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Viruses have adapted a broad range of unique mechanisms to modulate the cellular translational machinery to ensure viral translation at the expense of cellular protein synthesis. Many of these promote virus-specific translation by use of molecular tags on viral mRNA such as internal ribosome entry sites (IRES) and genome-linked viral proteins (VPg) that bind translation machinery components in unusual ways and promote RNA circularization. This review describes recent advances in understanding some of the mechanisms in which animal virus mRNAs gain an advantage over cellular transcripts, including new structural and biochemical insights into IRES function and novel proteins that function as alternate met-tRNA<sub>met</sub> carriers in translation initiation. Comparisons between animal and plant virus mechanisms that promote translation of viral mRNAs are discussed.

**Introduction**

Viruses use diverse mechanisms to outcompete cellular mRNAs for translation machinery and minimal genome sizes (summarized in Table 1). This review will focus on only three of many categories of viral translation control mechanisms, thus readers are referred to a more comprehensive review of the other mechanisms [1*].

Viruses generally exploit the dependency of the host translation machinery on the m<sup>7</sup>G cap structure at the 5' end of the mRNA. The 5' cap is recognized by the eukaryotic initiation factor 4F protein complex (eIF4F; Figure 1). The 43S complex is recruited through interactions between the eIF4G moiety of eIF4F and the 40S-bound eIF3 to form the 48S preinitiation complex (Figure 1). The 40S ribosome then scans for the AUG initiator codon where the 60S ribosome subunit joins to initiate translation. Interactions between cap-bound eIF4G and the poly(A)-bound poly(A) binding protein produce a closed loop mRNP that enhances cap-dependent translation [2,3]. Although the precise explanation for mRNA circularization is unknown, it is hypothesized to increase binding affinity of eIF4F for the cap and the efficiency of ribosome recycling for subsequent translation initiation events [4–6].

Many plant and animal virus mRNAs are differentiated from host mRNAs by being uncapped, and therefore cannot recruit eIF4F by canonical means. Viruses inhibit cap-dependent translation through many mechanisms, including cleavage of translation initiation factors (reviewed in [7]). This affords virus mRNAs a competitive advantage by increasing availability of translational machinery for cap-independent translation. While many animal viruses cleave initiation factors to promote viral translation, this mechanism is not conserved in plant viruses, as a translation factor-specific protease has not been identified.

**New concepts for IRES-mediated translation initiation in animal viruses**

A lack of dependence on 5' cap structures is a major mechanism exploited by many viruses to functionally distinguish and promote virus mRNA translation. IRES elements are RNA sequence or structures that function in lieu of the cap to recruit required translation factors and ribosomal subunits to the vicinity of the start codon. Cap-independent translation using IRESs was first observed in the poliovirus (PV) and EMCV genomic RNAs, and has since been characterized in many viral and cellular mRNAs including all picornaviruses, hepatitis C virus and pestiviruses, c-myc, p53 and the yeast <i>URE2</i> IRES element [8–12]. Even DNA viruses such as Kaposi’s Sarcoma Associated Herpes Virus, Epstein-Barr Virus and Herpes simplex virus utilize IRES elements, the latter for production of thymidine kinase, which is associated with pathogenicity and drug resistance [13]. IRES RNA structures are typically situated upstream of the initiating AUG codon, however HIV and eIF4GI contain IRES elements within the open reading frame [14–16]. Animal virus IRES elements are analogous to plant virus 3' cap-independent translation enhancers (3'CITEs; reviewed in companion article), which function as bipartite pseudo-IRES elements to recruit initiation factors. A crucial feature of IRES-mediated translation allows continued or enhanced expression of virus proteins during cell stress when cap-dependent translation is repressed.

Virus IRES elements are currently grouped into classes based on their requirement for canonical translation.
initiation factors (as outlined in [17]). Type 1 and 2 IRES elements, in which type 2 lack a scanning step after ribosome binding, require several canonical initiation factors, including the C-terminus of eIF4G (a product of viral proteases) that recruits the 40S subunit via interaction with eIF3 (note similarity to cap-dependent translation; Figure 2). Type 1 IRES elements include PV and Hepatitis A Virus IRESs and Type 2 IRES elements include EMCV. Type 3 IRES elements, such as HCV, require only eIF3 and eIF2. Type 4 IRES elements like Cricket paralysis virus intergenic region (CrPV; IGR) and Plautia stali intestine virus IGR require no translation initiation factors, and bypass the need for met-tRNA<sub>met</sub> by initiating at an alanine codon [18].

