2004), whereas for HCMV, replication induces an increase in the overall abundance of the eIF4F components eIF4E and eIF4G, and also of PABP relative to the translational repressor 4E-BP1 (Walsh *et al.*, 2005). However, liberation of eIF4E from 4E-BP1 in the case of HSV-1 is insufficient to accelerate eIF4E incorporation into the eIF4F complex. A recent study showed that the HSV-1 ICP6 gene product binds to eIF4G promoting association of eIF4E with the N-terminus of eIF4G and facilitating eIF4E phosphorylation. This suggests a chaperone role for ICP6 in eIF4F assembly (Walsh and Mohr, 2006).

4E-BP1 is hyperphosphorylated (Fig. 7) following infection by *Epstein–Barr Virus* (EBV; family Herpesviridae, subfamily Gammaherpesvirinae) (Moody *et al.*, 2005) or Human papillomavirus (HPV; family Papillomaviridae) (Moody *et al.*, 2005; Munger *et al.*, 2004; Oh *et al.*, 2006).

3. Modification of eIF4G

a. Cleavage of eIF4G The large modular protein eIF4G serves as a docking site for initiator factors and other proteins involved in initiation of RNA translation. Due to the central role of eIF4G in translation initiation, many viruses belonging to the families Picornaviridae, Retroviridae, and Caliciviridae have evolved mechanisms to modify the function of eIF4G so as to prevent cell protein synthesis. These viruses induce cleavage of eIF4G, separating the N-terminal eIF4E-binding domain from the C-terminal eIF4A- and eIF3-binding domains (Fig. 8). As a consequence, the capacity of eIF4G to connect capped mRNAs to the 40S ribosome is abolished by the virus, inducing host translation shutoff.

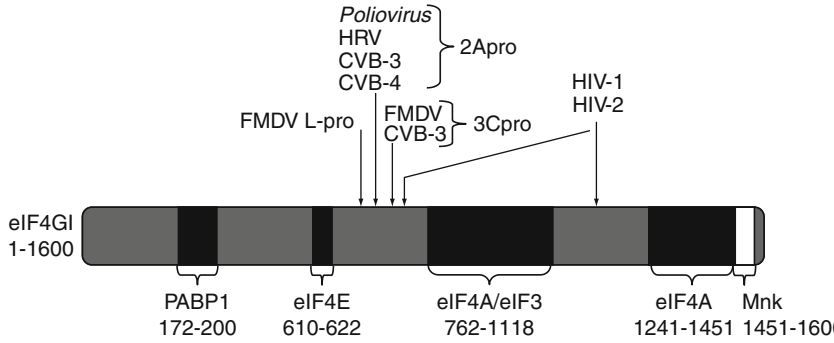


FIGURE 8 eIF4GI protein-binding sites and cleavage sites by viral proteases. Black or white rectangles represent regions of eIF4G interacting with other proteins. Numbers correspond to aa. Arrows correspond to sites of cleavage.

Host shutoff during infection by picornaviruses such as Poliovirus, HRV and human Coxsackie virus B (CVB)-3 and CVB-4 results in part from cleavage of eIF4GI by the viral 2A protease (2Apro) at aa 681/682 (Baxter *et al.*, 2006; Lamphear *et al.*, 1993; Sommergruber *et al.*, 1994; Sousa *et al.*, 2006). The Poliovirus and HRV 2Apro also cleave eIF4GII (at aa 699/670) but more slowly than cleavage of eIF4GI (Gradi *et al.*, 1998; Svitkin *et al.*, 1999). FMDV has evolved an alternate papain-like protease, L-pro in place of 2Apro to cleave both isoforms of eIF4G (Gradi *et al.*, 2004); it cleaves eIF4GI 7 aa upstream of 2Apro (Fig. 8), and eIF4GII 1 aa downstream of the 2Apro cleavage site (reviewed in Lloyd, 2006). Poliovirus infection also activates two cell proteases that cleave eIF4GI close to the 2Apro cleavage site (Zamora *et al.*, 2002). The 3Cpro of FMDV and the 2Apro and 3Cpro of CVB-3 also cleave eIF4GI (Fig. 8) (Chau *et al.*, 2007; Strong and Belsham, 2004). Degradation of eIF4GI has been observed in CD4+ cells infected with Human immunodeficiency virus 1 (HIV-1; family Retroviridae) (Ventoso *et al.*, 2001). The HIV-1 protease efficiently cleaves eIF4GI at multiple sites, but not eIF4GII (Ohlmann *et al.*, 2002). Proteases of HIV-2 and of members of the family Retroviridae (Human T-lymphotropic virus 1 (HTLV-1), Simian immunodeficiency virus, and Mouse mammary tumor virus (MMTV)) also cleave eIF4GI (Alvarez *et al.*, 2003; reviewed in Lloyd, 2006). Finally, infection of cells with FCV leads to cleavage of eIF4GI and eIF4GII and host translation shutoff (Willcocks *et al.*, 2004); the identity of the protease responsible for cleavage of eIF4G is unknown, but it could be a cellular protease activated by the infection.

