Mechanism and regulation of translation in *C. elegans**

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Abstract

***C. elegans* represents a favorable system to study the extraordinarily complicated process of eukaryotic protein synthesis, which involves over 100 RNAs and over 200 polypeptides just for the core machinery. Initial research in protein synthesis relied on fractionated mammalian and plant systems, but in the mid-1970s, the powerful genetics of *Saccharomyces cerevisiae* began to yield new insights for translation in all**

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eukaryotes. *C. elegans* has many features of higher eukaryotes that are not shared by yeast. This allows protein synthesis researchers to combine biochemistry, cell biology, developmental biology, genetics, and genomics to study regulation of gene expression at the translational level. Most components of the core translational machinery have been identified in *C. elegans*, including rRNAs, 5S RNA, tRNAs, ribosomal proteins, and aminoacyl tRNA synthetases. *C. elegans* has amino acid sequence homologs for 56 of the known initiation, elongation, and release factor polypeptides, but few of these have been isolated, functionally identified, or studied at the biochemical level. Similarly, *C. elegans* has homologs for 22 components of the major signal transduction pathways implicated in control of protein synthesis. The translational efficiency of individual mRNAs relies on *cis*-regulatory elements that include either a 7-methylguanosine- or 2,2,7-trimethylguanosine-containing cap, the 5'-terminal spliced leader, sequence elements in the 3'-untranslated regions, and the 3'-terminal poly(A) tract. Several key developmental pathways in *C. elegans* are predominantly governed by translational mechanisms. Some evidence has been presented that well described regulatory mechanisms in other organisms, including covalent modification of translation factors, sequestration of translation factors, and mRNA-specific changes in poly(A) length, also occur in *C. elegans*. The most interesting unexplored questions may involve changes in the translation of individual mRNAs during development, in response to physiological changes, or after genetic manipulations. Given the highly developed state of *C. elegans* genomics, it can be expected that future application of computational tools, including data visualization, will help detect new instances of translational control.

1. Introduction

Although "gene expression" is often used synonymously with "transcription", the steady-state levels of proteins in eukaryotic cells are also strongly dependent on translational regulatory mechanisms. Two very different types of translational control occur: global and mRNA-specific. Global control generally involves alterations in the levels, intrinsic activities, or availability of translation factors, whereas mRNA-specific control involves proteins or RNAs that interact with a subset of mRNAs. The overall rate of protein synthesis as well as the translational efficiencies of individual mRNAs are regulated in response to nutritional, hormonal, cellular stress, and developmental signals (Sonenberg et al., 2000).

C. elegans represents an especially favorable system to study the extraordinarily complicated process of eukaryotic protein synthesis, which involves over 100 RNAs and over 200 polypeptides just for the core machinery. The first decades of research in eukaryotic protein synthesis relied on fractionated mammalian and plant systems, with little or no input of genetics. This began to change in the 1970's when the powerful genetics of *Saccharomyces cerevisiae* was brought to bear on central questions in protein synthesis. From this research came important new insights for translation in all eukaryotes, including discovery of the initiation codon scanning mechanism (Sherman and Stewart, 1975), new protein synthesis factors and regulatory kinases (Hinnebusch, 1997), previously unknown interactions among initiation factors (Asano et al., 2000), the core structure of eIF3, the most complex of the initiation factors (Phan et al., 1998), and new regulatory pathways for the control of protein synthesis (Hinnebusch and Fink, 1983). *C. elegans*, however, has many features of higher eukaryotes that are *not* shared by yeast, *e.g.*, tissues, organs, muscles, a nervous system, developmental stages, cell lineages, *etc*., which involve processes regulated at the translational level. Furthermore, signaling pathways leading to protein synthesis are considerably more similar between *C. elegans* and humans than between yeast and humans. Thus, *C. elegans* allows protein synthesis researchers to combine biochemistry, cell biology, genetics, and genomics to understand fundamental questions about the regulation of gene expression at the translational level.

2. The Translational machinery

2.1. Mechanism of translation in eukaryotes

From studies in mammals, yeasts, and plants, it is known that the three steps of protein synthesis are catalyzed by three groups of proteins: initiation, elongation, and release factors (Hershey and Merrick, 2000). A different class of initiation factors (eIF1, eIF2, etc.) catalyzes each step of initiation (Figure 1). [A uniform nomenclature system for translation factors is used here (Clark et al., 1996)]. A ternary complex of eIF2•GTP•Met-tRNA$_i$ binds to the 40S ribosomal subunit to form the 43S initiation complex. Recruitment of mRNA to the 43S initiation complex to form the 48S initiation complex requires eIF3, the poly(A)-binding protein (PABP), and the eIF4 proteins. eIF3 is a ~800-kDa multimer that is also required for Met-tRNA$_i$ binding to the 40S subunit (molecular masses refer to the mammalian factors). PABP is a 70-kDa protein that specifically binds poly(A) and homo-oligomerizes. The eIF4 factors consist of: eIF4A, a 46-kDa RNA helicase; eIF4B, a 70-kDa RNA-binding and RNA-annealing protein;

eIF4H, a 25-kDa protein that acts with eIF4B to stimulate eIF4A helicase activity; eIF4E, a 25-kDa cap-binding protein; and eIF4G, a 185-kDa protein that specifically binds to and co-localizes all of the other proteins involved in mRNA recruitment on the 40S subunit.