In addition to canonical translation initiation factors, other proteins enhance and regulate activity of many IRES elements (IRES trans-acting factors; ITAFs). ITAFs are thought to provide chaperone function, but may play other roles that are important in overcoming translation restriction during cell stress or innate immune blockades [19]. More tightly folded IRESs are proposed to create less dependence on eIFs and ITAFs for function [20]. Consistent with this observation, structural data indicate the Type 3 (HCV) and Type 4 (CrPV) IRESs are very compact [21,22].

Though many reports catalog dependency of IRESs on ITAFs, little is known about how larger Type 1 or 2 IRESs actually interact with ribosomes and how ITAFs and canonical initiation factors contribute to activity. PCBP2 plays multifunctional and crucial roles for PV translation by binding the 5′ terminal cloverleaf structure, stemloop IV of the IRES, and also PABP on the poly(A) tail to circularize the PV RNA after PABP cleavage by a viral protease [23,24]. Interestingly, PCBP2 requires the cellular splicing factor SRp20 for function as an ITAF on PV RNA [25,26]. The precise mechanism is unknown, but SRp20 may provide a ribosome recruitment/bridging role (Figure 2). Polypyrimidine tract binding protein (PTB) augments translation of PV, and host Cat-1 and c-myc IRES elements [27–30]. PTB functions as an RNA chaperone to reorganize the PV IRES RNA structure in a manner that increases the affinity of eIF4G for the IRES element [31,32].

Recent reports indicate that diverse IRESs may interact with initiation factors and ribosomes in very similar ways. Despite a lack of sequence relatedness, both Type 1 and Type 2 viral IRESs bind eIF4GI and eIF4A in analogous regions immediately upstream of the same Yn-Xm-AUG stem loop motif (Figure 2; [33]). This induces conformational changes in RNA structure at the 3′ border of the IRES and suggests a model for both IRES types in which eIF4G binds the IRES first, and then recruits eIF4A and eIF4B that promote conformational changes to allow 43S binding at an adjacent site (Figure 2). Similarly, IRESs from diverse groups may interact with the ribosome in comparable unifying mechanisms. Small ribosome subunit protein 25 (Rps25) is a crucial interaction partner for both HCV and IGR activity [34], without which they cannot bind 40S ribosomes. Since binding of both HCV and IGR induce related conformational remodeling in the 18S RNA, it will be interesting to determine if Rps25p is involved in these conformational changes. CryoEM analysis of WT and Rps25p deleted ribosomes with IGR reveals that Rps25p interacts with IRES RNA
near the head domain of the ribosome, and together with neighboring Rps5, constitute the major binding domain on the ribosome. Though other IRES RNA loops interact with the ribosome decoding center, they do not contribute to IRES-ribosome binding affinity [35]. Finally, both the conserved HCV pseudoknot and the P-site binding domain of CrPV IGR fold into tRNA-like structures to mimic tRNA interaction with mRNA [21,22,36]. These results indicate that though IRESs are diverse, their basic mechanisms for interaction with factors and ribosomes may be quite similar.

Recently a new report on the understudied HIV IRESs indicates they may straddle Type 2 and 3 IRES classifications. A conserved core stem loop structure located in HIV-1, HIV-2 and SIV-IRESs was found to bind eIF3 and 40S ribosomes, similar to Type 3 IRESs (Figure 2). However, analysis of stalled initiation complexes on these IRESs showed they contain all canonical initiation factors except eIF4E and eIF1. The latter is surprising since eIF1 normally binds 40S subunits in conjunction with eIF5, eIF1A, and eIF3. This result suggests the HIV IRES uses pools of 40S subunits containing only eIF3 to assemble initiation complexes [37].

Use of alternative factors for initiator tRNA delivery
Animal RNA virus infection often produces double-stranded RNA and cell stress responses that activate eIF2α kinases PKR or HRI, respectively, which
phosphorylate the alpha subunit of eIF2 (reviewed in [38]) and result in repression of global translation by depleting the ternary complex (Figure 1; [39]). Some viruses evade the antiviral activation of PKR through interesting antagonistic mechanisms (reviewed in [40,41]). Viruses also encode proteins to directly deal with limited ternary complexes. For instance, Herpes simplex virus protein ICP34.5 recruits protein phosphatase P1, known to dephosphorylate eIF2α, to reactivate translation after an initial phase of inhibition [42,43]. This mechanism is recapitulated during coronavirus and African swine fever virus by Gene 7 and DP71L, respectively.
Alternatively, several viruses have evolved alternate pathways to avoid the requirement for eIF2 ternary complex binding to 40S ribosomes to support viral translation during eIF2 phosphorylation. The Dicistroviridae class of viruses (including CrPV) contain IGR IRES elements resembling tRNAs, which efficiently bind the P-site of the ribosome and promote initiation often at an alanine codon [18,46]. This circumvents the need for translation initiation using met-tRNA\textsubscript{\text{met}} since translation is initiated using elongator tRNAs.

