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Review

Role of translation initiation factor 4G in lifespan regulation and age-related health

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ABSTRACT

Inhibiting expression of eukaryotic translation initiation factor 4G (eIF4G) arrests normal development but extends lifespan when suppressed during adulthood. In addition to reducing overall translation, inhibition alters the stoichiometry of mRNA translation in favor of genes important for responding to stress and against those associated with growth and reproduction in *C. elegans*. In humans, aberrant expression of eIF4G is associated with certain forms of cancer and neurodegeneration. Here we review what is known about the roles of eIF4G in molecular, cellular, and organismal contexts. Also discussed are the gaps in understanding of this factor, particularly with regard to the roles of specific forms of expression in individual tissues and the importance of understanding eIF4G for development of potential therapeutic applications.

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1. Introduction

While the functional importance of many translation factors is known in a general sense, more appreciation is being given to their role in determining which mRNAs are given preference for translation, both spatially and temporally, under different conditions. Regulating gene expression at the level of translation acts as an important point of control for diverse processes including growth, cellular differentiation, programmed cell death, and for responding to environmental changes. Most of this control is exerted during the steps immediately preceding peptide synthesis, called translation initiation, which is usually the rate-limiting step of mRNA translation (Hershey et al., 2012).

Some of the interest in the specificity of mRNAs selected for translation has undoubtedly been generated by studies carried out in animal models showing that altering expression of translation factors and machinery can increase lifespan (Chen et al., 2007; Chiocchetti et al., 2007; Curran and Ruvkun, 2007; Hansen et al., 2007; Henderson et al., 2006; Pan et al., 2007; Steffen et al., 2008; Syntichaki et al., 2007). Reducing eukaryotic translation initiation factor 4G (eIF4G) in yeast (Smith et al., 2008) and during adulthood in nematodes (Curran and Ruvkun, 2007; Hansen et al., 2007; Henderson et al., 2006; Pan et al., 2007) leads to a robust increase

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in lifespan. In mammals, elevated expression of eIF4G is associated with cancer. However, regular eIF4G expression is essential early in life for a normal rate of growth. In addition, diminished levels under certain conditions may lead to neurodegeneration. Here, we briefly review the general role of eIF4G in translation initiation and then discuss what is known about the functional importance of the timing, tissue-specificity, and form (homolog, splice variant, or cleavage product) of this factor, especially with regard to lifespan determination and age-related disease.

1.1. eIF4G and translation initiation

Regulation of protein synthesis is essential during organismal development and for responding to environmental input. Translation involves an intricate three stage process of initiation, elongation, and termination. Although translation is subject to regulation at each stage, the rate-limiting step is usually initiation, which centers on recruitment of ribosomal subunits to mature mRNA (Hershey et al., 2012). Translation initiation involves protein-RNA and protein-protein interactions synchronized by multiple translation initiation factors. eIF4G acts as a major hub in initiation and mediates recruitment of additional initiation factors, providing a scaffold for ribosome/mRNA-bridging (Sonenberg et al., 1978).mRNA is co-transcriptionally modified by the addition of a methyl-guanosine (m7GpppX) on the 5′ end, which protects the mRNA from exonuclease activity (Izaurralde et al., 1992) and serves to recruit factors important for initiating translation (Muthukrishnan et al., 1975). The methyl-guanosine addition to the transcript is called the "5′ cap" and translation predominately occurs as a cap-dependent process. Although capped-mRNA is favored for protein synthesis, translation can occur in a cap-independent process that relies on alternate mRNA features (Svitkin et al., 2005). eIF4G plays a crucial role in both processes.

In cap-dependent translation, the cap-binding protein eIF4E binds to eIF4G, which further enhances the affinity of eIF4E for the cap (Haghighat and Sonenberg, 1997). eIF4G also helps recruit the mRNA helicase eIF4A. Together, these three factors make up eIF4F, also known as the cap-binding complex. Through this complex, eIF4G bridges the 5′ untranslated region (UTR) with the polyadenylated 3′ UTR via polyA binding protein (PABP). Association of PABP with eIF4G induces mRNA circularization so that eIF4E at the 5′ cap links with the PABP and the 3′ tail (Tarun Jr and Sachs, 1996). Circularization of mRNA enhances initiation and mRNA stability (Gallie, 1991).