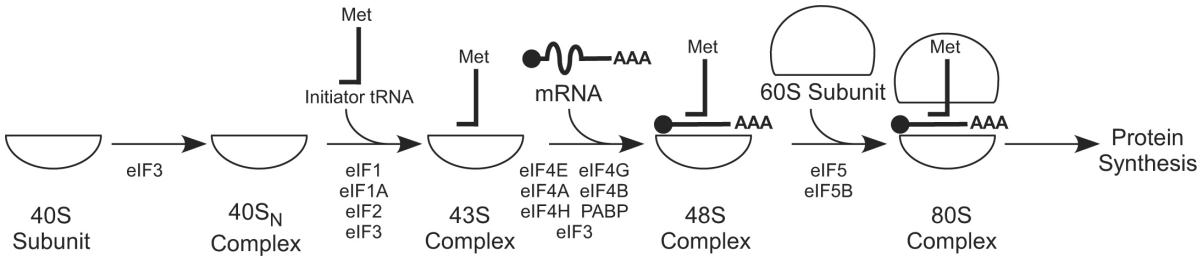

Figure 1. Complexes formed and factors participating in the initiation of protein synthesis.

The 48S complex consists of the eIF4 factors plus PABP, eIF1, eIF1A, eIF3, eIF5, and the eIF2•GTP•Met-tRNA$_i$ ternary complex bound to the 40S subunit (Figure 2). It scans until the first AUG in good sequence context is encountered. Scanning requires ATP hydrolysis by eIF4A and the presence of eIF1 and eIF1A. Then eIF5 and eIF5B stimulate GTP hydrolysis by eIF2, followed by 60S joining to form the 80S complex. The released eIF2•GDP is recycled to eIF2•GTP by the guanine nucleotide exchange factor eIF2B. The first elongator aminoacyl-tRNA is brought to the ribosomal A-site by eEF1, after which the first peptide bond is formed. This is followed by a cycle of GTP hydrolysis and exchange. Translocation is catalyzed by eEF2 with another cycle of GTP hydrolysis and exchange. When the ribosome reaches a termination codon, the release factor eRF1 catalyzes termination, and then the GTPase eRF3 ejects eRF1 from the ribosome.

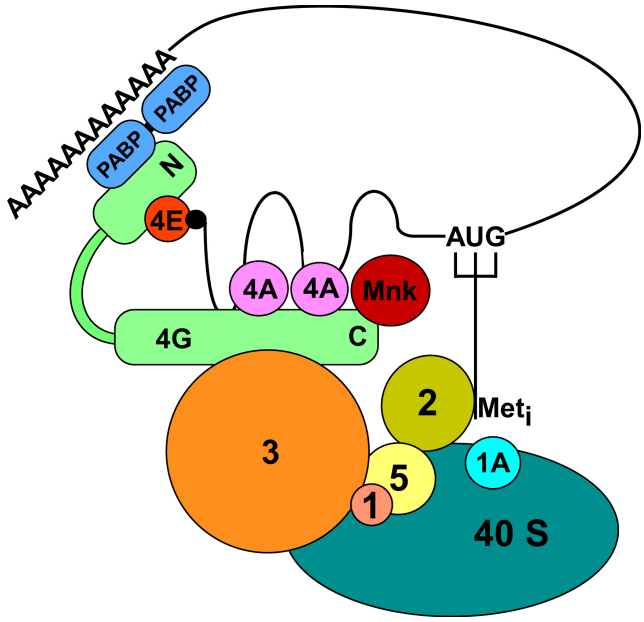

Figure 2. Model for the 48S initiation complex. The interactions among eIF1, eIF2, eIF3, eIF4A, eIF4E, eIF4G, eIF5, Mnk, PABP, mRNA, and the 40S ribosomal subunit are shown. The thin line represents mRNA, with the wavy line indicating mRNA secondary structure. Met$_i$ is the initiator tRNA. The sizes of protein depictions are roughly proportion to their molecular masses.

2.2. Ribosomes, tRNA, and aminoacyl tRNA synthetases

Many components of the translational machinery have been identified in *C. elegans*, including rRNAs (Albertson, 1984; Ellis et al., 1986; Files and Hirsh, 1981), ribosomal proteins (Jones and Candido, 1993; Zorio et al., 1994; Gonczy et al., 2000), 5S RNA (Nelson and Honda, 1985), tRNA (Schaller et al., 1991; Tranquilla et al., 1982; Khosla and Honda, 1989; Lee et al., 1990), and aminoacyl tRNA synthetases (Amaar and Baillie, 1993; Gabius et al., 1983; Gonczy et al., 2000).

2.3. Translation factors

Of the 56 initiation factor (eIF), elongation factor (eEF), and release factor (eRF) polypeptides that we and others have identified (Table 1), only ~10% have been isolated and characterized. In the following overview, information not explicitly cited is taken from WormBase, release WS138.

