Eukaryotic initiation factor 4E (eIF4E) has long been known as the cap-binding protein that participates in recruitment of mRNA to the ribosome. A number of recent advances have not only increased our understanding of how eIF4E acts in translation but also uncovered non-translational roles. New structures have been determined for eIF4E in complex with various ligands and for other cap-binding proteins. We have also learned that most eukaryotic organisms express multiple eIF4E family members, some involved in general translation but others having specialized functions, including repression of translation. A number of new eIF4E-binding proteins have been reported, some of which tether it to specific mRNAs.

The 7-methylguanosine-containing “cap” plays an essential role at each stage of the mRNA “life cycle”: transcription, splicing, nuclear export, translation, translational repression, and degradation. This is mediated by specific cap-binding proteins, of which at least 10 have been discovered so far (supplemental Table S1). The most widely studied and best understood of these cap-binding proteins is eIF4E.2 eIF4E was discovered as a protein that promotes translation initiation, and most of the work on its structure, function, and regulation has been performed with this role in mind. As a canonical initiation factor involved in recruitment of mRNA to the ribosome, eIF4E has the potential to influence expression of virtually every protein in the cell. It is against this backdrop of eIF4E serving as a translational enhancer that discoveries over the past decade have been so surprising, that eIF4E can also function as a translational repressor. Another unexpected result of recent research is that nearly all eukaryotes express multiple eIF4E family members and that they can have different functions in the cell. A third research trend has been the discovery of new eIF4E-binding partners, some of which tether eIF4E to specific mRNAs. This minireview touches on all of these new directions in eIF4E research.

Role of eIF4E in Translation

Recruitment of mRNA to the 43 S initiation complex to form the 48 S initiation complex requires eIF3, the poly(A)-binding protein, and the eIF4 proteins (Fig. 1B) (1). The eIF4 factors consist of eIF4A, a 46-kDa RNA helicase; eIF4B, a 70-kDa RNA-binding and RNA-annealing protein; eIF4E, a 25-kDa cap-binding protein; eIF4H, a 25-kDa protein that acts with eIF4B to stimulate eIF4A helicase activity; and eIF4G, a 185-kDa protein that co-localizes all of the other proteins involved in mRNA recruitment on the 40 S subunit.3 At least four cis-acting elements affect the efficiency of mRNA translation: the cap, the poly(A) tail, sequence elements in the 5'-UTR, and sequence elements in the 3'-UTR. It is well established that eIF4E stimulates translation of capped mRNAs, but mRNAs differ in their dependence on eIF4E. For instance, mRNAs with extensive 5'-UTR secondary structure have a greater requirement for the eIF4E-based unwinding machinery recruited by eIF4E (Fig. 1B) (2).

The tertiary structures of mouse, yeast, human, and wheat eIF4Es have been solved (3–6). The specificity of eIF4E interaction with the cap results primarily from cation–π bond stacking between Trp-56 and Trp-102 and H-bonds between Glu-103 and the N-1 and N-2 protons of 7-methylguanine.4 Following the initial structure determination of eIF4E, structures have emerged for a number of non-eIF4E cap-binding proteins (supplemental Table S1). Interestingly, the cation–π bond interaction between the m7G moiety and aromatic amino acid residues is a feature shared by most of these proteins. An exception is the decapping enzyme Dcp2, which, unlike eIF4E, binds the cap only when attached to the RNA body (7).

eIF4E Family Members

It is common to have protein families with multiple members, but eIF4E was initially assumed (albeit tacitly) to be a single protein, in part because only a single 25-kDa polypeptide was obtained from mammalian sources by affinity chromatography. When the Ravel laboratory made the unexpected discovery that wheat germ contained two versions of eIF4E (8), termed eIF4E and eIF(iso)4E, it seemed to be a peculiarity of this organism. More than 10 years later, it was reported almost simultaneously that Arabidopsis thaliana expresses not only eIF4E and eIF(iso)4E but also nCBP (9); Homo sapiens expresses a second family member, 4EHP (10); and Caenorhabditis elegans expresses three eIF4E family members, IFE-1, -2, and -3 (11). It is now recognized that the wheat germ “oddity” is the norm; virtually all eukaryotes express multiple eIF4E family members. Multiple family members have been found for other initiation factors as well, e.g. eIF4A and eIF4G.