Recent reports have emerged of a resistance strategy unique to animal viruses to cope with eIF2\textsubscript{\alpha} phosphorylation; the use of alternative proteins for initiator tRNA delivery. These include eukaryotic initiation factor 2A, a single polypeptide unrelated to the heterotrimeric complex eIF2 [47,48], Ligatin (also known as eIF2D; [49,50]), MCT1/DENR [50], and eukaryotic initiation 5B (eIF5B) (Figure 3; [51,52]). Identification of these proteins indicates a more diverse repertoire of pathways exists for translation initiation than previously thought, and highlights the need to investigate translation initiation of other viruses displaying eIF2-independent translation.

eIF2A was first identified based on its ability to direct binding of met-tRNA\textsubscript{\text{met}} with 40S ribosomal subunits in an AUG codon-dependent manner [48]. In yeast, eIF2A was shown to act as a suppressor of cap-independent initiation on the URE2, PABP and GIC1 IRES elements [53,54]. The authors hypothesized that kinetic limitations of the eIF2A-dependent pathway for met-tRNA\textsubscript{\text{met}} delivery inhibit initiation while eIF2 is active (perhaps because of overlapping binding sites on the ribosome). However, when eIF2 is inactivated, translation can still proceed on IRES-containing transcripts at a slower rate. This hypothesis has yet to be directly tested, but positions eIF2A as an important stress-responsive protein for translation of RNA viruses. Consistent with this hypothesis, eIF2A is important for ongoing Sindbis virus translation when high levels of eIF2\textsubscript{\alpha} phosphorylation are observed [55]. New data indicate that eIF2A can mediate delivery of met-tRNA\textsubscript{\text{met}} to the 40S subunit to form 48S complexes on the HCV IRES element using purified components [56]. Identification of these proteins indicates a more diverse repertoire of pathways exists for translation initiation than previously thought, and highlights the need to investigate translation initiation of other viruses displaying eIF2-independent translation.

In an attempt to further characterize the role of eIF2A, Dmitriev \textit{et al.} discovered an important role for ligatin
in 48S complex formation on the HCV IRES element (Figure 3C; [49]). Interestingly, ligatin, which they termed eIF2D, can promote 48S complex formation using phenylalanine-tRNA on the HCV IRES element when the initiating AUG is mutated to a UUU codon. This result suggests alternative initiation codons may be used to produce proteins with altered functions or half-lives. Skabkin et al. extended these findings to show Ligatin can promote formation of 48S complexes on the CSFV IRES element and the Sindbis virus 26S RNA [50]. Interestingly, the proteins MCT1 and DENR, which are homologous to the N and C-termini of ligatin, respectively, can work simultaneously to promote 48S complex formation (Figure 3C). Further work is necessary to delineate in vivo activity of ligatin in translation initiation of these viral mRNAs.

Eukaryotic initiation factor 5B is the eukaryotic homolog of bacterial initiation factor 2 (IF2; [57]). The domain architecture of mammalian eIF5B is highly reminiscent of archaeal eIF5B with the exception of a large N-terminal extension on mammalian eIF5B that may regulate met-tRNA_{i}^{met} binding (compare Figure 3A and B; [58]). Indeed, archaeal eIF5B can directly bind met-tRNA_{i}^{met}, although S. cerevisiae eIF5B has a relatively low affinity [59]. These results suggest the N-terminus of mammalian eIF5B must be removed in order for it to function as a met-tRNA_{i}^{met} carrier molecule. Consistent with this hypothesis, poliovirus 3C protease cleaves eIF5B during infection liberating the C-terminal fragment and potentiating its use in met-tRNA_{i}^{met} delivery [60]. The C-terminus is then capable of enhancing IRES-mediated translation of PV when ternary complex is depleted [52]. Interestingly, HCV and CSFV have also been shown to act in an eIF2-independent mode using eIF5B to assemble initiation complexes [51,61]. In the cases of the HCV and CSFV IRES elements, eIF5B can function in the presence of the N-terminal extension. Therefore, it will be of interest to delineate the role of the N-terminus in regulating met-tRNA_{i}^{met} delivery, and determine whether either cleavage or posttranslational modification contribute to this function during viral infection.

Although viruses differ in the route to efficient initiation of protein synthesis, many plus sense RNA viruses can employ similar strategies to enable ongoing protein synthesis during global translation inhibition by eIF2 phosphorylation. Interestingly, plant viruses do not contend with robust eIF2 phosphorylation despite the presence of PKR in plant cells [62]; these viruses clearly have a different set of parameters to enable expression of viral proteins. Perhaps activity of alternative met-tRNA_{i}^{met} delivery proteins is higher on plant virus RNAs thereby making them more competitive with ongoing cellular protein synthesis.