Table 1. *C. elegans* translational initiation, elongation, and termination factors

Predicted translation factor	Transcript (splice variants)	CGC/ Other names	Predicted identity or function	Number of amino acids	Identity to *C. briggsae*/*H. sapiens* homologs (%)
Initiation factors					
eIF1	T27F7.3b	-/PIG-B	Similar to SUI1	109	100/65
eIF1A	H06H21.3	–	Translation initiation factor 1A	216	72/65
eIF2A	E04D5.1 (a, b)	–	Contains similarity to translation initiation factor eIF2A	618, 225	96/34
eIF2α	Y37E3.10	–	Translation initiation factor 2, α subunit	342	88/47
eIF2α	K04G2.1	–	Translation initiation factor 2, α subunit	250	82/58
eIF2γ	Y39G10AR.8	–	Translation initiation factor 2, γ subunit	469	97/72
eIF2B	C01G10.9	–	Translation initiation factor related to eIF-2B,α/β/δ subunits	366	84/43
eIF2Bα	ZK1098.4	–	eIF-2B,α subunit/GCN3	305	94/42
eIF2Bβ	Y47H9C.7	–	eIF-2B,β subunit	340	99.7/25
eIF2Bε	D2085.3	–	eIF-2Bε subunit/ GCD6	666	99.8/23
eIF2Bγ	C15F1.4	PPP-1	Translation initiation factor 2B, γ subunit/ pyrophosphorylase family	404	79/29
eIF2C-1	T22B3.2 (a, b)	–	Translation initiation factor 2C and related proteins	1032, 1035	99.9/36
eIF2C-2	ZK757.3 (a, b, c)	TAG-76	Translation initiation factor 2C and related proteins	1040, 1037, 55	99.9/42
eIF2C-3	R09A1.1	–	Translation initiation factor 2C	1121	98/27
eIF3a	C27D11.1	EGL-45/eif-3.A	Homologs to eIF3a	1076	72/37
eIF3a	F55H2.6	CLU-1	Involved in mitochondrial morphology/ distribution	1247	80/40
eIF3b	Y54E2A.11a	EIF-3.B	Translation initiation factor 3, subunit b	725	89/34

Predicted translation factor	Transcript (splice variants)	CGC/ Other names	Predicted identity or function	Number of amino acids	Identity to *C. briggsae*/*H. sapiens* homologs (%)
eIF3c	T23D8.4	EIF-3.C	Translation initiation factor 3, subunit c	898	89/39
eIF3d	R08D7.3	EIF-3.D	Translation initiation factor 3, subunit d	570	94/45
eIF3e	B0511.10	EIF-3.E	Translation initiation factor 3, subunit e	432	74/49
eIF3f	D2013.7	EIF-3.F	Translation initiation factor 3, subunit f	294	61/35
eIF3g	F22B5.2	EIF-3.G	Translation initiation factor 3, subunit g	256	90/31
eIF3h	C41D11.2	EIF-3.H	Translation initiation factor 3, subunit h	365	97/39
eIF3i	Y74C10AR.1	EIF-3.I	Translation initiation factor 3, subunit i	327	93/43
eIF3j	Y40B1B.5	–	Translation initiation factor eIF3, p35 subunit	212	69/20
eIF3k	T16G1.11	EIF-3.K/*pqn-69*	Eukaryotic initiation factor 3, p25 subunit	240	89/35
eIF3l	C17G10.9 (a.1, a.2, b)	–	RNA polymerase I-associated factor - PAF67	535-537	99/41
eIF4A	F57B9.6	INF-1	Protein with high similarity to eukaryotic initiation factor 4A	402	97/72 to eIF4A-2, 71 to eIF4A-1
eIF4A	F57B9.3	–	Translation initiation factor 4F, helicase subunit (eIF4A) and related helicases	363	62/52 to eIF4A-1, 51 to eIF4A-2
eIF4A-3	Y65B4A.6	–	ATP-dependent RNA helicase FAL1, involved in rRNA maturation	399	93/82 to eIF4A-3, 66 to eIF4A-2, 61 to eIF4A-1
eIF4A-3	F33D11.10	–	ATP-dependent RNA helicase FAL1, involved in rRNA maturation	399	94/81 to eIF4A-3, 66 to eIF4A-2, 62 to eIF4A-1
eIF4A-p56	C07H6.5	CGH-1	Conserved germline helicase	430	97/71 to DDX6 (p56); 40 to eIF4A-1
eIF4A-47	C26D10.2 (a, b)	HEL-1	ATP-dependent RNA helicase	425/268	97/78 to nuclear BAT1 (p47)
eIF4A-DDX47	T26G10.1	–	ATP-dependent RNA helicase	489	-/61 to DDX47
eIF4A-DDX19	T07D4.4 (a, b, c)	–	ATP-dependent RNA helicase	1022, 638, 613	99.8/49 to DDX19
eIF4A-Prp5	F53H1.1 (a, b)	–	RNA helicase	970, 747	99.9/46 to Prp5
eIF4B	Y73B6BL.33	f3	Splicing factor	610	62/31

