From factors to mechanisms: translation and translational control in eukaryotes

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Biochemical and genetic studies are revealing a network of interactions between eukaryotic translation initiation factors, further refining or redefining perceptions of their function. The notion of translated mRNA as a ‘closed-loop’ has gained support from the identification of physical and functional interactions between the two mRNA ends and their associated factors. Translational control mechanisms are beginning to unravel in sufficient detail to pinpoint the affected step in the initiation pathway.

Introduction

The translation of eukaryotic mRNAs is a highly competitive and tightly regulated step in gene expression. Control is most commonly exerted on it at the rate-limiting initiation phase. Factors involved in translation initiation have been known for some time and their biochemical activities were used to build the salient model for cap-dependent initiation of translation [1]. According to this model, the 5′ cap structure (m7GpppN) attracts the eukaryotic initiation factor eIF4E (eIF4F) complex to the mRNA (Figure 1). eIF4F is a heteromultimeric complex composed of the cap-binding protein eIF4E, the RNA-dependent ATPase eIF4A, and the modular factor eIF4G. The small (40S) ribosomal subunit binds to the 5′ end of an mRNA as a 43S complex including eIF3, a multisubunit factor, and the ternary complex of eIF2 with GTP and Met-tRNAi. eIF2 can contact eIF3 whereas eIF4A, stimulated by eIF4B, is thought to unwind secondary structure in the 5′ UTR. The resulting 48S complex then advances through the initiation cycle. A lateral movement of the 43S complex along the mRNA, termed scanning, is the most plausible explanation for a faithful recognition of the (usually) first AUG triplet as the start codon. Codon–anticodon base-pairing with Met-tRNAi triggers eIF2-bound GTP hydrolysis, catalysed by eIF5; it has been thought that this causes dissociation of initiation factors and large (60S) subunit joining to form the 80S ribosome.

The scope of our review is to summarise the recent progress in establishing a network of interactions between initiation factors and the mRNA substrate. We discuss physiological examples of specific translational control with an emphasis on the interface between regulatory mechanisms and the initiation pathway. As space is limiting, the focus of this review could not be extended to include interesting developments in the area of signal transduction to translation initiation factors or progress in viral mRNA translation.

Initiation factor function

Circularisation of mRNA

The 3′ poly(A) tail of mRNAs also participates in translation initiation [2] and acts synergistically with the cap structure [3]. In the mid nineties, a picture of the underlying mechanism began to emerge: an interaction between the poly(A)-binding protein Pab1p and both eIF4G homologues was discovered in yeast [4,5]. It was shown that this interaction is required for poly(A)-dependent recruitment of 43S complexes to the mRNA [5–7], leading to the hypothesis that simultaneous binding of eIF4E and Pab1p to eIF4G and concomitant circularisation of the mRNA template may form the biochemical basis of translational synergy between cap structure and poly(A) tail (Figure 1a).

Functional and physical evidence for such a circular conformation of the mRNA has now been obtained. In a yeast cell-free translation system, poly(A)-tail-promoted translation lacks an inherent directionality towards the mRNA 5′ end and can occur internally. The cap structure serves to anchor ribosome recruitment to the 5′ end, probably via Pab1p/eIF4G/eIF4E interactions. Translational synergy between the mRNA end modifications originates from a superior efficiency of this combined mode to attract initiation complexes, which becomes apparent when mRNAs are competing for limiting initiation factors as is usually the case [8,9••]. Using recombinant yeast factors eIF4E, eIF4G and Pab1p and a synthetic capped and polyadenylated RNA, circular complexes were directly observed by atomic force microscopy [10••].