Joshi et al. (12) combined published eIF4E sequences with sequences mined from GenBankTM to identify 411 eIF4E family members from 230 species. An unusual feature of the eIF4E sequence is the high content of Trp residues. Some of these are involved in the binding of the cap (supplemental Table S1) and

*This work was supported, in whole or in part, by National Institutes of Health Grant 2R01GM020818 from NIGMS. This minireview will be reprinted in the 2009 Minireview Compendium, which will be available in January, 2010.

1 The on-line version of this article (available at http://www.jbc.org) contains supplemental Table S1 and additional references.

2 The abbreviations used are: elF, eukaryotic initiation factor; UTR, untranslated region; nCBP, novel cap-binding protein; 4EHP, 4E homologous protein; d4EHP, Drosophila 4E homologous protein; 4E-BP, 4E-binding protein; CPE, cytoplasmic polyadenylation element; CPEB, CPE-binding protein; PARN, poly(A)-specific ribonuclide; FMRP, fragile X mental retardation protein.

3 Molecular masses refer to the mammalian proteins.

4 Amino acid positions refer to human eIF4E-1.
eIF4G (3–5, 13). These Trp residues allowed Joshi et al. (12) to discern a core region with consensus sequence H(\(X_5\))W(\(X_2\))W(\(X_8–12\))W(\(X_9\))F(\(X_5\))FW(\(X_20\))F(\(X_7\))W(\(X_10\))W(\(X_34–35\))W(\(X_32–34\))H in seven well established eIF4Es. They used this to subdivide eIF4E family members into three classes according to the residues corresponding to Trp-43 and Trp-56 of \(H.\ sapiens\) eIF4E-1.

Class I members contain Trp at both positions; Class II members, e.g. 4EHP, nCBP, IFE-4, and d4EHP, contain Tyr, Phe, or Leu at the first position and Tyr or Phe at the second position; and Class III members contain Trp at the first position and Cys or Tyr at the second position.

Prototypical eIF4Es bind the cap and eIF4G (or alternatively the 4E-BPs). As more and more eIF4E family members emerged, it became apparent that these binding capabilities were not necessarily conserved (Table 1). For instance, mammalian eIF4E-1 (Class I) binds the cap, eIF4G, and the 4E-BPs, but mammalian eIF4E-2 (Class II) binds only the cap and 4E-BPs, and mammalian eIF4E-3 (Class III) binds only the cap and eIF4G (14). \(D.\ rerio\) eIF4E-1B (Class I) fails to bind all three ligands (15). Some eIF4E family members have altered binding affinities. \(A.\ thaliana\) nCBP binds \(m^7\)GTP more tightly than \(A.\ thaliana\) eIF(iso)4E. \(C.\ elegans\) IFE-1, -2, and -5 bind both \(m^7\)G- and \(m^2,2,7\)G-containing caps, whereas IFE-3 and -4 bind only \(m^7\)G-containing caps (11, 16). These gains and losses in binding properties provide clues for the physiological roles of eIF4E family members.

**TABLE 1**

**Selected eIF4E family members with illustrative properties**

| Class | Examples | Unusual molecular properties | Specialized physiological roles |
|-------|----------|-----------------------------|-------------------------------|
| Class I | \(C.\ elegans\) IFE-1 | Binds both \(m^7\)G- and \(m^2,2,7\)G-containing caps (11); binds the P granule-resident protein PGL-1 (30) | Required for spermatogenesis (30) |
| | \(C.\ elegans\) IFE-2 | Binds both \(m^7\)G- and \(m^2,2,7\)G-containing caps (11) | Modulates oxidative stress and aging (32) |
| | \(D.\ rerio\) eIF4E-1B | Fails to bind \(m^7\)G-containing cap structures, eIF4G, or 4E-BP (15) | Expression is restricted to early embryos and gonads (15) |
| | \(S.\ pombe\) eIF4E-2 | Low affinity for eIF4G (41) | Translation in response to cellular stress (41) |
| | \(X.\ laevis\) eIF4E-1B | | Represses maternal mRNA translation in early oogenesis (33) |
| Class II | \(A.\ thaliana\) nCBP | Binds \(m^7\)GTP 5–20-fold tighter than eIF(iso)4E (9) | Translation of mRNA subset (31) |
| | \(C.\ elegans\) IFE-4 | | |
| | \(D.\ melanogaster\) 4EHP | Binds the cap but not eIF4G (42); interacts with Bicoid (35) and Brat (36) | Represses \textit{caudal} (35) and \textit{hunchback} (36) mRNA translation |
| | \(H.\ sapiens\) 4EHP | Fails to bind eIF4G or 4E-BPs (10) | |
| | \(M.\ musculus\) eIF4E-2 | Binds to 4E-BPs but not eIF4G (14) | |