Predicted translation factor	Transcript (splice variants)	CGC/ Other names	Predicted identity or function	Number of amino acids	Identity to *C. briggsae*/*H. sapiens* homologs (%)
			hnRNP-F and related RNA-binding proteins		
eIF4E-1	F53A2.6	IFE-1	mRNA cap-binding protein	212	95/40
eIF4E-2	R04A9.4	IFE-2	mRNA cap-binding protein	228	98/40
eIF4E-3	B0348.6 (a, b, c)	IFE-3	mRNA cap-binding protein	248, 251, 250	99/47
eIF4E-4	C05D9.5	IFE-4	mRNA cap-binding protein	212	95/30 to eIF4E and 48% to 4E-HP
eIF4E-5	Y57A10A.30 (a, b)	IFE-5	mRNA cap-binding protein	240,201	80/40
eIF4G	M110.4 (a, b)	IFG-1	Translation initiation factor 4F, ribosome/ mRNA-bridging subunit	1155, 1156	99/27
eIF4H	T12D8.2	–	mRNA cleavage and polyadenylation factor I complex, subunit RNA15	207	74/33
eIF5	C37C3.2 (a, b, c)	–	Translation initiation factor 5	436, 402, 413	99/48
eIF5A	F54C9.1	IFF-2	Translation initiation factor 5 homolog	161	99/61
eIF5A	T05G5.10	IFF-1	Translation initiation factor 5 homolog	161	99/57
eIF5B	Y54F10BM.2	–	Translation initiation factor 5B	1173	82/48
Elongation factors					
eEF1A	F31E3.5	EFT-3	Translation elongation factor 1α	436	99.8/83
eEF1A	R03G5.1 (a, b, c, d)	EFT-4	Translation elongation factor 1α	463, 77, 267, 429	99.8/84
eEF1B	Y41E3.10	–	Elongation factor 1 β/δ chain	285	50.5/40
eEF1B	F54H12.6	–	Elongation factor 1 β/δ chain	213	99.5/38
eEF2	F25H5.4	EFT-2	Homolog of translation elongation factor 2	852	89/76
eEF2	ZK328.2	EFT-1	Elongation factor 2	974	99/38
Termination factors					
eRF1	T05H4.6(a, b)	–	Peptide chain release factor 1	443, 559	99.8/80
eRF3	H19N07.1	–	Peptide chain release factor 3	532	99.8/63

eIF2 factors. Both eIF2 and eIF2A catalyze the binding of Met-tRNA$_i$ to the 40S ribosomal subunit, the former requiring GTP and the latter, an AUG codon (Zoll et al., 2002). eIF2 is composed of three subunits, α, β, and γ. eIF2β has also been reported to bind mRNA and contributes, together with eIF2γ, to GTP and Met-tRNA$_i$ binding. Inactivation of either of these genes is lethal. Surprisingly, eIF2α deletion mutants are viable but have defects in growth and larval development. Yeast eIF2A is not an essential protein, but deletion of *C. elegans* eIF2A is embryonically lethal. eIF2B is a heteropentameric complex that is essential in yeast and mammalian cells. In *C. elegans*, inactivation of either the β, γ (Kuwabara and Shah, 1994), or ε subunits causes growth defects, larval arrest, or embryonic lethality.

eIF4 factors. Two splice-variants of eIF4G, encoded by *ifg-1*, have been identified in *C. elegans* (Long et al., 2002; Kamath et al., 2003). Although IFG-1 shows low identity to human eIF4G, its role as a translation factor was confirmed by its retention on m^{7}GTP-Sepharose (Keiper and Rhoads, unpublished data) and by its presence in 48S initiation complexes (Dinkova et al., 2005). *ifg-1* inactivation results in developmental arrest and embryonic lethality (Long et al., 2002).

eIF4E is encoded by five genes in *C. elegans*, *ife-1* through *ife-5* (Jankowska-Anyszka et al., 1998; Keiper et al., 2000; Figure 3). The five proteins can be grouped into three classes based on amino acid sequence identity, cap-binding specificity, and knockout phenotype (Table 2). Some isoforms bind both 2,2,7-trimethylguanosine (TMG)-containing caps as well as 7-methylguanosine (MMG)-containing caps, whereas other isoforms bind only the latter. Cap selectivity is determined by the dimensions and flexibility of the cap-binding pocket (Miyoshi et al., 2002). IFE-1 is bound to P granules through an interaction with PGL-1 and is required for spermatogenesis (Amiri et al., 2001). In the case of IFE-4, inactivation of the gene produces an Egl phenotype, low brood size, and a defect in food sensation (Dinkova et al., 2005). The translational efficiency (polysomal distribution) of only ~1% of mRNAs is affected by *ife-4* deletion, but diminished levels of the encoded proteins are consistent with the complex phenotype.

Table 2. Properties of five *C. elegans* isoforms of eIF4E

Class	eIF4E isoform	Cap-binding specificity	RNAi phenotype	Tissue distribution	Knockout mutant phenotype	Postulated physiological role
A	IFE-3	MMG	Lethal	Soma Germ line	Emb	General translation
B	IFE-1	MMG TMG	Viable[a] Spe	Germ line	Spe	Regulation of P granules mRNA translation
	IFE-2	MMG TMG	Viable[a]	Soma	Unknown	Unknown
	IFE-5	MMG TMG	Viable[a]	Unknown	Unknown	Unknown
C	IFE-4	MMG	Viable Egl	Neurons Muscle	Egl	Specific mRNA translation during development
References		Jankowska-Anyszka et al., 1998; Keiper et al., 2000; Miyoshi et al., 2002; Stachelska et al., 2002	Keiper et al., 2000; Amiri et al., 2001; Dinkova et al., 2005	Amiri et al., 2001; Dinkova et al., 2005	Amiri et al., 2001; Dinkova et al., 2005	Amiri et al., 2001; Dinkova et al., 2005; Trutschl et al., 2005

[a]The combination of RNAi for all three IFEs from Class B is lethal.