Poly(A)-binding protein (PABP) binds to eIF4G in plant and mammalian systems too. Wheat germ PABP interacts with both cognate eIF4F isoforms and eIF4B, and a binding determinant was found in the amino-terminal region of
iso-eIF4G. In a purified system composed of cap analogue, (iso-)eIF4F, PABP and polyribo(A), all binding interactions were found to positively reinforce each other [11,12]. The interaction between the mammalian proteins involves a previously unrecognised amino-terminal region of eIF4G, as demonstrated by two independent studies. First, eIF4G was found by the two hybrid assay to interact with the rotaviral NSP3 protein which itself is associated with the very 3′ end of the (nonadenylated) rotaviral mRNAs [13••]. NSP3 and PABP association with eIF4F were found to be mutually exclusive in Rotavirus infected cells. Second, the presence of additional sequence at the amino-terminus of the highly similar eIF4GII [14], prompted the cloning of additional 5′ cDNA sequence of eIF4GI. Co-precipitation assays in vivo and in vitro demonstrated an interaction of PABP with the amino-terminal extension of both eIF4Gs [15•], which maps to the region that binds NSP3. These findings uncover a new viral strategy to usurp the cellular translation machinery: NSP3 evicts PABP from the eIF4F complex and acts as its functional replacement specifically for viral mRNAs.
RNA circularisation is thus emerging as a central feature of eukaryotic translation initiation. The functional significance of circularisation may be to increase translational fidelity by ensuring that only properly processed and exported mRNA molecules are translated [10••]. Translational synergy could arise as a consequence of cooperative binding events along the path to 43S recruitment. This could, for instance, affect the formation of the eIF4F/PABP bridging complex or the binding of the 40S subunit itself. Another interesting and not mutually exclusive possibility is that components of the translation machinery (i.e. the ribosome) may be recycled on the same mRNA molecule after termination, aided by the proximity of the termini. This inherently attractive concept divides the translational life of an mRNA into the first and subsequent rounds of translation which may differ in their initiation factor requirement. This issue was addressed by employing poliovirus protease 2A as a tool [16•], which cleaves eIF4GI and II carboxy-terminally from the eIF4E/PABP binding regions to block translation [17]. Under conditions of near complete cleavage of eIF4GI and II, cellular mRNAs continued to be translated for hours whereas, for instance, a newly transcribed reporter mRNA was very poorly translated [16•]. This points to a differential requirement for physically intact eIF4G during first and subsequent rounds of translation. The 2A-cleavage of eIF4G does not separate the eIF4F and PABP binding regions and additional interlocking interactions may exist which help to bridge between the mRNA ends [10••] and terminating ribosomes once the first translation complex has been assembled.

Interestingly, an eIF4G-related protein called PAIP, for PABP-interacting protein, has been discovered which binds eIF4A but not eIF4E [18•]. PAIP may provide an additional contact between the poly(A) tail and the initiation machinery.

**Ribosomal scanning**

The scanning model for initiation in eukaryotes can explain the general adherence of eukaryotic mRNAs to the first start codon rule, and is compatible with pseudocircular mRNA substrates. Its popularity notwithstanding, direct evidence for scanning or insight into its mechanism has proven hard to obtain [19].

A reconstitution approach using highly pure or recombinant components and a toe-printing assay (i.e. the arrest of primer extension by reverse transcriptase at the leading edge of mRNA-associated complexes), may now begin to shed light onto this question [20••]. Addition of 40S subunits, ATP, eIF2, 3, 4A, 4B, and 4F led to formation of a cap-proximal complex I (leading edge 21–24 nucleotide from the 5’ end), which could not be chased towards the initiator codon. Inclusion of eIF1 and 1A, however, led to formation of an authentic 48S complex, centred over the AUG (complex II, leading edge 15–17 nucleotides 3’ of the AUG). eIF1 and 1A act synergistically in this assay and, when added to complex I formed in their absence, require a cycle of dissociation/reassociation to assemble into complex II. Thus, although complex I is not a direct precursor of complex II, eIF1 and 1A are the first initiation factors intimately linked to the positioning of the small ribosomal subunit at the translation initiation codon (Figure 1b).

They might positively affect the processivity of scanning and/or form part of a clamp that closes over the mRNA-binding cleft of the 40S subunit [21,22•].

**Interaction networks**

The yeast SUI (suppressor of initiator codon mutations) mutants which allow initiation at a UUG codon are affected in either eIF1, 2, or 5 [23], eIF1 itself was found to interact with the Nip1p subunit of yeast eIF3 (known as p110 in human) [22•,24], which also binds eIF5 [25•]. In turn, eIF5 interacts with eIF2 [26], thus outlining an arrangement of factors involved in the final step of ‘scanning’: the recognition of the initiation codon (Figure 1). Completion of the cDNA cloning of all 10 subunits of mammalian eIF3 [27] allowed an exhaustive search for identifiable homologues in the yeast genome. Five yeast genes — *PRT1*, *TIF32*, *NIP1*, *TIF34*, and *TIF35* — were found, and all five encoded proteins are part of a functional eIF3 complex [25•]; thus, they are considered to constitute a conserved core of eIF3 (Figure 1c). The composition of yeast eIF3 preparations varies with the purification procedure [28,29] and three additional polypeptides — encoded by the genes *SUI1* (a yeast homologue of eIF1), *GCD10*, and *TIF31* — have been implicated as either more loosely bound eIF3 subunits or as factors interacting with the complex. A complex involving eIF3 with its several RNA-binding subunits is an additional candidate for the above mentioned clamp that could embed the mRNA in the 40S-binding cleft [19,22•]. Information on which of the eIF3 subunits interact with eIF4G is eagerly awaited.