**Class III**

| Examples | Binds to eIF4G but not 4E-BPs (14) |

eIF4G (3–5, 13). These Trp residues allowed Joshi \emph{et al.} (12) to discern a core region with consensus sequence H(\(X_5\))W(\(X_5\))W(\(X_8–12\))W(\(X_9\))F(\(X_5\))FW(\(X_20\))F(\(X_7\))W(\(X_10\))W(\(X_34–35\))W(\(X_32–34\))H in seven well established eIF4Es. They used this to subdivide eIF4E family members into three classes according to the residues corresponding to Trp-43 and Trp-56 of \(H.\ sapiens\) eIF4E-1. Class I members contain Trp at both positions; Class II members, e.g. 4EHP, nCBP, IFE-4, and d4EHP, contain Tyr, Phe, or Leu at the first position and Tyr or Phe at the second position; and Class III members contain Trp at the first position and Cys or Tyr at the second position.

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**Binding Partners for eIF4E**

eIF4E was initially discovered as a single polypeptide, but when it was subsequently found in complexes with eIF4G, it was redefined as a subunit of a new initiation factor in mammals termed eIF4F. However, the pioneering work of the Sonenberg and Lawrence laboratories showed that eIF4E can have other binding partners besides eIF4G, namely 4E-BP1, -2, and -3 (49, 50). The number of known eIF4E-binding partners has grown substantially over the past decade (Table 2). Many of the new roles that have been discovered for eIF4E are mediated by its interaction with these new binding partners.

eIF4E participates in mRNA recruitment through specific and high affinity binding to eIF4G (Fig. 1B). X-ray crystallogra-
MINIREVIEW: eIF4E: New Family Members/Binding Partners/Roles

TABLE 2
eIF4E-binding partners

| Protein     | Consequences of binding                                                                 | Residues in the binding partner that interact with eIF4E* |
|-------------|----------------------------------------------------------------------------------------|----------------------------------------------------------|
| eIF4G       | Recruits the eIF4A-driven unwinding machinery                                         | KRYDREFLIGF (13, 18)                                     |
| 4E-BP1      | Represses highly cap-dependent mRNA translation                                       | I1I91DKFLMEC (13)                                       |
| p20         | Represses cap-dependent translation in S. cerevisiae                                   | I9K71TDIEFQL (43)                                       |
| Maskin      | Represses translation of CPE-containing mRNAs                                          | EFLKJAFEDLAA (19)                                       |
| eIF4A       | Transports eIF4E into the nucleus                                                      | PHTYRTKELLHDKELP (44)                                   |
| Lipoxygenase 2 | Competes for binding of eIF4E by eIF4G                                               | LKK1KRKEELE (45)                                        |
| Vpg         | Reduces eIF4E affinity for the cap and inhibits host translation                       | Mapped to aa 59–93 of TuMV Vpg; interaction abolised by mutation of Asp-77 (26) |
| PGL-1       | Localizes IF-1 to P granules                                                           | YTRSRLM (23, 24)                                       |
| Cup         | Represses translation of nanos and oskar mRNAs                                        | NV8191FVPLNPQ (35)                                     |
| Bicoid      | Represses translation of caudal mRNA                                                  | RLQ61S1LRIG (46)                                       |
| BTF3        | Competes for binding of eIF(iso)4E by eIF(iso)4G                                      | NTHL domain (36)                                       |
| Brat        | Represses translation of hunchback mRNA                                               | LKLPF6K and YAEVEQ (48)                                 |
| Gemin5      | Inhibits both cap-dependent and IRES-driven translation                               | YTPEKGL, YQDKVLKVT, and YVPPRVL (21)                   |
| Neurogulin  | Represses translation of CPE-containing mRNAs                                          | LL121D8KR5SEC (22)                                     |
| CYFIP1      | Represses translation of mRNAs that bind FMRP                                        |                                                           |