b. Phosphorylation of eIF4G eIF4G is 10-fold more phosphorylated in Influenza virus-infected than in noninfected cells and phosphorylated eIF4G still interacts with eIF4A and eIF4E. Cleavage of eIF4G by the

Poliovirus 2Apro inhibits translation of the Influenza virus mRNAs (Feigenblum and Schneider, 1993; Garfinkel and Katze, 1992). Phosphorylation of eIF4G in HCMV-infected cells is one of the mechanisms that enhances eIF4F activity during the viral replication cycle (Kudchodkar *et al.*, 2004; Walsh *et al.*, 2005). eIF4G phosphorylation is induced throughout infection with SV40 (Yu *et al.*, 2005).

4. Cleavage of PABP

Certain viruses cleave the C-terminal domain of PABP thereby destroying its interactions with eIF4B, eRF3, or Paip1 (Fig. 4A). PABP is targeted for cleavage by the 2Apro and 3Cpro of Poliovirus and CVB-3 (Joachims *et al.*, 1999; Kerekatte *et al.*, 1999; Kuyumcu-Martinez et al., 2002, 2004b), by L-pro of FMDV (Rodríguez Pulido *et al.*, 2007), and by 3Cpro of HAV (Zhang *et al.*, 2007). PABP is proteolytically processed by the calicivirus 3C-like protease (Kuyumcu-Martinez *et al.*, 2004a), and HIV-1 and HIV-2 proteases are also able to cleave PABP in the absence of other viral proteins (Alvarez *et al.*, 2006). The contribution of PABP cleavage versus eIF4G cleavage in shutoff of host or viral protein synthesis has not been compared directly. Poliovirus cleavage of PABP appears to be promoted by the interaction of PABP with translation initiation factors, ribosomes or poly(A)-containing RNAs (Kuyumcu-Martinez *et al.*, 2002; Rivera and Lloyd, 2008). Processing of PABP could either occur through one of the components that provides shutoff of host translation or could favor the switch from translation to replication of viral genomes as for example PABP cleavage by 3Cpro in Poliovirus- and HAV-infected cells (Bonderoff *et al.*, 2008; Zhang *et al.*, 2007).

5. Substitution of PABP

Severe inhibition of host mRNA translation due to competition between the viral protein NSP3 and PABP for eIF4G was shown in cells infected with rotaviruses. The viral NSP3 protein binds to the conserved motif UGACC located at the 3′ end of the viral mRNA, and circularizes the mRNA via interaction with eIF4G (Fig. 4C). Since NSP3 has a higher affinity for eIF4G than does PABP, it replaces PABP and disrupts host mRNA circularization (Michel *et al.*, 2000; Vende *et al.*, 2000). NSP3–eIF4G interaction results in reduced efficiency of host mRNA translation. NSP3-mediated circularization has been reported to enhance Rotavirus mRNA translation (Vende *et al.*, 2000) and to be dispensable for translation of the viral mRNAs (Montero *et al.*, 2006). X-ray structure and biophysical studies have shown that NSP3 forms an asymmetric homodimer around the conserved motif at the 3′ end of Rotavirus mRNAs (Deo *et al.*, 2002).

6. Cleavage of PBCP2

During the mid-to-late phase of *Poliovirus* infection, PCBP2 is cleaved by the viral proteases 3C and 3CD (Fig. 4B); the cleaved protein is no longer able to bind to the IRES and initiate translation, but it binds to the 5′-terminal cloverleaf structure or simultaneously to the cloverleaf structure and to the adjacent C-rich spacer circularizing the viral genome for replication. Hence, the formation of two different closed loop structures could favor the switch from translation to replication of the *Poliovirus* genome (Gamarnik and Andino, 1998; Herold and Andino, 2001; Perera *et al.*, 2007; Toyoda *et al.*, 2007).