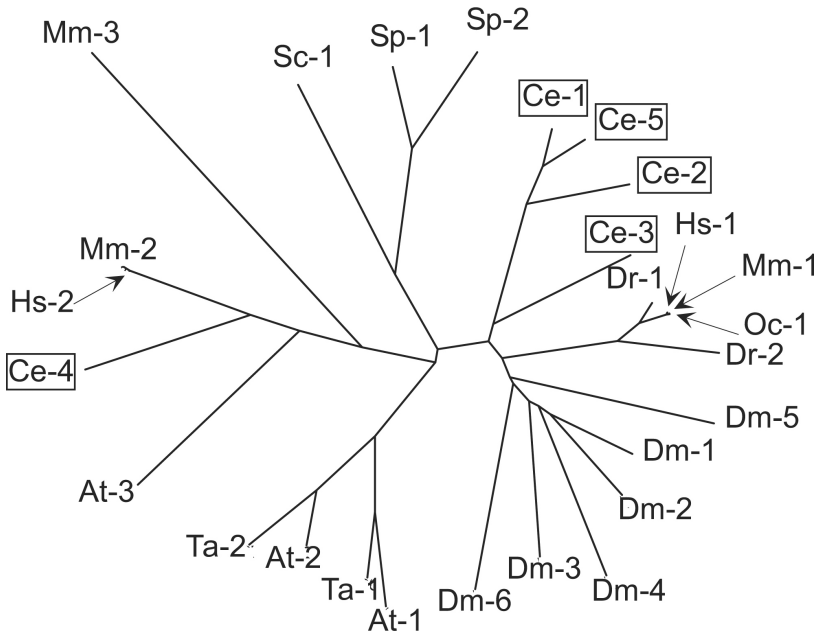

Figure 3. Homologies among eIF4E isoforms. Amino acid sequence alignments were performed using Vector NTI 9.0.0 with a gap penalty of 3.0 and a gap extension penalty of 0.1. Multiple sequence alignments were used to calculate protein distance values and construct a phylogenetic tree with PHYLIP software on the Institut Pasteur server. eIF4E isoforms from *C. elegans* are indicated in *boxes*. NCBI accession numbers are indicated. *A. thaliana*: At-1, Y10548; At-2, Y10547; At-3, AF028809. *C. elegans*: Ce-1, NM_067350; Ce-2, NM_075693; Ce-3, NM_171920; Ce-4, AF214651; Ce-5, NM_064207. *D. rerio*: Dr-1, AF257519; Dr-2, AF176317. *D. melanogaster*: Dm-1, NM_168334; Dm-2, NM_139795; Dm-3, NM_139903; Dm-4, NM_166870; Dm-5, NM_143397; Dm-6, NM_139937. *H. sapiens*: Hs-1, M15353; Hs-2, AF047695. *M. musculus*: Mm-1, M61731; Mm-2, AF068116; Mm-3, AK005054 *O.cuniculus*: Oc-1, X61939. *S. cerevisiae*: Sc-1, M15436. *S. pombe*: Sp-1, X99444; Sp-2, AL031852, *T. aestivum*: Ta-1, Z12616; Ta-2, M95819.

Nine *C. elegans* gene products are homologous to eIF4A (Table 1; Roussell and Bennett, 1992; Gonczy et al., 2000). The products of F57B9.6 and F57B9.3 are the most homologous to mammalian eIF4A-1 and eIF4A-2. Others (Y65B4A.6 and F33D11.10) may be involved in splicing or nonsense-mediated decay, similar to mammalian eIF4A-3. Some may play a specific role in germline cells (C07H6.5) or in nuclear export (C26D10.2, T26G10.1, T07D4.4, and F53H1.1). Knockout of any eIF4A-like gene except T07D4.4 causes reproductive defects or embryonic lethality.

Other initiation factors and interacting proteins. eIF1, eIF3, and eIF5 form a multifactor complex in yeast that is required for assembly of the 43S initiation complex. *C. elegans* eIF5 and eIF1 are essential for growth and embryonic development. There are *C. elegans* homologs for all 12 eIF3 subunits present in higher eukaryotes (Asano et al., 1997), whereas yeast eIF3 has only five subunits. Loss of eIF3a (C27D11.1) produces an Egl phenotype (Desai and Horvitz, 1989). Both eIF3a and eIF3d are involved in meiotic divisions (Gonczy et al., 2000). Another eIF3a homolog (F55H2.6) is possibly involved in mitochondrial morphology and distribution. Inactivation of eIF5B results in larval arrest and sterility (Maeda et al., 2001). *C. elegans* contains three PABP homologs. PAB-2 (F18H3.3) has the highest similarity to human cytoplasmic PABP. PAB-1 (Y106G6H.2) is essential for gonad development, and PAB-2 is apparently important for somatic development (Ciosk et al., 2004). PAB-3 (C17E4.5) is more similar to human nuclear PABP and is probably not involved in translation.

Elongation and termination factors C. elegans has two identical eEF1A homologs that are products of different genes, *eft-3* (Seydoux and Fire, 1994) and *eft-4* (Kamath et al., 2003). EFT-3 is required for embryonic viability, fertility, and germline maintenance. There are two homologs of eEF1B, one of which (F54H12.6) is essential for viability while the other (Y41E3.10) is not. The two eEF2 homologs, EFT-1 (Ofulue and Candido, 1992) and EFT-2 (Ofulue and Candido, 1991; Nollen et al., 2004), are expressed during all stages and are encoded by essential genes. eRF1 has two splice variants whereas eRF3 has only one. Both genes are essential for embryonic and larval development, growth, and locomotion.

