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Review

Structure and functions of the translation initiation factor eIF4E and its role in cancer development and treatment

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ABSTRACT

In eukaryotic cells, protein synthesis is a complex and multi-step process that has several mechanisms to start the translation including cap-dependent and cap-independent initiation. The translation control of eukaryotic gene expression occurs principally at the initiation step. In this context, it is critical that the eukaryotic translation initiation factor eIF4E bind to the 7-methylguanosine (m7G) cap present at the 5′-UTRs of most eukaryotic mRNAs. Combined with other initiation factors, eIF4E mediates the mRNA recruitment on ribosomes to start the translation. Moreover, the eIF4E nuclear bodies are involved in the export of specific mRNAs from the nucleus to the cytoplasm. In this review, we focus on the eIF4E structure and its physiological functions, and describe the role of eIF4E in cancer development and progression and the current therapeutic strategies to target eIF4E.

Introduction

The majority of eukaryotic mRNAs are translated through a mechanism that is dependent on the presence of a 7-methylguanosine (m7G) cap structure located at their 5′ end. This translation pathway is called a “cap-dependent” translation (Marintchev and Wagner, 2004; Sonenberg and Hinnesbusch, 2009; Aitken and Lorsch, 2012; Hinnebusch, 2014). All translation steps including initiation, elongation, termination and ribosome recycling are regulated, especially the rate-limiting initiation step (Sonenberg and Hinnesbusch, 2009; Jackson et al., 2010). The binding between the mRNA and the 43S pre-initiation complex (43S PIC) is crucial to start the translation. The assembly of the 43S PIC requires the ternary complex eIF2-GTP-Met-tRNAi, several eukaryotic initiation factors (eIFs) including eIF1, eIF1A, eIF3 and eIF5, and the 40S small ribosomal subunit (Hinnebusch, 2014). Additionally, the mRNA activation requires the eIF4F complex consisting of the cap-binding protein eIF4E, the DEAD (Asp-Glu-Ala-Asp)-box helicase eIF4A, and the “scaffold” protein eIF4G. eIF4E binds the mRNA cap structure; eIF4A is needed to unwind the secondary structures present in the near region of the 5′ end of mRNA; the interaction of eIF4G with eIF4E and poly(A)-binding proteins (PABPs) that also involves both ends of the mRNA is required to assemble a circular “closer-loop” mRNA-protein complex (Wells et al., 1998; Kaye et al., 2009; Yanagiya et al., 2009; Park et al., 2011). Moreover, the interaction of eIF4G with eIF3 and eIF1 is fundamental in facilitating the attachment of the 43S PIC to the 5′ end of mRNA (Yanagiya et al., 2009; Park et al., 2011). It was also observed that there was a significant increase of eIF4A helicase activity when eIF4G interacted with eIF4A (Rogers et al., 2001; Oberer et al., 2005; Rozovsky et al., 2008; Marintchev et al., 2009; Özeş et al., 2011; Parsyan et al., 2011; Marintchev, 2013). Following the mRNA binding, the 43S PIC searches for a start codon and starts moving along the mRNA 5′-UTR in a 5′-to-3′ direction. This process is called “scanning” and requires the ATP hydrolysis, and the 43S PIC switches the “open” conformation to a “closed” one during this scanning process (Aitken and Lorsch, 2012; Hinnebusch, 2014). The unwinding of secondary structures in the mRNA 5′-UTR is mediated not only by the eIF4A but also by other helicases such as DED1 (ATP-dependent DEAD-box RNA helicase) in yeast and DHX29 (DExH-box helicase 29) in mammals (Chuang et al., 1997; Berthelot et al., 2004; Pisareva et al., 2008; Hilliker et al., 2011). The initiation codon recognition by the anticodon of Met-tRNAi leads to arrest of the scanning (Cigan et al., 1988). Although generally, the translation begins on the nearest AUG codon of the 5′ end of the mRNA, many mammalian mRNAs used a downstream AUG codon as the translation start site. This scanning process is called “leaky scanning” (Kozak, 2002; Wang and Rothnagel, 2004;

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Elfakess et al., 2011). After scanning arrest, the 60S subunit joining leads to the formation of the 80S ribosomal complex, which is now ready to move to the elongation step (Hinnebusch, 2014).