IV. ELONGATION OF TRANSLATION

A. Frameshift

This is the mechanism whereby during the course of peptide chain elongation, certain ribosomes shift from the original ORF (0 frame) on the mRNA by one nt, either in the 5′ direction (−1 frame) or in the 3′ direction (+1 frame), and continue protein synthesis in the new frame. This results in the synthesis of two proteins, the ''stopped'' and ''transframe'' proteins; they are identical from the N-terminus to the frameshift site but differ thereafter, and the stopped protein is always the more abundant of the two proteins (reviewed in Farabaugh, 2000). The occurrence of −1 frameshift is more frequent and has been more extensively studied than +1 frameshift. −1 Frameshift is common among (+) strand RNA viruses; it has been found in most retroviruses, in coronaviruses, L-A viruses of yeast and in several plant viruses belonging to diverse groups (Table III). Frameshift is observed during translation of RNA genomes exhibiting overlapping gene arrangements. It usually allows the expression of the viral replicase, the transframe protein in most cases harboring the polymerase or the reverse transcriptase. It has recently been reported (Chung *et al.*, 2008) that TuMV, in addition to synthesizing a large polyprotein that undergoes cleavage, also harbors a frameshift protein embedded in the P3 region of the polyprotein: frameshift leads to the expression of a protein designated P3-PIPO. PIPO is essential for infectivity of the virus, although its precise role has not been established.

Three RNA signals are important in −1 frameshifting, a slippery heptanucleotide sequence where frameshift occurs, a downstream hairpin that in many instances can additionally form a pseudoknot, and a spacer element between the slippery sequence and the hairpin structure; the length of the spacer varies between 4 and 9 nts, depending on the viral genome. The viral sequences appear to be optimized for a suitable level of stopped and transframe proteins required for viral replication rather than for maximum frameshift (Kim *et al.*, 2001).

TABLE III Viruses of eukaryotes shown or postulated to regulate elongation of translation by frameshifting

Family/genus	RNA	Type of FS	Proteins	References
Plant viruses[a]				
Carlavirus				
PVM	1	−1	CP/12K	Gramstat *et al.* (1994)
Sobemovirus				
BWYV	1	−1	66K/67K	Veidt *et al.* (1988, 1992)
CoMV	1	−1	64K/56K	Mäkinen *et al.* (1995)
Closteroviridae				
Closterovirus				
BYV	1	+1	295K/48K	Agranovsky *et al.* (1994)
CCSV	1	+1	ORF1a/b	ten Dam *et al.* (1990)
CTV	1	+1	349K/57K	Karasev *et al.* (1995)
Crinivirus				
LIYV	1	+1	217K/55K	Klaassen *et al.* (1995)
Luteoviridae				
Enamovirus				
PEMV	1	−1	84K/67K	Demler and de Zoeten (1991)
	2	−1	33K/65K	Demler *et al.* (1993)
Luteovirus				
BYDV-PAV	1	−1	39K/60K	Di *et al.* (1993)
Polerovirus				
PLRV	1	−1	70K/67K	Prüfer *et al.* (1992)
Tombusviridae				
Dianthovirus				
CRSV	1	−1	27K/54K	Kujawa *et al.* (1993) and Ryabov *et al.* (1994)
RCNMV	1	−1	27K/57K	Kim and Lommel (1994) and Xiong *et al.* (1993)
SCNMV	1	−1	27K/57K	Ge *et al.* (1993)
Animal viruses				
Pseudoviridae[b]				
Pseudovirus				
SceTy1V	1	+1	Gag/Pol	Belcourt and Farabaugh (1990) and Clare *et al.* (1988)

(*continued*)

TABLE III (*continued*)