*These were determined from sequence alignments. The residues in italics align with Tyr of H. sapiens eIF4G-1 shown in the first row. The residues shown underlined and in boldface are implicated in eIF4E binding by mutational studies.

et al. (20) have recently found that the timing of polyadenylation is governed by a “combinatorial code” of CPEs and Pumilio-binding elements in the 3′-UTRs of these mRNAs.

A similar mechanism appears to operate during neurogenesis, in which Neuroguidin binds to eIF4E and represses translation of CPE-containing mRNAs (21). The protein is detected in axons and dendrites of the mammalian nervous system and contains three eIF4E-binding motifs (Table 2). Neural tube closure and neural crest migration are arrested in X. laevis embryos if Neuroguidin is depleted, suggesting that Neuroguidin regulates the translation of CPE-containing mRNAs to direct neural development. Another eIF4E-binding protein that functions in neuronal dendrites is CYFIP1 (22). FMRP is an RNA-binding protein that is important for synaptic maturation. FMRP recognizes mRNAs through G quartets and U-rich sequences as well as through small noncoding RNAs. A binding partner of FMRP, CYFIP1, is also an eIF4E-binding protein (Table 2). Stimulation of neurons by neurotrophic factors causes CYFIP1 to dissociate from eIF4E at synapses, thereby resulting in translation of mRNAs previously repressed by FMRP.

eIF4E-binding proteins are also involved in embryogenesis. In the early Drosophila melanogaster embryo, Nanos protein represses the translation of hunchback mRNA, permitting posterior development. The 3′-UTR of nanos mRNA contains stem/loop structures that repress the translation of unlocalized nanos mRNA. Two of these stem/loops bind Smaug, a sequence-specific RNA-binding protein that functions as a translational repressor. Nelson et al. (23) showed that Smaug interacts with Cup and that Cup is an eIF4E-binding protein (Table 2). Nakamura et al. (24) also found Cup to be an eIF4E-binding partner, but in this case mediating the repression of oskar mRNA translation during its localization to the posterior of the oocyte. Repression is mediated by Bruno, a protein that binds the 3′-UTR of oskar mRNA. Likewise, Zappavigna et al. (25), studying oogenesis in D. melanogaster, showed that Cup was an eIF4E-binding partner.

The Vpg proteins of plant potyviruses and human caliciviruses are covalently linked to the 5′-end of the viral genome but also act as eIF4E-binding proteins (26, 27). This apparently pro-
vides the virus with a translational advantage over the host (Table 2). Naturally occurring potyviral resistance has been mapped to the genes for either elf4E or elf(iso)4E, depending on the species (28).

**Physiological Roles for Specific elf4E Family Members**

Hernández and Vazquez-Pianzola (29) have suggested that there is one elf4E family member in each organism that is ubiquitously and constitutively expressed to carry out general translation and that others are involved in specialized functions, both translational and non-translational. Examples of this are beginning to emerge (Table 1).

**IFE-1 and Spermatogenesis**—IFE-1, one of five elf4E family members in *C. elegans* (11, 16), is enriched in the germ line. It is the only one of the five to bind the P granule-resident protein PGL-1, which localizes IFE-1 to P granules (30). Depletion of IFE-1 shows that it is required for spermatogenesis, specifically progression through the meiotic divisions and production of sperm. IFE-1 shows that it is required for spermatogenesis, specifically progression through the meiotic divisions and production of sperm, in both hermaphrodites and males, whereas oogenesis is not affected. Sequestration of IFE-1 in P granules may regulate its level or function during spermatogenesis.