eIF4E is phosphorylated at a conserved Ser 209 in response to external stimuli such as growth factors, hormones and mitogens, resulting in enhanced cap-binding [30,31]. On the basis of crystal structure data, phosphorylated Ser 209 can form a salt bridge with Lys 159, which may serve as an another type of clamp over the bound mRNA [32]. A MAP kinase activated protein kinase, Mnk1 was found independently, by two-hybrid studies [33•] and by co-precipitation assays *in vivo* and *in vitro* [34•], to bind the carboxyl-terminus of mammalian eIF4GII&II as well as the eIF4G-related protein p97 (or NAT-1/DAP-5). eIF4G can thus provide a docking site for efficient and specific phosphorylation of eIF4E assembled into eIF4F, whereas p97, which cannot bind eIF4E, could play a regulatory role by sequestering Mnk1.

It came as a major surprise that the bacterial initiation factor 2 (IF2) was found to be conserved throughout evolution, with homologues identified in archaea, yeasts, mammals, zebrafish, and maize [35••,36•]. *S. cerevisiae* strains lacking the *FUN12* gene, which encodes yeast (y)IF2, show a drastic shift from polysomes to inactive
Iron regulatory proteins

Iron regulatory proteins (IRPs) inhibit ferritin translation by binding to specific 5′ UTR sites, the iron-responsive elements (IREs). Using a novel procedure to purify initiation complexes, the regulatory mechanism was analysed in the rabbit reticulocyte lysate system. The cap-proximal binding of IRP-1 to the IRE was shown to permit assembly of eIF4F and eIF4B on the mRNA but to impede the association of eIF3 and the 40S ribosomal subunit [37••]. As one might predict, moving the repressor complex further away from the cap allows the recruitment of mammalian 43S complexes to the mRNA. After temporary stalling, they then progress linearly through the IRE to the initiator codon [38]. The apparent scanning arrest is probably overcome by active displacement of IRP-1, because the passive dissociation rate is slow. Regarding the mechanism of initiation, these results also indicate that eIF4F can bind to the cap without prior association with 40S-bound eIF3. The data also indicate that the RNA-helicase activity of eIF4A/4B alone does not suffice for IRP-1 displacement [37••], a property that the 48S complex seems to possess [38]; it is thus uncertain whether eIF4A/4B could serve as the sole ‘motor’ of scanning.

Developmental control – masking and polyadenylation

The 3′ UTR of mRNAs is a common location of cis-acting elements that control their localisation and/or translation, particularly during oogenesis and early embryogenesis. At first glance, involvement of 3′ UTR elements in translational regulation seems counter-intuitive. However, this appears in a different light when one considers the role of the poly(A) tail and the importance of 5′/3′ end interactions.

Two originally quite separate notions of translational control mechanisms in development, mRNA masking and cytoplasmic polyadenylation, have begun to converge. Different possible explanations for an interdependence between masking and regulated polyadenylation have been proposed [39]: First, a 3′ UTR element represses translation by maintaining a short poly(A) tail; second, polyadenylation is required to inactivate a 3′ UTR repressor element/protein, or third, 3′ UTR element(s) control polyadenylation and translation independently — an elongated tail may then reinforce translational activity (Figure 2). The latter may act through counteracting a default deadenylation pathway that sets in during maturation [40•] and/or to boost the translational efficiency of the mRNA in the competitive cellular environment [8]. Several recent studies described below highlight the interrelation between masking and polyadenylation in different systems but do not (yet) allow one to propose a unifying model of the underlying mechanism(s).

Tissue-type plasminogen activator (tPA) mRNA is dormant in primary mouse oocytes and has a short poly(A) tail of ~50 adenosines. Meiotic maturation leads to translational activation and cytoplasmic polyadenylation. Both, the initial poly(A) shortening and the subsequent elongation

Translational regulation

Improved understanding of the translation initiation pathway provides a much stronger basis for understanding translational control mechanisms. Translation can be regulated globally by affecting initiation factor function (e.g. through phosphorylation of eIF4E, the 4E-binding proteins [31], and eIF2α, or by eIF4G cleavage [17]). Such global control affects many cellular mRNAs and thus total protein synthesis. In addition, translational regulation of specific mRNAs has been studied and is generally exerted through cis-acting elements on the mRNA. Recent progress in the latter area is discussed below.

