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Translational control by viral proteinases

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Abstract

Most RNA viruses have evolved strategies to regulate cellular translation in order to promote preferential expression of the viral genome. Positive strand RNA viruses express large portions, or all of their proteome via translation of large polyproteins that are processed by embedded viral proteinases or host proteinases. Several of these viral proteinases are known to interact with host proteins, particularly with the host translation machinery, and thus, encompass the dual functions of processing of viral polyproteins and exerting translation control. Picornaviruses are perhaps the best characterized in regards to interaction of their proteinases with the host translation machinery and will be emphasized here. However, new findings have shown that similar paradigms exist in other viral systems which will be discussed.
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1. Brief overview cap-dependent translation initiation

Translation can be divided into the three phases of initiation, elongation and termination. Most translation regulation mechanisms regulate the initiation phase, including viral regulation schemes, thus, initiation will be emphasized here. Most cellular mRNAs are translated by mechanisms that are dependent on the 5′ cap structure. De novo initiation of typical mRNA requires recognition of the 5′ m7GpppN cap structure by the trimeric translation factor complex eIF4F, and subsequent recruitment of a 43S ribosomal subunit (containing a 40S ribosomal subunit, eukaryotic initiation factors (eIFs) eIF1, eIF1a, eIF2, eIF5, eIF3 and Met-tRNAi^{Met}) and other initiation factors to form a 48S ribosomal preinitiation complex. The 48S complex is functional for scanning the mRNA sequence in a 5′–3′ direction for initiation codons in a favorable consensus sequence. There is no clear evidence that the cap structure is released by eIF4E during the scanning process, although it is often depicted this way (see Fig. 3). The initiation phase of translation is completed when the 60S ribosomal subunit has joined, and then the 80S ribosome completes the translation of the mRNA. For recent reviews on this complex topic, see (Gebauer and Hentze, 2004; Gingras et al., 1999; Merrick, 2004; Preiss and Hentze, 2003; Rogers et al., 2002; Schneider and Mohr, 2003). Note that for clarity, only initiation factors that play a role in viral proteinase-mediated translation regulation mechanisms are discussed further below.

eIF4F is a heterotrimeric complex consisting of eIF4G, eIF4E and eIF4A and can be isolated as a salt-stable complex from mammalian cells. eIF4G is a multivalent scaffolding protein that contains binding domains for cap-binding protein eIF4E and the prototype DEAD-box helicase eIF4A. eIF4G also contains binding sites for poly(A)-binding protein (PABP) and MNK-1 kinase (Fig. 1). eIF4F is also associated with eIF4B, which interacts with eIF4A in RNA unwinding assays but may not be required for cap-binding functions (Grifo et al., 1984; Ray et al., 1985; Rozen et al., 1990). There are two major forms of eIF4G, termed eIF4GI and eIF4GII that share only 46% homology but are highly conserved in key regions that bind other translation factors (Gradi et al., 1998a). eIF4GI is the dominant form in HeLa cells, comprising approximately 90% of total eIF4GI (Marissen and Lloyd, 1998). Further, a complex translation initiation scheme involving alternate initiation codon selection at five AUGs and alternate splicing produces a set of five isoforms of eIF4GI that vary at the N-terminus. The smallest isoform lacks the PABP-binding site (Byrd et al., 2002, 2005).

The primary function of eIF4F is to facilitate binding of 40S ribosomal subunits to the 5′ cap structure of mRNA and then aid ribosomal scanning. Because eIF4G can simultaneously bind all these initiation factors, it performs two critical linking or bridging functions. First, eIF4G-mediated linkage of eIF3 (which is bound to 40S ribosomal subunits), and eIF4E, completes a molecular bridge which binds the mRNA to the

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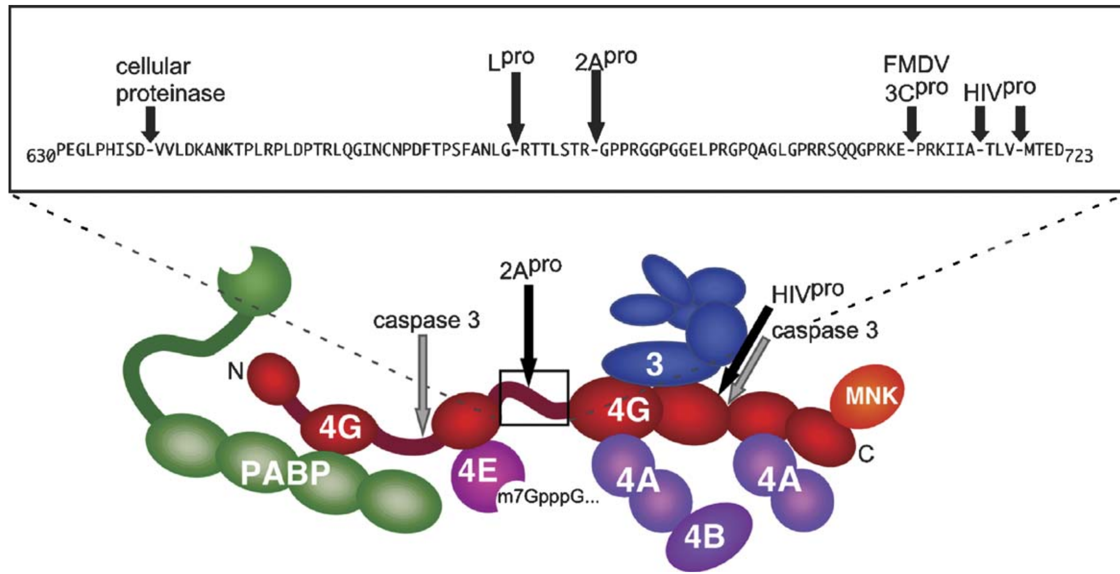