3. Structural features of mRNA that affect translational efficiency

A distinctive feature of *C. elegans* is the presence of polycistronic pre-mRNA transcribed from operons (Blumenthal and Gleason, 2003). Translational control of individual mRNAs relies on *cis*-regulatory elements that

include the cap, the 5'-terminal spliced leader (SL), and additional sequence elements in 5'- and 3'-untranslated regions (UTRs).

3.1. 5'-terminal structures

Spliced leaders. A SL is added to mature mRNA via *trans*-splicing in nematodes and some other metazoans (Bektesh et al., 1988; Evans et al., 1994; Stover and Steele, 2001). The SL consists of a conserved 22-nt sequence (Conrad et al., 1991; Blumenthal and Steward, 1997). In *C. elegans*, either SL1 or SL2 (or a variant such as SL3, SL4, *etc*.) is added to 70% of pre-mRNAs (Blumenthal and Gleason, 2003). SL1 is usually *trans*-spliced to mRNAs transcribed from the first cistron in an operon or to monocistronic mRNAs, whereas SL2 and its variants are *trans*-spliced to products of downstream cistrons.

Caps. Those mRNAs that undergo *trans*-splicing carry a TMG-cap and SL, whereas those that undergo only. *cis*-splicing carry an MMG-cap and no SL (Van Doren and Hirsh, 1990). The small nuclear RNA that donates the SL contains a TMG-cap (Zorio et al., 1994; Evans et al., 1997). MMG- and TMG-caps are recognized by some but not all eIF4E isoforms (Table 2).

5'UTR. Regulatory features of the 5'UTRs of mRNAs in general involve length, secondary structure, upstream open-reading frames, and specific sequences that interact with RNA binding proteins (Gingras et al., 1999). The *trans*-splicing processing of many *C. elegans* mRNAs results in a relatively short 5'UTR in which the SL is located near the AUG codon (Blumenthal and Steward, 1997). A few *C. elegans* mRNAs, e.g., *gna-2*, contain long 5'UTRs that harbor upstream open-reading frames (Lee and Schedl, 2004), which have a profound effect on translation efficiency in other organisims (Morris and Geballe, 2000).

Effects of 5'-terminal structures on translational efficiency. Mechanisms of regulation mediated by 5'-terminal structures remain largely unknown for *C. elegans*. Both MMG- and TMG-containing mRNAs are found on polysomes (Liou and Blumenthal, 1990). In *Ascaris lumbricoides*, mutations in the SL1 sequence alter efficiency of translation (Maroney et al., 1995). TMG-capped mRNAs are poorly translated in mammalian cell-free translational systems (Darzynkiewicz et al., 1988), but a TMG-cap and SL stimulate translation in an *Ascaris suum* translation system (Lall et al., 2004). Interestingly, an optimal distance from SL to AUG for translational efficiency can be demonstrated in this system. The translational synergism between cap and poly(A) is greater for TMG than MMG. The well described translational regulator GLD-1 also interacts with 5'UTR sequences (Lee and Schedl, 2004).

3.2. 3'-terminal structures

3'UTR. Translational regulatory elements at the 3'UTR play important roles in *C. elegans* mRNA expression (see WormBook chapters on Translational control of maternal RNAs and RNA-binding proteins). The elements first described as DREs (direct repeat elements; Goodwin et al., 1993) and later re-named TGEs (*tra* GLI elements; Jan et al., 1997) are found within the 3'UTR of *tra-2* mRNA and negatively regulate its expression in germ line and somatic cells. The *trans*-acting factor for TGEs was identified as GLD-1 (Jan et al., 1999). A 5-nucleotide sequence element in the 3'UTR of *fem-3* mRNA, cuUCUUGu, also exerts translational regulation (Anderson and Kimble, 1997). Another kind of 3'UTR element that represses translation is the *lin-4* complementary element (LCE) found in *lin-14* and *lin-28* mRNAs (Wightman et al., 1993; Seggerson et al., 2002). This element is bound by the microRNA *lin-4* (Moss et al., 1997; see *C. elegans* microRNAs). Mutations in these 3'UTR elements disrupt the translational regulation of their mRNAs (see WormBook chapters referenced above).

poly(A) The poly(A) tract is added by a poly(A) polymerase after specific cleavage during mRNA splicing. The nuclear polyadenylation signal consists of an AAUAAA sequence 20-30 nt upstream of the cleavage site (Blumenthal, 1995; Hajarnavis et al., 2004). In *C. elegans*, GLD-2 is a putative catalytic subunit of cytoplasmic poly(A) polymerase that is likely recruited to mRNAs by interaction with RNA binding proteins such as GLD-3 (Wang et al., 2002). Cytoplasmic polyadenylation also requires a cytoplasmic polyadenylation element (CPE), located upstream of the polyadenylation site, which is recognized by specific proteins (CPEBs).

Effects of 3'-terminal structures on tranlational efficiency. Although there are many instances in which specific structures in the 3'UTR have been shown to affect translational efficiency in *C. elegans* and other organisms (Kuersten and Goodwin, 2003), the molecular interactions responsible for these effects are only partially understood. In *Xenopus* oocytes, CPEB binds and sequesters eIF4E through an intermediary protein, Maskin (Mendez and Richter, 2001). In *Drosophila* embryos, there is a similar interaction between the 3'UTR-binding factor Smaug and eIF4E, mediated by another protein, Cup (Nelson et al., 2004). However, in *C. elegans* the translational

component(s) involved in GLD-1-mediated regulation remain unknown (Jan et al., 1999; Marin and Evans, 2003; Lee and Schedl, 2004). The other 3'-terminal element, the poly(A) tract, increases the rate of translational initiation in yeast and plants due to the binding of PABP to a specific site near the N-terminus of eIF4G (Tarun and Sachs, 1996; Le et al., 1997; see Figure 2). Poly(A) stabilizes the PABP•eIF4G•eIF4E complex, which in turn leads to enhanced translational re-initiation (Wakiyama et al., 2000). As discussed below, there are several regulatory mechanisms in *C. elegans* that involve changing the poly(A) length.