Long-range RNA interactions that increase translation competitiveness

Animal viruses with capped genomes or mRNAs must also compete for translational machinery, but must navigate downregulation of cap-dependent translation that is often associated with infection. Closed loop structures mediated by long range RNA:RNA kissing interactions are a common paradigm in plant viruses that have rarely been described in animal viruses. However, in animal viruses the 3′UTRs can enhance viral IRES-mediated translation, though precise mechanisms are lacking [63–70].

One example of the influence of the 3′UTR on translation of a 5′ capped, non-polyadenylated animal virus is observed in the Dengue virus (DEN) mRNA. Two conserved dumbbell-shaped RNA structures within the 3′ UTR not only form local pseudoknots important for RNA replication, but also work cooperatively to stimulate translation [71]. DEN can switch from cap-dependent to a non-canonical cap-independent translation mode when eIF2-4E is limiting. The mechanism does not involve an IRES, but requires a closed loop [72]. The details of this mechanism are unclear but probably involves RNA:RNA hybridization through the cyclization sequence (CS) and the upstream AUG region (UAR) [73,74]. PABP may stimulate translation by enhancing closed loop formation by binding the 3′UTR [74] and eIF4F simultaneously, despite the lack of a poly(A) tail. The dumbbell structures in the 3′ UTR may also help to recruit trans-acting or initiation factors to stimulate translation. The 3′UTR of DEN mRNA has been demonstrated to interact with typical ITAFs PTB, La, and YB-1 [75–77], which could function to enhance DEN translation in a manner similar to their influence in IRES-mediated translation. Overall, the RNA elements in the DEN 3′ UTR may function similarly to many plant viruses with 3′ UTR CITEs (see companion review in this issue) to stimulate translation when eIF4E becomes limited from stress or innate immunity activation. It will be important to further elucidate host factors that interact with the sequences in the 3′ UTR and identify their precise mechanisms of translational regulation.

Long range RNA kissing interactions have also been described for HCV, where the RNA domain 5BSL3.2 within the 3′ region of the NS5B ORF base pairs with a portion of the HCV IRES. Unlike DEN, this RNA:RNA interaction downregulates HCV IRES translation and may play a role in directing viral RNA to switch from translation to RNA replication [78]. Further, PCBP2, which functions as an ITAF in PV translation, binds both HCV 5′ and 3′ UTR. Electron microscopy demonstrated that PCBP2, probably via dimerization, converted RNA from linear to circular forms. Interaction of PCBP2 with HCV replicons
stimulated translation, perhaps via formation of closed loops, though the mechanism was not determined [79]. These results indicate that HCV circularization modulates translation in multiple, possibly temporal ways.

Long range RNA interactions linking the 5’ and 3’ UTRs have otherwise only been described in the FMDV viral RNA [80]. Despite a known importance for the 3’UTR of FMDV in stimulating IRES-mediated translation [68], the functional relevance of this interaction is only speculative. More studies dedicated to understanding the functional relevance of interactions between the 5’ and 3’ UTRs, or possibly 3’ coding regions, of animal viruses may highlight important roles in recruiting translation factors, similar to the paradigm in plant CITEs. Studies of plant RNA virus translation systems may identify additional, noncanonical proteins that are important for efficient competition with cellular mRNAs for the translational machinery.

**Perspectives and future directions**

Animal and plant viruses have evolved cunning mechanisms to ensure competition with cellular mRNAs for the translation machinery. IRESs share key functions with the 3’ CITEs prevalent in plant virus systems, including the emerging theme of tRNA mimicry; however, no animal virus has yet been found with a 3’ CITE. This is despite the recurring animal virus theme of 5’-3’ closed loop mRNA structures that in principle could allow ribosome recruitment to 3’ structures in spatial proximity to nearby 5’ initiator codons. The principle of complex recruitment to one end of the RNA and transfer to the other end exists in enteroviruses, where the negative strand RNA replication complex assembles on a 5’ cloverleaf structure that, within a closed loop, positions the replicase near the 3’ end of the template to initiate replication on the other end of the template (reviewed in [81,82]). It is unclear whether this paradigm exists for translation in animal cells, but it may partly emerge with further study of flaviviruses such as DEN. Avoidance of innate immunity and stress responses could explain the sharp divergence between plant and animal systems regarding these responses and how viruses must adapt. This is highlighted in the novel responses to stress inhibition of translation where animal viruses employ different cellular proteins to deliver met-tRNA<sub>met</sub> to the ribosome. The differences between plant and animal virus translation, and translation of cellular mRNAs indicate that themes are paralleled between the mRNA templates with slight variations to account for organism-specific translational regulation. Additional mechanistic insights could be gained if more attention is devoted towards bridging common translational control mechanisms in the animal and plant virus kingdoms.