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require a UA-rich element, the ACE or CPE (adenylation control or cytoplasmic polyadenylation element) in the tPA 3’ UTR. Cytoplasmic polyadenylation additionally requires the ‘nuclear’ polyadenylation hexanucleotide [39]. Injection of ACE competitor transcripts into oocytes now shows that the short poly(A) tail in primary oocytes alone is insufficient for dormancy and that a titrateable factor needs to bind to the ACE. A candidate for this masking function is an approx. 80 kDa protein which cross-links to the ACE. Removal of the factor, however, only leads to awakening of the tPA mRNA in primary oocytes if at least a short poly(A) tail is present. It also induces a more rapid polyadenylation of the mRNA during maturation [40*]. Thus, the findings with tPA mRNA are most consistent with the third scenario listed above.

The mRNA for Xenopus FGF receptor-1 (XFGFR–1) is repressed in immature oocytes as a result of the translation inhibitory motif in its 3’ UTR. Oocyte maturation induces polyadenylation and activation of translation. When maturation is induced directly, by injection of maturation-promoting factor, XFGFR translation occurs at normal levels concomitant with only minimal poly(A) tail elongation on the mRNA. Treatment of c-mos-depleted oocytes with progesterone, by contrast, does not induce progression through meiosis or XFGFR translation but the mRNA gets efficiently polyadenylated [41*]. Here, masking as well as unmasking can be uncoupled from polyadenylation and unmasking can occur in the presence of a short tail.

Translational activation of Xenopus cyclin B1 mRNA during oocyte maturation also coincides with CPE-dependent polyadenylation. Injection of excess CPE competitor RNA into immature oocytes causes translational unmasking of the endogenous mRNA in the absence of poly(A) tail elongation [42*], consistent with the third hypothesis above. By contrast, reporter mRNAs bearing the cyclin B1 3’ UTR with functional CPEs, a tail of 30 adenosines, but without the hexanucleotide polyadenylation motif are not activated during oocyte maturation. This latter result is more suggestive of the second explanation. The CPE-binding protein (CPEB) is essential for cytoplasmic polyadenylation. Additionally, its binding activity correlates strongly with translational repression. These findings raise the possibility that CPEB could function both positively and negatively at different stages of development. Interestingly, an EMCV internal ribosome entry site-driven reporter mRNA is much less sensitive to CPE-mediated repression. Internal ribosome entry site-driven translation, because of differential initiation factor requirement, may not depend on interactions that are necessary for the cellular cyclin B1 transcript. It has also been suggested that polyadenylation may function by stimulating cap-ribose methylation [43].

Recent studies with maternal surf clam mRNAs also highlight the interplay between masking and polyadenylation. p82 was originally found to bind a U-rich masking element in the 3’ UTR of ribonucleotide reductase mRNA and to mediate translational repression in vitro; recently it was identified as clam CPEB [44*,45*]. The ribonucleotide reductase mRNA 3’ UTR contains six CPE-like motifs, including two in the masking element, which together with the hexanucleotide motif support p82-mediated polyadenylation in egg extract. Fertilisation leads to translational activation of masked mRNAs and p82 is phosphorylated by a cdc2-like kinase before being degraded.

The onset of spermatogenesis in the Caenorhabditis elegans hermaphrodite depends on translational repression of tra-2 mRNA. Tra-2 repression is mediated via two 28 nucleotide direct repeat elements (DREs) or TGEs [tra-2 and GLI elements] in the 3’ UTR [46]. A yeast three-hybrid-screen identified GLD-1, a germline-specific member of the STAR-family of proteins, as a specific TGE-binding factor. GLD-1 is a component of the complex that forms on TGEs with worm extracts. Translational repression mediated through the TGEs by GLD-1 was demonstrated in a yeast in vitro system and depends on a functional KH-domain in the recombinant protein. Ectopic expression of GLD-1 and reporter constructs in somatic cells causes specific repression in vivo [47*]. Intriguingly, both TGE-mediated control and the STAR protein family are evolutionarily conserved.