Family/genus	RNA	Type of FS	Proteins	References
Metaviridae[b]				
Metavirus				
SceTy3V	1	+1	Gag/Pol	Hansen *et al.* (1992)
Errantivirus				
DmeGypV	1	−1	Gag/Pol	Bucheton (1995)
Retroviridae[b]				
Alpharetrovirus				
ASLV	1	−1	Pro/Pol	Arad *et al.* (1995)
Betaretrovirus				
MMTV	1	−1	Gag/Pro/Pol	Jacks *et al.* (1987)
Deltaretrovirus				
HTLV-1	1	−1	Gag/Pro/Pol	Nam *et al.* (1993)
Lentivirus				
HIV-1	1	−1	Gag/Pro	Parkin *et al.* (1992)
Totiviridae[c]				
Totivirus				
ScV-L-A	1	−1	Gag/Pol	Dinman *et al.* (1991)
Leishmaniavirus				
LRV1-1	1	+1	CP/RdRp	Stuart *et al.* (1992)
Astroviridae[a]				
Astrovirus				
HAstV	1	−1	ORF1a/ORF1b	Lewis and Matsui (1996)
Coronaviridae[a]				
Coronavirus				
IBV	1	−1	Pol1a/Pol1b	Brierley *et al.* (1987, 1989)
SARS-CoV				Plant and Dinman (2006)
Torovirus				
EqTV	1	−1	ORF1a/ORF1b	Lai and Cavanagh (1997)
Arteriviridae[a]				
Arterivirus				
EAV	1	−1	ORF1a/ORF1b	den Boon *et al.* (1991) and Napthine *et al.* (2003)

(*continued*)

TABLE III (*continued*)

Family/genus	RNA	Type of FS	Proteins	References
Unassigned virus[a]				
APV	1	−1	ORF1/ ORF2	van der Wilk *et al.* (1997)
Measles virus	1	−1	P/R	Liston and Briedis (1995)
BLV				Rice *et al.* (1985)

For each virus the genome segments that undergo frameshifting (FS), the type of FS, and the "stopped" and "transframe" proteins involved are indicated.
[a] (+) Sense single-stranded RNA viruses.
[b] Reverse-transcribing RNA viruses.
[c] dsRNA viruses.

B. Modification of elongation factors

eEF-1 is composed of eEF1A (formerly called eEF-1α) the transporter of aa-tRNAs to the A site on the ribosomes during elongation in conjunction with GTP hydrolysis, and a trimeric complex known as eEF1B (formerly called eEF-1βγδ) responsible for the regeneration of GTP from GDP on eEF-1A (Slobin and Moller, 1978). eEF-2 promotes translocation of the aa- or peptidyl-tRNA from the A to the P site on the ribosome in a GTP-dependent reaction.

Given the fact that strong evidence for deviations from the norm during elongation of protein synthesis does not seem to exist, it is not surprising that the cases of modification of elongation factors caused by viral infection appear to be virtually nonexistent. Indeed, such modifications would most likely equally affect cellular and viral protein synthesis. Nevertheless, a case of elongation factor modification has been documented during infection by viruses of the *Herpesviridae* family.

The mammalian eEF-1δ subunit of eEF1B is phosphorylated *in vitro* in the same position by the cell kinase cdc2, and hyperphosphorylated by a viral kinase conserved in all the subfamilies of the *Herpesviridae* family, such as the HSV-1 UL13 kinase, the EBV BGLF4 kinase, and the HCMV UL97 kinase (Kato *et al.*, 2001; Kawaguchi *et al.*, 1999, 2003). How phosphorylation of eEF-1δ by the viral kinases affects translation elongation remains obscure.

V. TERMINATION OF TRANSLATION

Termination of translation occurs when the ribosome encounters one of the three termination codons that defines the 3′ boundary of the ORF on the mRNA: UAG, UGA, or UAA. It involves termination codon recognition at the ribosomal A site, peptidyl-tRNA hydrolysis, and release of ribosomes from the mRNA. The participation of two proteins, the eukaryotic release factors eRF1 and eRF3, in termination codon recognition has been demonstrated (Drugeon *et al.*, 1997; Janzen *et al.*, 2002; Karamysheva *et al.*, 2003). The three termination codons are decoded by eRF1 that catalyzes ester bond hydrolysis in peptidyl-tRNA at the ribosomal peptidyl-transferase center. eRF1 functions cooperatively with the GTPase eRF3 whose activity is ribosome and eRF1 dependent (Kononenko *et al.*, 2008; Pisareva *et al.*, 2006). Final events leading to complete disassembly of the posttermination 80S ribosome require eIF1, eIF1A, and eIF3 (Pisarev *et al.*, 2007). Efficiency of termination appears to be determined by competition between eRF binding to the ribosome and alternative translational events that allow ribosomes to continue decoding. The processes that can circumvent termination codons include: ribosomal frameshift, readthrough or suppression of termination by natural cellular tRNAs, and binding of release factors.