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**References and recommended reading**

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Lopez-Lastra M, Ramdohr P, Letelier A, Vallejos M, Vera-Otara J, Valiente-Echeverria F: Translation initiation of viral mRNAs. Rev Med Virol 2010, 20:177-195.

2. Galile DR: A tale of two termini: a functional interaction between the termini of an mRNA is a prerequisite for efficient translation initiation. Gene 1998, 216:1-11.

3. Mazumder B, Sheshadi V, Fox PL: Translational control by the 3’-UTR: the ends specify the means. Trends Biochem Sci 2003, 28:91-98.

4. Amrani N, Ghosh S, Mangus DA, Jacobson A: Translation factors promote the formation of two states of the closed-loop mRNP. Nature 2008, 453:1276-1280.

5. Bonderoff JM, Lloyd RE: Time-dependent increase in ribosome processivity. Nucleic Acids Res 2010, 38:7054-7067.

6. Kahvejian A, Svitkin YV, Sukarieh R, M'Boutchou MN, Sonenberg N: Mammalian poly(A)-binding protein is a eukaryotic translation initiation factor, which acts via multiple mechanisms. Genes Dev 2005, 19:104-113.

7. Lloyd RE: Translational control by viral proteinases. Virus Res 2006, 119:76-88.

8. Jang SK, Krausslich HG, Nicklin MJ, Duke GM, Palmenberg AC, Wimmer E: A segment of the 5’ nontranslated region of encephalomyocarditis virus RNA directs internal entry of ribosomes during in vitro translation. J Virol 1988, 62:2636-2643.

9. Komar AA, Lesnik T, Cullin C, Merrick WC, Trachsel H, Altmann M: Internal initiation drives the synthesis of Ure2 protein lacking the prion domain and affects [URE3] propagation in yeast cells. EMBO J 2003, 22:1199-1209.

10. Nanbru C, Lafon I, Audigier S, Gensac MC, Vagner S, Huez G, Prats AC: Alternative translation of the proto-oncogene c-myc by an internal ribosome entry site. J Biol Chem 1997, 272:32061-32066.

11. Pelletier J, Sonenberg N: Internal initiation of translation of eukaryotic mRNA directed by a sequence derived from poliovirus RNA. Nature 1988, 334:320-325.

12. Stonely M, Paulin FE, Le Quesne JP, Chappell SA, Willis AE: C-Myc 5’ untranslated region contains an internal ribosome entry segment. Oncogene 1998, 16:423-428.

13. Griffiths A, Coen DM: An unusual internal ribosome entry site in the herpes simplex virus thymidine kinase gene. Proc Natl Acad Sci USA 2005, 102:9667-9672.

14. Byrd MP, Zamora M, Lloyd RE: Translation of eukaryotic translation initiation factor 4GI (eIF4GI) proceeds from multiple mRNAs containing a novel cap-dependent internal ribosome entry site (IRES) that is active during poliovirus infection. J Biol Chem 2005, 280:18610-18622.

15. Herbreteau CH, Weill L, Decimo D, Prevost D, Darlix JL, Sargueil B, Ohlmann T: HIV-2 genomic RNA contains a novel type of IRES located downstream of its initiation codon. Nat Struct Mol Biol 2005, 12:1001-1007.

16. Weill L, James L, Ulryck N, Chamond N, Herbreteau CH, Ohlmann T, Sargueil B: A new type of IRES within gag coding region recruits three initiation complexes on HIV-2 genomic RNA. Nucleic Acids Res 2010, 38:1367-1381.
17. Hellen CU: IRES-induced conformational changes in the ribosome and the mechanism of translation initiation by internal ribosomal entry. *Biochim Biophys Acta* 2009, 1789:558-570.

18. Hertz MI, Thompson SR: Mechanism of translation initiation by Dicistroviridae IGR IRESs. *Virology* 2011, 411:355-361.

19. Komar AA, Hatzoglou M: Cellular IRES-mediated translation: the war of IF1As in pathophysiological states. *Cell Cycle* 2011, 10:229-240.

20. Filbin ME, Kieft JS: Toward a structural understanding of IRES RNA function. *Curr Opin Struct Biol* 2009, 19:267-276.

21. Lavender CA, Ding F, Dokholyan NV, Weeks KM: Robust and generic RNA modeling using inferred constraints: a structure for the hepatitis C virus IRES pseudoknot domain. *Biochemistry* 2010, 49:4931-4933.

Computer modeling of the pseudoknot domain of HCV predicts RNA-like molecular mimicry.