Unlike the majority of eukaryotic mRNAs that are translated in a cap-dependent manner, other mRNAs are translated through a different mechanism called a "cap-independent" translation. These mRNAs do not require the m7G cap, since they have structural elements called internal ribosome entry sites (IRES). The IRES elements mediate the direct ribosome recruitment and, consequently, the translation initiation occurs in the absence of the cap (Jackson et al., 2010; Komar et al., 2012; Thompson, 2012; Jackson, 2013). In addition to the IRES that mediates the non-canonical translation, there are other mRNA *cis*-acting regulators present at the 5′ leader sequence of specific mRNAs. Among these are the upstream open reading frames (uORFs). The uORFs are localized upstream of the main AUG. The translation control driven by uORFs is associated with a reduction in protein synthesis (Morris and Geballe, 2000; Calvo et al., 2009). Often, the ribosome scanning translates the uORF; when the uORF translation is completed, the dissociation of both ribosomal subunits occurs and the main ORF is not translated. In this way, a small peptide is synthesized. The uORF termination codon may be recognized as a premature codon by the nonsense-mediated mRNA decay (NMD) pathway, resulting in degradation of mRNAs. Contrarily, the translation of a very short uORF retains the ribosome small subunit linked to mRNA. In this context, the scanning process continues until the main start codon is reached, resulting in translation of mRNAs (Meijer and Thomas, 2002; Pöyry et al., 2004).

eIF4E: features and biological roles

Structure and classification of eIF4E

eIF4E is a protein that plays an important role in the translation initiation. Indeed, eIF4E binds the m7G cap structure at the 5′ end of most eukaryotic mRNAs, and along with other initiation factors, it mediates the recruitment of the mRNA on the 40S ribosomal subunit to start the translation (Rhoads, 2009).

The three-dimensional structure of eIF4E was characterized in different organisms, such as yeast, wheat, mouse and human (Marcotrigiano et al., 1997; Matsuo et al., 1997; Tomoo et al., 2002; Monzingo et al., 2007; Borden, 2016). This structure consists of eight antiparallel β-strands with three α-helices on the dorsal surface (Marcotrigiano et al., 1997; Matsuo et al., 1997; Tomoo et al., 2002; Monzingo et al., 2007). Two major binding sites are present on the eIF4E structure: the cap-binding site and the dorsal surface (Fig. 1) (Borden, 2016). The interaction between the eIF4E and the cap is primarily determined by the formation of cation-π bond stacking between the 7-methylguanine and the two conserved tryptophan residues located within the cap-binding pocket of eIF4E (Trp-56 and Trp-102 in human eIF4E-1). The hydrogen bonds between a conserved glutamate residue (Glu-103 in human eIF4E-1) and the N1 and N2 protons of 7-methylguanine further stabilize the interaction (Tomoo et al., 2002; Kubacka et al., 2015). The dorsal surface of eIF4E shows an invariant hydrophobic/acidic portion and is responsible for the binding of eIF4E partner proteins, including eIF4G and 4E-BPs (eIF4E-binding proteins; see below) (Marcotrigiano et al., 1999). Several studies have indicated the presence of the consensus eIF4E-binding motif YXXXXLΦ (where X is any amino acid and Φ is a hydrophobic amino acid residue) in eIF4G and 4E-BPs, which allows for the binding of eIF4G and 4E-BPs with eIF4E (Marcotrigiano et al., 1999). Moreover, the interaction of eIF4E with the eIF4G involves Trp-43 and Trp-73 in human eIF4E-1 (Joshi et al., 2005). Because eIF4G and 4E-BPs bind to the same site of eIF4E, their interaction is mutually exclusive (Gingras et al., 2004).