In contrast to most other cellular mRNAs, metazoan histone mRNAs lack a poly(A) tail. They end with a conserved stem-loop that fulfils many of the functions of the poly(A) tail. It is essential for translation [48], and interacts with SLBP (stem-loop binding protein) in mammalian somatic cells. SLBP participates in pre-mRNA processing [49] and is a component of polyribosomal histone mRNPs. Xenopus oocytes possess two SLBPs. SLBP-2 is oocyte-specific, present at high levels in early oogenesis and degraded during early embryogenesis. SLBP-1 is the homologue of mammalian SLBP and displays a reciprocal temporal expression pattern [50*]. This suggests the possibility of a masking phenomenon also for this nonadenylated mRNA, namely that exchange of SLBP-2 for -1 on the 3’ stem-loop could activate histone mRNA translation at oocyte maturation.

Developmental control – mRNA localisation and translation

Normal progression through oogenesis and embryogenesis in Drosophila requires coupling between translational control and mRNA localisation to achieve proper temporal and spatial protein expression [51]. For instance, translation of maternal oskar mRNA is silenced during transport to the posterior pole of the oocyte and until Oskar protein is required. These processes require the 3’ UTR of oskar mRNA and do not involve noticeable changes in mRNA poly(A) tail length. The Bruno protein recognises repeated conserved 3’ UTR sequences, the Bruno response elements (BREs). Bruno prevents premature translation and colocalises with oskar mRNA [52]. Oskar mRNA is
translated as two functional isoforms by alternative start codon usage on its mRNA and an element between the two AUGs activates translation from both codons exclusively on localised mRNA [53**]. This region is a derepressor rather than an activator element, because it is only required when the 3′ BREs are active. Two proteins, p50 and p68 (distinct from Bruno), interact with the 5′ element and p50 also binds to the 3′ BRE, apparently simultaneously with Bruno. These observations demonstrate a highly complex mechanism involving a growing list of factors to achieve localisation-dependent derepression of oskar mRNA translation. The functional interactions between 5′ UTR derepressor and 3′ UTR repressor elements again reflects the recurrent theme of end-to-end communication.

Conclusions and future directions

Research on the translation initiation pathway is progressing towards a more complete picture of molecular interactions during its different phases. In particular, the concept of 5′ and 3′ end interactions opens up new possibilities to address poly(A)-tail-dependent and poly(A)-tail-independent means of translational regulation by specific mRNA-binding proteins in a more informed context.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as: * of special interest ** of outstanding interest


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Together with [24], this study identifies an eIF3 core complex conserved between yeast and mammals and charts a map of intersubunit interactions and contacts with other initiation factors.


See annotation [34].


This paper and [33] identify a physical link between mitogen- and stress-activated signaling and translation initiation. Mnk1 docks onto eIF4E to phosphorylate binding site 4E-A.


In addition to highlighting an unexpected universal conservation of a bacterial and a yeast initiation factor, this report and [39] indicate the existence of an additional GTP-hydrolysis step in eukaryotic initiation.


See annotation [35].


This paper describes a new method to specifically capture and purify translation initiation complexes formed on a given mRNA. Analysis of the composition of such complexes reveals the mechanism of translational control by a 5′ UTR-binding protein at ‘initiation factor resolution’.


The complex interdependence between translational masking and control of cytoplasmic polyadenylation is elegantly demonstrated for tissue-type plasmoingen activator mRNA.


The role of a 3′ UTR motif in the appropriate timing of Xenopus FGF receptor 1 translation during meiotic maturation is highlighted. The study provides an example of an apparent lack of a relationship between translational activation and polyadenylation.

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Here, an involvement of 3′ UTR CPEs in both translational masking and unmasking of cyclin B1 mRNA during Xenopus oocyte maturation is demonstrated.


See annotation [45].


This paper and [44] illustrate a functional linkage between masking/unmasking and cytoplasmic polyadenylation.


Translational repression through 3′ UTR elements is mediated by the KH-domain protein GLD-1, a member of the STAR-family of proteins. A comprehensive study providing both in vivo and biochemical evidences.


This study demonstrates that Xenopus oocytes have two SLBPhs whose levels are inversely regulated during oogenesis. The authors suggest that an exchange of SLBP isoforms on the histone 3′ ends regulates their translational activation.


5′ derepressor and 3′ UTR repressor elements cooperate to achieve spatially restricted oskar mRNA binding during Drosophila oogenesis. This is the first detailed report that identifies an active role of a 5′ element in mediating derepression from 3′ UTR silencing.