22. Zhu J, Korostelev A, Costantino DA, Donohue JP, Noller HF, Kieft JS: Crystal structures of complexes containing domains from two viral internal ribosome entry site (IRES) RNAs bound to the 70S ribosome. *Proc Natl Acad Sci USA* 2011, 108:1839-1844.

X-ray crystallography of IGR IRES elements bound to the 70S ribosome resemble tRNA:ribosome interactions.

23. Herold J, Andino R: Poliovirus RNA replication requires genome circularization through a protein-protein bridge. *Mol Cell* 2001, 7:581-591.

24. Sean P, Nguyen JH, Semler BL: Computer modeling of the pseudoknot domain of HCV predicts RNA-like molecular mimicry.

25. Bedard KM, Daijogo S, Semler BL: A nucleo-cytoplasmic SR protein functions in viral IRES-mediated translation initiation. *EMBO J* 2007, 26:459-467.

26. Fitzgerald KD, Semler BL: Re-localization of cellular protein SRp20 during poliovirus infection: bridging a viral IRES to the host cell translation apparatus. *PLoS Pathog* 2011, 7:e1002127.

27. Cobbold LC, Spriggs KA, Haines SJ, Dobbny HC, Hayes C, de Moor CH, Lilley KS, Bushell M, Willis AE: Identification of internal ribosome entry segment (IRES)-trans-acting factors for the Myc family of IRESs. *Mol Cell Biol* 2008, 28:40-49.

28. Cobbold LC, Wilson LA, Sawicka K, King HA, Kondrashov AV, Spriggs KA, Bushell M, Willis AE: Upregulated c-myc expression in multiple myeloma by internal ribosome entry results from increased interactions with and expression of PTB-1 and YB-1. *Oncogene* 2010, 29:2884-2891.

29. Hellen CU, Witherell GW, Schmid M, Shin SH, Pestova TV, Gil A, Wimmer E: A cytoplasmic 57-kDa protein that is required for translation of picornavirus RNA by internal ribosomal entry is the cytoplasmic 57-kDa protein that is required for translation of picornavirus RNA by internal ribosomal entry. *Cell Biol* 2005, 328:589-605.

30. Li Y, Zhang C, Chen X, Yu J, Wang Y, Yang Y, Du M, Jin H, Ma Y, He B et al.: ICP34.5 of herpes simplex virus facilitates the initiation of protein translation by bridging eIF2(alpha) and eIF-2B. *J Biol Chem* 2011, 286:24785-24792.

31. Verpoorten D, Feng Z, Vaiyi-Nagy T, Ma Y, Jin H, Yan Z, Zhang C, Cao Y, He B: Dephosphorylation of eIF2alpha mediated by the gamma34.5 protein of herpes simplex virus 1 facilitates viral neuroinvasion. *J Virol* 2009, 83:12625-12630.

32. Cruz JL, Sola I, Becares M, Alberca B, Plana J, Enjuanes L, Zumiga S: Coronavirus gene 7 counteracts host defenses and modulates virus virulence. *PLoS Pathog* 2011, 7:e1002090.

33. Zhang F, Moon A, Childs K, Goodbourn S, Dixon LK: The African swine fever virus DP71L protein recruits the protein translation catalyst subunit to dephosphorylate eIF2alpha and inhibits CHOP induction but is dispensable for these activities during virus infection. *J Virol* 2010, 84:10681-10689.

34. Hertz MI, Thompson SR: In vivo functional analysis of the Dicistroviridae intergenic region internal ribosome entry sites. *Nucleic Acids Res* 2011, 39:7276-7288.

35. Adams SL, Safer B, Anderson WF, Merrick WC: Eukaryotic initiation complex formation. Evidence for two distinct pathways. *J Biol Chem* 1975, 250:9083-9089.

36. Merrick WC, Anderson WF: Purification and characterization of homogeneous protein synthesis initiation factor M1 from rabbit reticulocytes. *J Biol Chem* 1975, 250:1197-1206.

37. Dmitriev SE, Terenin IM, Andreev DE, Ivanov PA, Dunaevsky JE, Skabkin MA, Skabkina OV, Dhote V, Komar AA, Hellen CU, Pestova TV: Activities of Ligatin and MCT-1/DERN in eukaryotic translation initiation and ribosomal recycling. *Genes Dev* 2010, 24:1787-1801.

Role for Ligatin and MCT1/DERN in delivery of initiator tRNA to HCV-like IRES elements and SV 26S mRNA.

38. Terekhov IM, Dmitriev SE, Andreev DE, Skabtsov IN: Eukaryotic translation initiation machinery can operate in a bacterial-like mode without eIF2. *Nat Struct Mol Biol* 2008, 15:836-841.