**IFE-4 and Egg Laying**—IFE-4, a Class II elf4E family member in *C. elegans*, is expressed in neurons, muscle, spermatheca, and vulva (31). Knock-out of *ife-4* produces a pleiotropic phenotype that includes a defect in egg laying. A global analysis of the polysomal distribution of individual mRNAs revealed that translation of only a small subset of mRNAs is affected by *ife-4* loss. The steady-state levels of proteins encoded by these mRNAs are correspondingly reduced, the functions of which can explain some of the phenotypic traits of *ife-4* knock-out mutants.

**IFE-2 and Aging**—A third *C. elegans* family member, IFE-2, is expressed in somatic tissues. Knock-out of the *ife-2* gene reduces global protein synthesis, protects from oxidative stress, and extends life span (32). The signaling through IFE-2 appears to be different from that of previously discovered longevity pathways. A model was proposed in which down-regulation of protein synthesis in the soma facilitates cellular maintenance and repair by diminishing the large energy requirement of translation, thus delaying the decline of somatic functions and senescence.

**elf4E-1B and Oogenesis**—A study by Minshall et al. (33) combined two themes covered above: a specific elf4E family member (Table 1) and an elf4E-binding partner tethered to 3′-UTR sequence motifs (Table 2). These authors found that the oocyte-specific *X. laevis* elf4E-1B is responsible for repressing translation of CPE-containing mRNAs early in oogenesis when Maskin is absent. They found that CPEB specifically interacts with an RNA helicase (Xp54), two RNA-binding proteins (Pat1 and RAP55), an elf4E-binding partner (4E-T), and elf4E-1B. Further evidence for elf4E-1B-mediated translational repression comes from a very recent study by Esvikov and Márin de Esvikova (34), who depleted elf4E-1B in fully grown stage VI oocytes of *Xenopus tropicalis* and observed acceleration of oocyte maturation after progesterone induction.

**d4EHP and Embryonic Patterning**—Another example of a specific elf4E family member being tethered to a specific 3′-UTR sequence motif occurs with *D. melanogaster* 4EHP (Table 1). In the *D. melanogaster* embryo, Caudal protein is synthesized asymmetrically because translation of its mRNA is inhibited in the anterior region by Bicoid. Cho et al. (35) found that the Class II elf4E family member d4EHP, which binds the cap but not elf4G, specifically interacts with Bicoid to suppress *caudal* mRNA translation. The inhibition is dependent on the Bicoid-binding region present in the 3′-UTR of *caudal* mRNA. In another study, Cho et al. (36) found that translation of *hunchback* mRNA is regulated by the same elf4E family member, d4EHP, but in this case, the elf4E-binding partner is Brat (Table 2). This system appears similar to the Maskin model (Fig. 1C).

**Conclusions and Future Directions**

This minireview has attempted to highlight several recent trends in research involving elf4E: discovery of new elf4E family members, discovery of new elf4E-binding partners, and the involvement of both in developmental processes. One is struck, however, by the growing number of elf4E family members (umbicc3-215.umbi.umd.edu/iisstart.asp) and the rapidly expanding number of elf4E-binding partners compared with the paucity of well understood mechanisms for how they act, suggesting there is still much to learn. Furthermore, a new chapter in the regulation of translation is opening with the discovery of microRNAs that interfere with initiation of translation in an mRNA-specific manner (37). elf4E family members and elf4E-binding partners could well play a role in microRNA-mediated translational control. elf4E should also prove to be central to our understanding of P-bodies and mRNA degradation because P-bodies lack ribosomes and all translation initiation factors except elf4E (37). The involvement of elf4E in malignant transformation and metastasis is the subject of intense research (38), including its utility as a marker for cancer stage and potential to serve as a target for novel anticancer therapies (39, 40). Further knowledge of the factors that influence elf4E function should aid in our understanding of malignant transformation and in the development of therapeutic strategies.

**Acknowledgments**—I am grateful to Tzvetanka Dinkova (Universidad Nacional Autónoma de México), Rosemary Jagus (University of Maryland), and Nancy Standart (University of Cambridge) for helpful suggestions.

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