4. Regulation of Translation

Many of the translational mechanisms that have been well described and characterized in other organisms (Sonenberg et al., 2000) have not yet been demonstrated in *C. elegans*. These can be divided into two broad classes, modification of translation factors and modification of mRNA structure. However, the existence of homologous translation factors (Table 1) and signal transduction components (Table 3) suggests that previously discovered mechanisms operate in *C. elegans* as well.

Table 3. Components of signal transduction pathways implicated in translational control

Predicted signal transduction component	Transcript (splice variants)	CGC/ Other names	Predicted identity or function (WormBase, release WS138)
P70S6K	Y47D3A.4	CKU-70	DNA-binding subunit of a DNA-dependent protein kinase
TAP42	Y71H2B.3		Protein phosphatase 2A-associated protein
TIP41	ZK688.9		Uncharacterized conserved protein
SIT4.1	Y75B8A.30	PPH-4.1	Serine/threonine-specific protein phosphatase involved in glycogen accumulation
SIT4.2	Y49E10.3a	PPH-4.2	Serine/threonine-specific protein phosphatase involved in glycogen accumulation
Akt	C12D8.10 (a, b, c)	AKT-1	Ortholog of serine/threonine kinase Akt/PKB
PERK	F46C3.1	PEK-1	Human PERK kinase homolog
PEK	Y38E10A.8		eIF2α kinase PEK/EIF2AK3
MKK7/JNKK2	K08A8.1	MEK-1/ KIN-17	MKK7/JNKK2
MKK7/JNKK2	F35C8.3	JKK-1	JNK Kinase
MKK4	F42G10.2	MKK-4	MKK (MAP kinase kinase) homolog
MAPK7/ERK5	W06B3.2	SMA-5	MAPK7/ERK5
MAPK7	C04G6.1	MAP-2	Mitogen-activated protein kinase 7, isoform 1
MAPK7	F09C12.2		Mitogen-activated protein kinase
MAP2K	Y54E10BL.6	MEK-2/ LET-537/ GLV-1	MAP kinase kinase or ERK kinase
ERN1/IRE1	C41C4.4	IRE-1	IRE1 kinase related
TOR	B0261.2	LET-363	Ortholog of *S. cerevisiae* Tor1p and Tor2p and human FRAP1
PI3K	C46B6.6	SMG-1/ MAB-1	PI-3-kinase-related kinase SMG-1 isoform 2
PI3K like	T06E4.3	ATL-1	ATM (ataxia telangectasia mutated)-like
PI4K	ZC8.6		Phosphatidylinositol 4-kinase
PI4K	C56A3.8		Phosphatidylinositol 4-kinase
Raptor	C10C5.6 (a, b)	DAF-15	Abnormal dauer formation

4.1. Mechanisms involving translation factor modification

Covalent modification of a translation factor. The unfolded protein response (UPR) is a transcriptional and translational signaling pathway activated by the accumulation of unfolded proteins in the endoplasmic reticulum (ER; Zhang and Kaufman, 2004). This involves activation of an eIF2α kinase, PEK, causing global inhibition of translation initiation and allowing time to remedy the folding problem. *C. elegans* PEK-1 was expressed in yeast and found to inhibit growth by hyperphosphorylation of eIF2α and inhibition of eIF2B (Sood et al., 2000). UPR gene transcription and survival upon ER stress also requires *ire-1*-mediated splicing of *xbp-1* mRNA (Shen et al., 2001). *ire-1/xbp-1* acts with *pek-1* in complementary pathways that are essential for worm development, survival, and ER homeostasis. Furthermore, *pek-1* mutants have shortened life spans (Harding et al., 2003).

Sequestration of a translation factor. TOR is a highly conserved protein kinase that controls cell growth and division in eukaryotes. In mammals, mTOR regulates translation by phosphorylation of p70 S6 kinase (S6K) and the eIF4E-binding protein 4E-BP1 (Gingras et al., 2001). The latter event releases eIF4E from a sequestered form, making it available to bind eIF4G (Figure 2). Raptor is a mTOR-binding protein that is necessary for the mTOR-catalyzed phosphorylation of 4E-BP1 and S6K (Hara et al., 2002). In yeast, TOR also regulates translation through eIF4E by a mechanism involving the phosphatases Sit4 and PP2A and the phosphatase-binding protein Tap42 (Jiang and Broach, 1999). Tip41 negatively regulates TOR by binding and inhibiting Tap42 (Jacinto et al., 2001).

In *C. elegans*, cTOR (*let-363*) deficiency causes developmental arrest and intestinal atrophy (Long et al., 2002). The phenotype resembles that of RNAi knockdown of eIF4G, eIF2α, and eIF2β, but not S6K, Tip41, or Tap42. RNAi of Raptor (*daf-15*) yields an array of phenotypes resembling those of cTOR knockout. Deficiency of both *let-363* (Vellai et al., 2003) and *daf-15* (Jia et al., 2004) extends adult lifespan, while mutations in either gene result in dauer-like larval arrest (Jia et al., 2004). To date, a *C. elegans* 4E-BP1 homolog has not been identified. The protein phas-1 (WP:CE30964; Agostoni et al., 2002; another name for 4E-BP1 is PHAS-I) is unrelated to mammalian and *Drosophila* 4E-BP1.