A. Readthrough

In readthrough, a cellular aa-tRNA, called a natural suppressor, decodes the termination codon and translation continues in the same frame up to the next in-frame termination codon. Readthrough is commonly encountered in plant single-stranded RNA viruses and in some animal viruses. Table IV presents the families, genera, and viruses whose genomes have been shown or postulated to resort to readthrough. Readthrough usually allows the synthesis of the RdRp, the reverse transcriptase or of a CP-fusion protein, depending on the virus. The CP-fusion protein is present in the virus particles and is needed for encapsidation and/or for vector transmission.

Readthrough of termination codons requires the positioning of a suppressor aa-tRNA in the ribosomal A site where it competes with eRF1 for the termination codon. Two proteins are produced in the presence of a suppressor aa-tRNA that recognizes the termination codon at the 3′ end of an ORF: the expected ''stopped'' protein that terminates at the termination codon of the ORF, and the longer ''readthrough'' protein that extends to the next in-frame termination codon. The two proteins are identical over the total length of the stopped protein. Synthesis of the stopped protein is always more abundant than that of the readthrough protein.

TABLE IV Viruses shown or postulated to regulate termination of translation by readthrough

Family/genus	RNA	Termination codon	Proteins	References
Plant viruses[a]				
Benyvirus				
BNYVV	2	UAG	CP/75K	Niesbach-Klosgen *et al.* (1990) and Schmitt *et al.* (1992)
Furovirus				
SBWMV	1	UGA	150K/209K	Shirako and Wilson (1993)
	2	UGA	CP/84K	Yamamiya and Shirako (2000)
Peclovirus				
PCV	1	UGA	103K/191K	Herzog *et al.* (1994)
Pomovirus				
BVQ	1	UAA	149K/207K	Koenig *et al.* (1998)
	2	UAG	CP/54K	Koenig *et al.* (1998)
BSBV	1	UAA	145K/204K	Koenig and Loss (1997)
	2	UAG	CP/104K	Koenig *et al.* (1997)
Tobamovirus				
TMV	1	UAG	126K/183K	Ishikawa *et al.* (1986), Pelham (1978), and Skuzeski *et al.* (1991)
Tobravirus				
PEBV	1	UGA	141K/201K	MacFarlane *et al.* (1989)
TRV	1	UGA	134K/194K	Hamilton *et al.* (1987)
Tombusviridae				
Avenavirus				
OCSV	1	UAG	23K/84K	Boonham *et al.* (1995)
Carmovirus				
CarMV	1	UAG,UAG	27K/86K/98K	Guilley *et al.* (1985)
CCFV	1	UAG	28K/87K	Skotnicki *et al.* (1993)
MNSV	1	UAG	29K/89K	Riviere and Rochon (1990)
		UAG	7K/14K	Riviere and Rochon (1990)

(*continued*)

TABLE IV (*continued*)

Family/genus	RNA	Termination codon	Proteins	References
TCV	1	UAG	28K/88K	White *et al.* (1995)
Machlomovirus				
MCMV	1	UAG	50K/111K	Nutter *et al.* (1989)
		UGA	9K/33K	Nutter *et al.* (1989)
Necrovirus				
TNV	1	UAG	23K/82K	Meulewaeter *et al.* (1990)
Tombusvirus				
AMCV	1	UAG	33K/92K	Tavazza *et al.* (1994)
CNV	1	UAG	33K/92K	Rochon and Tremaine (1989)
CyRSV	1	UAG	33K/92K	Grieco *et al.* (1989)
TBSV	1	UAG	33K/92K	Hearne *et al.* (1990)
Luteoviridae				
Enamovirus				
PEMV	1	UGA	CP/55K	Demler and de Zoeten (1991)
SbDV	1	UAG	CP/80K	Rathjen *et al.* (1994)
Luteovirus				
BYDV-PAV	1	UAG	CP/72K	Dinesh-Kumar *et al.* (1992), Filichkin *et al.* (1994), Miller *et al.* (1988), and Wang *et al.* (1995)
Polerovirus				
BWYV	1	UAG	CP/74K	Brault *et al.*, 1995 and Veidt *et al.*, 1988, 1992
PLRV	1	UAG	CP/80K	Bahner *et al.* (1990) and Rohde *et al.* (1994)
Animal viruses				
Retroviridae[b]				
Gammaretrovirus				
MLV	1	UAG	Gag/Pol	Etzerodt *et al.* (1984) and Herr (1984)
Epsilonretrovirus				
WDSV	1	UAG	Gag/Pro	Holzschu *et al.* (1995)