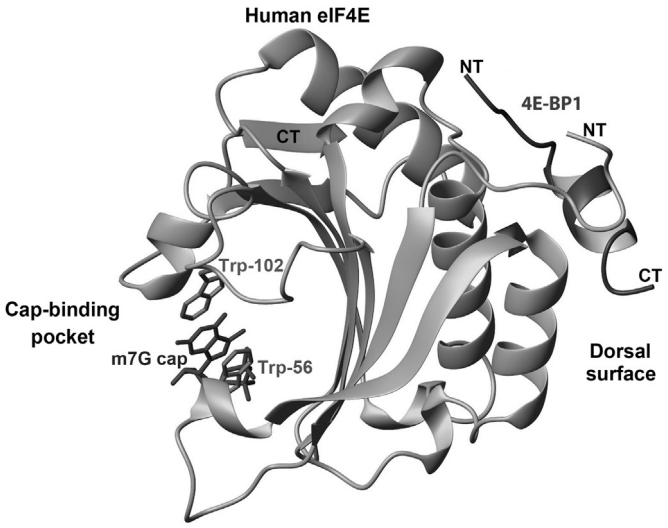

Fig. 1. The structure of human eIF4E. Three-dimensional structure of human eIF4E is characterized by eight antiparallel β-strands and three α-helices. The interaction of eIF4E with the cap structure happens in the cap-binding pocket, whereas the binding with the protein partners eIF4G and 4E-BPs occurs on the dorsal surface of eIF4E. CT, C-terminus; NT, N-terminus. This structure is adapted from Osborne and Borden (2015).

Previous study of affinity chromatography reported that eIF4E is a single 25-kDa polypeptide in mammals (Sonenberg et al., 1979). However, this result was refuted by the Ravel laboratory's discovery of two forms of eIF4E, at least in wheat germ (Browning et al., 1987). Subsequent studies confirmed the presence of multiple members of the eIF4E family in different organisms, including *Arabidopsis thaliana* (Ruud et al., 1998), *Caenorhabditis elegans* (Jankowska-Anyszka et al., 1998), *Homo sapiens* (Rom et al., 1998), and other mammals. In humans, the *EIF4E* gene is located on chromosome 4 and encodes the eIF4E-1 factor; alternative splicing of this gene results in multiple transcript variants. The *EIF4E2* gene, a paralog of *EIF4E*, is present on chromosome 2 and encodes eIF4E-2 (GeneBank: https://www.ncbi.nlm.nih.gov/gene/?term=human+eIF4E2). The *EIF4E3* gene, another paralog of *EIF4E,* is located on chromosome 3 and encodes eIF4E-3 (GeneBank: https://www.ncbi.nlm.nih.gov/gene/?term=human+eIF4E1). The eIF4E family members were grouped into three classes by Joshi et al. (2005) based on the correspondence of the amino acid residues to Trp-43 and Trp-56 of human eIF4E-1. Class I members maintain Trp residues at positions equivalent to Trp-43 and Trp-56; in class II members including eIF4E-homologous protein (4EHP), Trp residues are substituted by Tyr/Phe/Leu and Tyr/Phe at positions equivalent to Trp-43 and Trp-56, respectively; in class III members, a Trp residue is maintained at the position relevant to Trp-43, while the Trp residue relevant to Trp-56 is substituted by a Cys residue. Evolutionarily, not all members of the eIF4E family bind to the same ligands. For example, the ligands of mammalian class I member eIF4E-1 are the cap, eIF4G and 4E-BPs (see below); the mammalian class II member eIF4E-2 interacts only with the cap and the 4E-BPs; the mammalian class III member eIF4E-3 only binds to the cap and eIF4G (Joshi et al., 2004).

eIF4E: nuclear export of mRNAs and other functions

The studies leading to the characterization of eIF4E also allowed the determination of its nuclear localization in spherical bodies in the order of micron diameter (Fig. 2). The number of eIF4E spherical bodies is about 10 per nucleus. Additionally, eIF4E may also have a

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