Fig. 1. Schematic illustrating scaffolding protein eIF4GI (and eIF4GII) (shown in red) as an extended structure bearing a series of binding domains for other translation factors PABP, eIF4E, eIF4A (two sites), eIF3 and mnk-1. The NH2 and COOH-termini of eIF4G are shown. The locations of known protease cleavage sites are depicted with arrows. A central region of eIF4G linking eIF4E- and eIF3-binding domains has been expanded in the box to illustrate locations of individual proteinase cleavage sites.

ribosome (Fig. 3A). Second, eIF4G-mediated linkage of PABP and eIF4E simultaneously provides a second molecular bridge linking 5′ and 3′ ends of the mRNA in a pseudo-circularized structure (Wells et al., 1998). Thus, eIF4G is in many ways the centerpiece of the translation initiation complex. Therefore, it is not surprising that many viruses have evolved mechanisms to modify eIF4G functions in their bid to control cellular translation. Several non-proteolytic translation regulation mechanisms involving eIF4GI are detailed in other chapters herein. This chapter reviews only mechanisms involving cleavage of eIF4G and other factors.

2. IRES-mediated cap-independent translation

Picornavirus RNA does not contain a cap structure to aid ribosome binding. To compensate for this, the 5′ untranslated region (5′ UTR) contains a large RNA structure called an internal ribosome entry sequence (IRES) that recruits ribosomes to bind to internal sites in the RNA. IRES structures have been found in a wide range of virus and cellular mRNAs and are quite variable in sequence and structure. The mechanism of ribosome binding by HCV and picornavirus IRESs are best understood and they involve variable subsets of the canonical initiation factors, depending on the IRES. In addition, certain RNA-binding proteins such as La, PTB, UNR and PCBP2 have been described that stimulate the functional activity of certain IRES elements in biochemical assays (Bedard et al., 2004; Blyn et al., 1996, 1997; Boussadia et al., 2003; Costa-Mattioli et al., 2004; Hellen et al., 1993; Hunt et al., 1999; Meerovitch et al., 1989, 1993). Such IRES-transactivating factors (ITAFs) are thought to play a role in the selective pathogenesis and variable replication of several picornaviruses in different cell types and tissues (Pilipenko et al., 2000, 2001).

3. 5′–3′ interactions in translation and ribosome recycling

Poly(A)-binding protein (PABP) binds the poly(A) tail on mRNA via four conserved RNA-recognition motifs (RRMs) and contains a highly conserved C-terminal domain (CTD) linked by a proline-rich domain. Like eIF4GI, PABP also binds a large number of proteins, including eIF4G, eIF4B, translation termination factor eRF3, and three regulatory proteins, UNR, and PABP-interacting proteins 1 and 2 (Paip1 and Paip2) (Fig. 2) (Bushell et al., 2001; Chang et al., 2004; Imataka et al., 1997, 1998; Khaleghpour et al., 2001; Kozlov et al., 2004; Roy et al., 2002). The interaction between eIF4E/eIF4G and PABP is sufficient to circularize the mRNA, and provides the

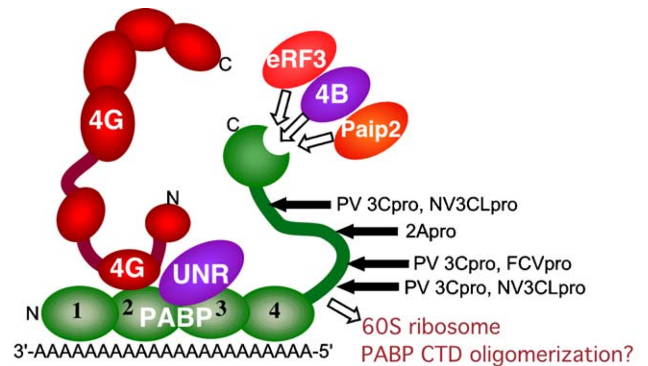

Fig. 2. Schematic illustrating PABP (shown in green) with its multiple binding partners. The structure of PABP is illustrated with four numbered RRM domains that interact with RNA, a flexible proline-rich linking domain and a structured COOH-terminal domain that contains a binding cleft for eRF3, eIF4B and PAIP2. RRMs 2 and 3 interact with eIF4G and UNR. A region near RRM 4 interacts with 60S ribosomal subunits in yeast and may be involved in PABP oligomerization. The location of viral proteinase cleavage sites is indicated. Other binding sites for PAIP1 and PAIP2 are not shown for clarity.

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