39. White JP, Reineke LC, Lloyd RE: Poliovirus switches to an eIF2-independent mode of translation during infection. *J Virol* 2011, 85:8884-8893.
53. Komar AA, Gross SR, Barth-Baus D, Strachan R, Hensold JO, Goos Kinny T, Merrick WC: Novel characteristics of the biological properties of the yeast Saccharomyces cerevisiae eukaryotic initiation factor 2A. J Biol Chem 2005, 280:15601-15611.

54. Reineke LC, Merrick WC: Characterization of the functional role of nucleotides within the URE2 IRES element and the requirements for eIF2A-mediated repression. RNA 2009, 15:2264-2277.

55. Ventoso I, Sanz MA, Molina S, Berlanga JJ, Carrasco L, Esteban M: Translational resistance of late alphavirus mRNA to eIF2alpha phosphorylation: a strategy to overcome the antiviral effect of protein kinase PKR. Genes Dev 2006, 20:87-100.

56. Kim JH, Park SM, Park JH, Keum SJ, Jang SK: eIF2A mediates translation of hepatitis C viral mRNA under stress conditions. EMBO J 2011, 30:2454-2464.

57. Lee JH, Choi SK, Roll-Mecak A, Burley SK, Dever TE: Universal conservation in translation initiation revealed by human and archaeal homologs of bacterial translation initiation factor IF2. Proc Natl Acad Sci USA 1999, 96:6342-6347.

58. Dever TE, Roll-Mecak A, Choi SK, Lee JH, Cao C, Shin BS, Burley SK: Universal translation subsequent to the initiation phase is eIF2-alpha-dependent and eIF2-independent modes of initiation on the CSFV IRES: a common role of domain II. EMBO J 2008, 27:1060-1072.

59. Guillorn L, Schmitt E, Blanquet S, Meculham Y: Initiator tRNA binding by eIF5B, the eukaryotic/archaeal homologue of bacterial initiation factor IF2. Biochemistry 2005, 44:15994-15961.

60. de Breyne S, Bonderoff JM, Chumakov KM, Lloyd RE, Hellen CU: Cleavage of eukaryotic initiator eIF5B by enterovirus 3C protease. Virology 2008, 378:118-122.

61. Pestova TV, de Breyne S, Pisarev AV, Abaeva IS, Hellen CU: eIF2-dependent and eIF2-independent modes of initiation on the non-polyadenylated 3' untranslated region of the dengue virus type 2 RNA that modulate translation and replication. J Biol Chem 2011, 286:22521-22534.

62. Edgil D, Polacek C, Harris E: Dengue virus utilizes a novel strategy for translation initiation when cap-dependent translation is inhibited. J Virol 2006, 80:2976-2986.

63. Alvarez DE, Filomatori CV, Gamarnik AV: Functional analysis of dengue virus cyclization sequences located at the 5' and 3'UTRs. Virology 2008, 375:223-235.

64. Polacek C, Friebe P, Harris E: Poly(A)-binding protein binds to the non-polyadenylated 3' untranslated region of dengue virus and modulates translation efficiency. J Gen Virol 2009, 90:687-692.

65. Lubian W, van Kuppeveld FJ, Melchers WJ: The structure-function relationship of the enterovirus 3'UTR. Virus Res 2009, 139:209-216.

66. Schwartz S, Felber BK, Fenyi EM, Pavlakis GN: Env and Vpu proteins of human immunodeficiency virus type 1 are produced from multiple bicistronic mRNAs. J Virol 1990, 64:5448-5456.

67. Zoll J, Heus HA, van Kuppeveld FJ, Melchers WJ: The structure-function relationship of the enterovirus 3'UTR. Virus Res 2009, 139:209-216.

68. Schaefer SR, Mackenzie JM, Pekosz A: The ORF7b protein of severe acute respiratory syndrome coronavirus (SARS-CoV) is expressed in virus-infected cells and incorporated into SARS-CoV particles. J Virol 2007, 81:718-731.

69. Horvath CM, Williams MA, Lamb RA: Eukaryotic coupled translation of tandem cistrons: identification of the influenza B virus BM2 polypeptide. EMBO J 1990, 9:2639-2647.
87. Ahmadian G, Randhawa JS, Easton AJ: Expression of the ORF-2 protein of the human respiratory syncytial virus M2 gene is initiated by a ribosomal termination-dependent reinitiation mechanism. EMBO J 2000, 19:2681-2689.

88. Napthine S, Lever RA, Powell ML, Jackson RJ, Brown TD, Brierley I: Expression of the VP2 protein of murine norovirus by a translation termination-reinitiation strategy. PLoS ONE 2008, 4:e8390.

89. Yueh A, Schneider RJ: Selective translation initiation by ribosome jumping in adenovirus-infected and heat-shocked cells. Genes Dev 1996, 10:1557-1567.