(*continued*)

TABLE IV (*continued*)

Family/genus	RNA	Termination codon	Proteins	References
Togaviridae[a]				
Alphavirus				
SINV	1	UGA	P123/nsP4	Strauss and Strauss (1994)

For each virus, the RNA segment whose protein undergoes readthrough, the nature of the suppressible termination codon, and the designation of the stopped (indicated as CP or by its size if not the CP) and readthrough proteins (indicated by the total size of the resulting protein) are indicated. Other members of the Alphavirus genus (O'nyong-nyong virus and SFV) have CGA (Arg); one SINV strain has UGU (Cys); in all cases, the importance of a C residue 3′ of UGA, CGA, or UGU has been emphasized.
[a] (+) Sense single-stranded RNA viruses.
[b] Reverse-transcribing RNA viruses.

A well-known example of readthrough occurs in the TMV (+) single-stranded RNA genome. The 5′-proximal ORF codes for the 126K protein that contains a putative methyltransferase and a helicase domain. Readthrough of its UAG termination codon leads to the synthesis of the 183K readthrough product that harbors the highly conserved GDD (Gly-Asp-Asp) motif, responsible for replicase activity (reviewed in Beier and Grimm, 2001; Maia *et al.*, 1996).

Many members of the genus Alphavirus harbor a suppressible UGA codon separating the regions coding for the NSP3 and NSP4 proteins. The NSP4 protein shares homologous aa sequences with the RdRp of *Poliovirus* and plant RNA viruses.

In addition to the termination codon, other *cis* elements on the mRNA are required for efficient readthrough. These elements are either the sequence surrounding the termination codon preferentially on the 3′ side and/or a hairpin or pseudoknot structure also located downstream of the suppressible termination codon. In the case of TMV RNA, the nature of the two codons following the suppressible UAG codon affects the level of readthrough (Valle *et al.*, 1992). The requirements in BYDV are very different: two elements are mandatory for readthrough of the UAG codon *in vitro* and *in vivo*: a proximal and a distal element located, respectively, 6–15 nts and about 700 nts downstream of the suppressible UAG codon (Brown *et al.*, 1996). The distal element is conserved among luteoviruses and in Pea enation mosaic enamovirus (PEMV, family Luteoviridae), suggesting that it might also participate in readthrough in these viruses.

Readthrough was clearly demonstrated in mouse cells infected with Murine leukemia virus (MLV; family Retroviridae). Here, most ribosomes terminate synthesis at the UAG codon to produce the Gag protein, but when termination is suppressed, a glutamine residue from Gln-tRNA^{Gln} is incorporated at the level of the UAG codon and elongation continues to

form the Gag–Pol product. This latter protein is then cleaved to yield Gag, a protease (whose corresponding gene segment harbors the suppressed UAG codon) and the reverse transcriptase (Yoshinaka *et al.*, 1985). In retroviruses, suppression of termination is controlled by structures within the RNA itself: it requires a few specific nts immediately downstream of the termination codon, followed by a spacer region of a few nts and a hairpin that in some cases forms a pseudoknot. In MLV, suppression of the *gag* UAG codon depends on specific downstream sequences and on a pseudoknot structure (reviewed in Gale *et al.*, 2000).

B. Suppressor tRNAs

Misreading of termination codons is achieved by a variety of naturally occurring suppressor tRNAs that normally recognize a cognate codon, but at times recognize one of the termination codons by ''improper'' base pairing (reviewed in Beier and Grimm, 2001).

