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# One for all? A viral protein supplants the mRNA cap-binding complex

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**Modulation of the host cell's translational machinery is a crucial part of viral infection strategies. Well-characterised mechanisms that aid viruses in manipulating translational activity include, for example, internal ribosomal entry sites, which allow viral RNA translation in the absence of some or many of the canonical host translation factors. New research shows that the nucleocapsid protein from a species of *Hantavirus* can replace several host cell translation factors in *in vitro* translation reactions, suggesting that hantaviruses may have evolved a novel strategy for modulating host cell translation in the form of a multifunctional translation factor.**

Cellular translation is an intricate and complicated process. Ribosomes need to bind to mRNAs with the correct frequency, they need to locate the correct start codon, then decode the mRNA using the right balance of speed and accuracy, and stop translation and release the nascent polypeptide when they encounter a termination codon. During normal cellular translation, the interplay of all of these processes is regulated by a complex repertoire of translation factors.

Translation of the majority of eukaryotic cellular mRNAs is dependent on the presence of a specific modification at their 5′-end, the $m^7G$ cap structure. Cap-dependent translation relies on a specific subset of translation factors termed the cap-binding complex (reviewed in Kapp and Lorsch, 2004; von der Haar *et al*, 2004; Sonenberg and Hinnebusch, 2007). The eIF4E subunit of this complex binds to the cap structure, and tethers another subunit, eIF4G, to the mRNA 5′-end. eIF4G has at least two specific roles in cap-dependent translation, namely the recruitment of the RNA helicase activity provided by eIF4A, which removes secondary structure from the site of attachment of the small ribosomal subunit; and the recruitment of the small ribosomal subunit itself, which occurs through contacts between eIF4G and other, small ribosomal subunit-associated translation factors.

During viral infection, the expression of viral genes is also achieved through the translational machinery of the host cell. Shut down of normal cellular translation is consequently one of the first cellular defence mechanisms against viral infection. Viruses have evolved many different tools that enable them to maintain translation of their own RNA despite attempts of the cell to shut down translation, and despite the competition of cellular mRNAs for access to the translational machinery. Although these tools differ between different viruses, most of them are built on a common principle: they involve the replacement of cellular translation factors with purpose-built viral factors that are efficient translational activators, and that are also usually highly selective for the viral RNA (Figure 1).

The currently best understood of these tools are the viral internal ribosomal entry sites (IRESs), in particular those from the Picornaviridae family (for a recent review, see e.g. Martinez-Salas *et al*, 2008). IRESs are secondary RNA structures that act *in cis*, mediating recruitment of ribosomal subunits by virtue of their three-dimensional structure. The actual mechanism of recruitment differs greatly between different viral families, and may involve direct contacts between the IRES and ribosome without involvement of any initiation factors as in the case of the Dicistroviridae intergenic IRESs, or may be mediated by subsets of translation factors that are also involved in ribosome recruitment during normal cap-dependent translation. Other viruses employ less well-

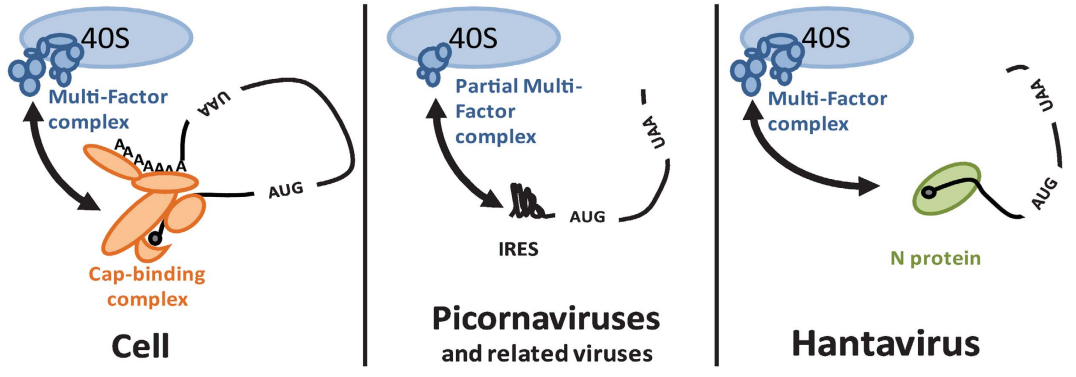


**Figure 1** Translation strategies for cellular and viral mRNAs. During normal cellular translation, ribosome recruitment is achieved through contacts between the cap-binding complex and the small ribosomal subunit-associated multifactor complex. Many viruses rely on internal ribosomal entry sites (IRESs) to maintain translation using only a subset of the normal translation factor complement. Hantaviruses appear to employ a novel strategy, which relies on a viral multifunctional translation factor (N protein), which replaces all or part of the cellular cap-binding complex.

 

understood mechanisms for hijacking the host cell translational machinery. For example, some plant viruses covalently link a translational regulator protein to the 5′-end of their RNA, whereas yet other viruses utilise 5′-poly(A) sequences for the recruitment of ribosomes.

Mir and Panganiban (2008) now show that at least one virus from the *Hantavirus* genus possesses a novel, previously unknown tool that may enable it to modify the host translational machinery. Hantaviruses comprise different members that generate high lethality rates when they infect humans, including among others the Hantaan virus (a cause of haemorrhagic fever) and the *Sin Nombre* virus (a cause of cardiopulmonary syndrome). The authors of this study demonstrate that recombinantly expressed nucleocapsid or N protein from the *Sin Nombre* virus binds to mRNA cap structures *in vitro*, and also interacts with initiation-competent small ribosomal subunits. *Hantavirus* N thus shows two of the biochemical activities normally associated with the cellular translation initiation factors eIF4E and eIF4G. Moreover, N can functionally replace these otherwise essential factors in *in vitro* translation reactions, and it can further replace the essential helicase activity provided by eIF4A. When added to *in vitro* translation reactions that contain normal complements of all cellular translation factors, N shows a general stimulatory activity on cap-dependent translation, with preferential stimulation of RNAs containing viral sequences at their 5′-end. These latter observations may explain the biological role of N during viral infection, as it may be part of an over-ride mechanism that can maintain translational activity despite the cellular attempts to shut down the translational apparatus.

The apparent multiple translation-related functions of N are all the more surprising as this protein has already been associated with other functions in the viral life cycle, including viral RNA encapsulation and genome replication. How a protein of just 48 kDa in size can perform these many roles is a question that remains to be answered in future work.

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