The presence of IFE-1 in P granules (Amiri et al., 2001) and its absence from initiation complexes (Dinkova et al., 2005) may represent another regulatory mechanism involving sequestration of a translation factor. A number of mRNAs have been found in P granules, some of which have been shown to be translationally controlled (Schisa et al., 2001). P granules also contain four GLH RNA helicases similar to eIF4A (Gruidl et al., 1996; Kuznicki et al., 2000). In *Drosophila*, VASA is a germline-specific ATP-dependent RNA helicase, homologous to the GLH proteins, that is required for translation of at least two mRNAs, *gurken* and *nanos*, through interaction with eIF5B (Styhler et al., 1998; Johnstone and Lasko, 2004). Also, eIF5A is required for PGL-1 localization (Hanazawa et al., 2004). The presence of all these translational components in P granules may signify regulation of germline-specific mRNA translation.

4.2. Mechanisms involving mRNA modification

The translation of some *C. elegans* mRNAs is regulated by 3'UTR-binding proteins that alter poly(A) length (Kuersten and Goodwin, 2003). There are four CPEB homologs, CBP-1, CPB-2, CPB-3, and FOG-1 (Luitjens et al., 2000). CPB-1 is essential for progression through meiosis and is present in germ cells just before spermatogenesis. CPB-1 physically interacts with FBF, another RNA-binding protein and 3' UTR regulator. Similarities between FOG-1 and the CPEB proteins of *Xenopus* and *Drosophila* suggest that FOG-1 controls germ cell fates by regulating the translation of specific messenger RNAs.

A specific mRNA that undergoes regulated changes in poly(A) length is *tra-2* mRNA, whose translation must be repressed for male development. A possible mechanism of action is suggested by the observation that TGEs control the length of the poly(A) tract in a *Xenopus* system (Thompson et al., 2000). Similarly, a 5-nt element in the 3'UTR of *fem-3* mRNA controls the length of the poly(A) tract (Ahringer and Kimble, 1991). *fem-3* must be downregulated to allow the switch from spermatogenesis to oogenesis. FBF and Nanos-3 interact with each other and repress translation of *fem-3* mRNA (Kraemer et al., 1999). GLD-3 also physically interacts with FBF to interfere with FBF binding to the 3'UTR of *fem-3* mRNA (Eckmann et al., 2002). GLD-3 promotes the transition from mitosis to meiosis together with the putative GLD-2 poly(A) polymerase. FBF also binds specifically to elements in the 3'UTR of *gld-3S* mRNA and regulates *gld-3* expression (Eckmann et al., 2004).

4.3. Known instances of translational regulation that occur but through unknown mechanisms

The translation of several other mRNAs is known to be regulated through the 3'UTR, but this cannot yet be explained within the framework of known translational control mechanisms. A 34-nucleotide region of the 3'UTR of *glp-1* mRNA contains two regulatory elements, one that represses translation in germ cells and posterior cells of the early embryo, and one that inhibits repressor activity to promote translation in the embryo (Marin and Evans, 2003). GLD-1 binds to this repressor element. MEX-3 is also expressed in anterior blastomere cells and is required for repression of *pal-1* mRNA translation (Hunter and Kenyon, 1996; Draper et al., 1996).

A different type of 3'UTR regulation is seen with the heterochronic genes, which are temporally controlled to specify the timing of developmental events. *lin-14* and *lin-28* encode proteins that are required for temporal execution of cell lineages during larval development. *lin-14*, *lin-28*, *lin-42*, and *daf-12* mRNAs contain a conserved element in the 3'UTR, the loss of which causes a gain of function (Seggerson et al., 2002). *let-7* encodes a temporally regulated 21-nucleotide RNA that is complementary to elements in heterochonic mRNA 3'UTRs and regulates their translation (Reinhart et al., 2000). A second regulatory RNA, *lin-4*, negatively regulates *lin-14* and *lin-28* through RNA-RNA interactions with their 3'UTR (Moss et al., 1997). *lin-28* is repressed during normal development by a mechanism that acts on its mRNA after translation initiation (Seggerson et al., 2002).

4.4. Future directions for protein synthesis research in *C. elegans*

As illustrated throughout this chapter, several key developmental pathways in *C. elegans* are predominantly governed by translational mechanism. However, translation *per se* has received little attention. Even though one can find *C. elegans* homologs for most of the RNAs and proteins that make up the translational machinery (Table 1), few of these have been isolated, functionally identified, or studied at the biochemical level. This deficiency obscures the molecular mechanisms responsible for well characterized physiological processes. Another shortcoming is the absence of a cell-free translation system, although such systems have been developed in two other nematodes, *Ascaris lumbricoides* (Maroney et al., 1995) and *Ascaris suum* (Lall et al., 2004). The most interesting unexplored questions may involve changes in the translation of individual mRNAs in various physiological conditions or after genetic manipulations. Given the highly developed state of *C. elegans* genomics, it can be expected that future application of computational tools, including data visualization (Trutschl et al., 2005), will help detect new instances of translational control.

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