90. Yueh A, Schneider RJ: Translation by ribosome shunting on adenovirus and hsp70 mRNAs facilitated by complementarity to 18S rRNA. Genes Dev 2000, 14:414-421.

91. Sen N, Cao F, Tavis JE: Translation of duck hepatitis B virus reverse transcriptase by ribosomal shunting. J Virol 2004, 78:11751-11757.

92. Racine T, Duncan R: Facilitated leaky scanning and atypical ribosome shunting direct downstream translation initiation on the tricistronic S1 mRNA of avian reovirus. Nucleic Acids Res 2010, 38:7260-7272.

93. Latorre P, Kolakofsky D, Curran J: Sendai virus Y proteins are initiated by a ribosomal shunt. Mol Cell Biol 1998, 18:5021-5031.

94. Fraser CS, Doudna JA: Structural and mechanistic insights into hepatitis C viral translation initiation. Nat Rev Microbiol 2007, 5:29-38.

95. Hellen CU, Pestova TV: Translation of hepatitis C virus RNA. J Viral Hepat 1999, 6:79-87.

96. Lukavsky PJ: Structure and function of HCV IRES domains. Virus Res 2009, 139:166-171.

97. Fletcher SP, Jackson RJ: Pestivirus internal ribosome entry site (IRES) structure and function: elements in the 5' untranslated region important for IRES function. J Virol 2002, 76:5024-5033.

98. Buck CB, Shen X, Egan MA, Pierson TC, Walker CM, Siliciano RF: The human immunodeficiency virus type 1 gag gene encodes an internal ribosome entry site. J Virol 2001, 75:181-191.

99. Low W, Harries M, Ye H, Du MQ, Boshoff C, Collins M: Internal ribosome entry site regulates translation of Kaposi's sarcoma-associated herpesvirus FLICE inhibitory protein. J Virol 2001, 75:2938-2945.

100. Firth AE, Chung BY, Fletton MN, Atkins JF: Discovery of frameshifting in Alphavirus 6K resolves a 20-year enigma. Virol J 2008, 5:108.

101. Baranov PV, Henderson CM, Anderson CB, Gesteland RF, Atkins JF, Howard MT: Programmed ribosomal frameshifting in decoding the SARS-CoV genome. Virology 2005, 332:498-510.

102. Park SJ, Kim YG, Park HJ: Identification of RNA pseudoknot-binding ligand that inhibits the -1 ribosomal frameshifting of SARS-coronavirus by structure-based virtual screening. J Am Chem Soc 2011, 133:10094-10100.

103. Mazauric MH, Seol Y, Yoshizawa S, Visscher K, Fourmy D: Interaction of the HIV-1 frameshift signal with the ribosome. Nucleic Acids Res 2009, 37:7654-7664.

104. Lewis TL, Matsui SM: An astrovirus frameshift signal induces ribosomal frameshifting in vitro. Arch Virol 1995, 140:1127-1135.

105. Lewis TL, Matsui SM: Astrovirus ribosomal frameshifting in an infection-transfection transient expression system. J Virol 1996, 70:2869-2875.

106. Daughenbaugh KF, Fraser CS, Hershey JW, Hardy ME: The genome-linked protein VPg of the Norwalk virus binds eIF3, suggesting its role in translation initiation complex recruitment. EMBO J 2003, 22:2852-2859.

107. Daughenbaugh KF, Wobus CE, Hardy ME: VPg of murine norovirus binds translation initiation factors in infected cells. Virol J 2006, 3:33.

108. Goodfellow I, Chaudhry Y, Gioldasi I, Gerondopoulos A, Natoni A, Labrie L, Laliberte JF, Roberts L: Calicivirus translation initiation requires an interaction between VPg and eIF 4 E. EMBO Rep 2005, 6:968-972.

109. Merrick WC: Cap-dependent and cap-independent translation in eukaryotic systems. Gene 2004, 332:1-11.

110. Easton LE, Locker N, Lukavsky PJ: Conserved functional domains and a novel tertiary interaction near the pseudoknot drive translational activity of hepatitis C virus and hepatitis C virus-like internal ribosome entry sites. Nucleic Acids Res 2009, 37:5537-5549.

111. Odreman-Macchioli FE, Tisminetzky SG, Zotti M, Baralle FE: Identification of RNA pseudoknot folding on the binding of cellular factors to the HCV IRES. Nucleic Acids Res 2000, 28:875-885.

112. Sizova DV, Kolupaeva VG, Pestova TV, Shatsky IN, Hellen CU: Specific interaction of eukaryotic translation initiation factor 3 with the 5' nontranslated regions of hepatitis C virus and classical swine fever virus RNAs. J Virol 1998, 72:4775-4782.