Once the cap-binding complex has bound and circularized the mRNA, eIF4G then helps mediate recruitment of the 40S ribosomal subunit to the mRNA through its association with ribosomal binding protein eIF3 (Lamphear et al., 1995). Prior to this recruitment, the 40S ribosomal subunit associates with eIF3, mRNA scanning proteins eIF1A and eIF1, and the ternary complex, composed of eIF2, GTP, and the methionyl-tRNA initiator (met-tRNAi), together forming the 43S pre-initiation complex (Marchione et al., 2013). eIF3 affixes the 43S pre-initiation complex onto the mRNA, assisted through eIF4G and eIF4E interactions (Etchison et al., 1982; Magnuson et al., 2012). The joined mRNA, pre-initiation complex, and eIF4F complex comprise the 48S pre-initiation complex. The 48S pre-initiation complex scans the 5′ UTR and migrates in a 5′–3′ fashion assisted by the selectivity of eIF1A and eIF1 for the start codon. Upon identification of the start codon, eIF5 triggers initiation by stimulating eIF2 hydrolysis of the ternary complex GTP and then detachment of all 40S-bound initiation factors (Unbehaun et al., 2004). Hydrolysis of GTP from the ternary complex triggers dissociation of initiation factors in the 48S pre-initiation complex and positions met-tRNAi into the P-site on the 40S ribosomal subunit associated with the start codon (Unbehaun et al., 2004). Ribosomal protein S6 within the 40S subunit is phosphorylated by S6 kinase, promoting the joining of both the 40S and 60S subunits, and formation of the 80S ribosome (Jefferies et al., 1994; Magnuson et al., 2012). Successful assembly of the ribosome completes initiation and protein synthesis begins, leaving eIF4G and other initiation factors available to begin a new round of translation initiation.

Cap-independent translation may take place if an internal ribosomal entry site (IRES) is present within the 5′ UTR of the mRNA (Pelletier and Sonenberg, 1988). However, capped mRNAs compete for translation against IRES-containing mRNAs (Svitkin et al., 2005). In the presence of an IRES, eIF4G is capable of initiating translation in the absence of a functional 5′ cap-binding complex (Ali et al., 2001), as is the case when eIF4E is sequestered by eIF4E Binding Protein 1 (4EBP1). When available eIF4E becomes limited, the sub-complex eIF4G/4A is able to bind to IRES-containing mRNAs to mediate translation (Svitkin et al., 2005). If eIF4G is unable to bind eIF4A, then IRES directed translation is abrogated (Lomakin et al., 2000). Therefore eIF4G plays an important role in both cap-dependent and cap-independent mediated translation.

2. Biological effects of eIF4G at the level of tissues and the whole organism

eIF4G was first characterized through a mammalian *in vitro* lysate experiment testing 5′ cap-binding during mRNA translation (Sonenberg et al., 1978). Further testing determined that removing eIF4G from this *in vitro* translation system effectively hinders initiation complex formation, thereby preventing protein synthesis (Ali et al., 2001). *In vivo*, eIF4G is essential, as studies in yeast and nematodes demonstrate that absence of expression results in developmental arrest and lethality (Contreras et al., 2008; Goyer et al., 1993). However, reducing its expression after development can increase lifespan, while overexpression is associated with malignant transformation of cells. In addition to modulation by transcription, there are homologs, isoforms, and cleavage products of eIF4G that alter the rate of translation and type of mRNA species that are translated. The following subsections address the timing, form, and tissue-specific effects of eIF4G expression in the context of development, longevity, response to stress, and age-associated pathology.

2.1. Importance of eIF4G during and after development and in response to stress

Expression of eIF4G is crucial during organismal development. Complete knockout of eIF4G in the yeast *Saccharomyces cerevisiae* is lethal (Goyer et al., 1993). A strain bearing a null mutation in the *C. elegans* eIF4G gene, *ifg-1* (ok1211), must be maintained as a heterozygote, as animals homozygous for the knockout mutation cannot develop past the second larval stage of development (Contreras et al., 2008). Subsequently, knock-down of eIF4G via RNAi feeding in *C. elegans* late in larval development diminishes fecundity and arrests growth in the subsequent generation (Long et al., 2002; Pan et al., 2007). RNAi knock-down is also associated with enlarged vesicle formation in the intestinal cells of offspring which is accompanied with severe intestinal atrophy (Long et al., 2002). Loss of function mutants exhibit increased apoptosis in germ cells concomitant with a shift in mRNA translation that reinforces the apoptotic cascade (Contreras et al., 2011). Thus, eIF4G removal or suppression is associated with negative development and growth of offspring.

In contrast to the deleterious effects of inhibiting eIF4G during development in *C. elegans*, multiple studies have concluded that reduced expression during adulthood leads to a significant lifespan extension (Curran and Ruvkun, 2007; Hansen et al., 2007;