1. Suppressors of UAG/UAA codons

The first natural UAG suppressor tRNA identified was the cytoplasmic $tRNA^{Tyr}$ bearing a GΨA anticodon purified from tobacco leaves and *Drosophila melanogaster* (Beier *et al.*, 1984; Bienz and Kubli, 1981). Pseudouiridine (Ψ) can form a classical base pair with adenosine. The Ψ modification at the second anticodon position is necessary to read the UAG codon; it enhances the unconventional G:G interaction at the first anticodon position. Mutating the suppressible TMV UAG codon to UAA leads to virion formation in plants, implying that a tRNA recognizing the UAA codon is present in the host. It was shown that the UAA codon, if placed in the TMV context, was also recognized *in vitro* by the suppressor tobacco $tRNA^{Tyr}$. A second UAG/UAA suppressor is the cytoplasmic $tRNA^{Gln}$ with CUG or UmUG (Um is 2′-O-methyluridine) anticodons. $tRNA^{Gln}$ is present in almost all prokaryotes and eukaryotes. Interaction of the two $tRNA^{Gln}$ isoacceptors with UAG or UAA requires an unconventional G:U base pair at the third anticodon position. Probably an unmodified A in the tRNA immediately 3′ of the anticodon facilitates noncanonical base pairing. Other UAG suppressors are the cytoplasmic $tRNA^{Leu}$ with a CAA or a CAG anticodon. Here, recognition of the UAG codon requires an unusual A:A pair in the second position of both the CAA and the CAG anticodons and also a G:U pair in the third position of the CAG anticodon.

2. Suppressors of UGA codons

Two UGA suppressors, a chloroplast and a cytoplasmic $tRNA^{Trp}$ with the anticodon CmCA (Cm is 2′-*O*-methylcytidine) were isolated from tobacco plants and shown to suppress the Tobacco rattle virus (TRV; genus, Tobravirus) RNA1 UGA codon. Several reports indicate that a $tRNA^{Trp}$

with UGA suppressor activity is also present in vertebrates (Cordell *et al.*, 1980; Geller and Rich, 1980). Recognition of the UGA codon by $tRNA^{Trp}$ requires an unusual Cm:A pair in the first position of the CmCA anticodon. A $tRNA^{Cys}$ with a GCA anticodon was isolated from tobacco plants and shown to suppress the UGA in TRV RNA1. Misreading of UGA by $tRNA^{Cys}$ involves a G:A pair at the first GCA anticodon position. The two $tRNA^{Arg}$ with an U*CG (U* is 5-methoxy-carbonylmethyluridine) or ICG anticodon stimulate UGA readthrough in the context of TRV RNA1. Interaction of $tRNA^{Arg}$ with the UGA codon requires a G:U base pair at the third U*CG anticodon position.

C. Binding of release factors

The reverse transcriptase of MLV interacts with eRF1. This interaction displaces eRF3 from the release factor complex and increases synthesis of the readthrough protein. This function of the reverse transcriptase is required for appropriate levels of the readthrough and stopped proteins (Orlova *et al.*, 2003; reviewed in Goff, 2004).

Interaction between the nascent peptidyl-tRNA during translation of the 22-codon upstream ORF2 (uORF2) and eRF1 of HCMV inhibits expression of the downstream UL4 gene. The peptide product of uORF2 inhibits its own translation termination by forming a stable peptidyl-prolyl-tRNA-ribosome complex that prevents peptide release and stalls the elongating ribosome at the uORF2 termination codon (Janzen *et al.*, 2002).

VI. CONCLUSIONS

The study of the regulation of gene expression has known various phases over the decades, ever since some of its major players, such as messenger RNAs and ribosomes had been identified. It first led to examining the initiation, elongation, and termination steps of protein biosynthesis using bacterial extracts and artificial RNAs or bacteriophage RNA genomes as mRNAs, and defining the proteins involved in each step. Thereafter, the availability of cell mRNAs greatly facilitated the study of protein biosynthesis in extracts of eukaryotic cells. This revealed the vast number of protein factors involved in particular at the initiation step of protein synthesis, and the mechanism of action of these factors. In recent years, the sequencing of an ever increasing number of viral RNA genomes shown to function as mRNAs has brought a wealth of new information regarding the fundamental role played by the modulation of the structure of mRNAs in regulating gene expression. It has, for instance, led to numerous studies that consider circularization of mRNAs an important

step in promoting protein synthesis. In addition, it has also highlighted the variety of strategies developed by viruses to perturb host protein synthesis so as to favor synthesis of viral proteins. Such evasion of host protein synthesis is now leading to a variety of fascinating studies showing that this involves a complex yet balanced interplay between the host cell translation machinery, the viral mRNA, and the viral proteins resulting from expression of the viral genome. Further experiments will undoubtedly unveil other new venues in this intriguing and multifaceted aspect of cell development.

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