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Invited Mini Review

Translational control of mRNAs by 3'-Untranslated region binding proteins

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Eukaryotic gene expression is precisely regulated at all points between transcription and translation. In this review, we focus on translational control mediated by the 3'-untranslated regions (UTRs) of mRNAs. mRNA 3'-UTRs contain *cis*-acting elements that function in the regulation of protein translation or mRNA decay. Each RNA binding protein that binds to these *cis*-acting elements regulates mRNA translation via various mechanisms targeting the mRNA cap structure, the eukaryotic initiation factor 4E (eIF4E)-eIF4G complex, ribosomes, and the poly (A) tail. We also discuss translation-mediated regulation of mRNA fate. [BMB Reports 2017; 50(4): 194-200]

INTRODUCTION

Translational regulation of mRNA is an immediate and precise mechanism to control gene expression in various biological processes, including development, differentiation, and responses to extracellular stress. Global quantification analysis indicates that the cellular abundance of proteins in mammals is predominantly controlled at the level of translation (1). *In vivo*, mRNAs do not exist as bare mRNA molecules but as mRNA-protein complexes with RNA-binding proteins (RBPs) (2-5). More than one thousand RBPs have been identified, and they bind to specific *cis*-acting elements, consisting of sequence elements, stem-loop structures and/or modified nucleotides (6-8). For many genes, alternative poly (A) addition and alternative splicing give rise to 3'-UTR variants (Fig. 1A and B). These variants are controlled by specific post-transcriptional regulation (9, 10).

The cap-dependent mRNA translational process is divided

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into three major steps: initiation, elongation, and termination. Each step is elaborately regulated by multiple mRNA 3'-UTR binding proteins in a cell type- and species-specific manner (11, 12). In this review, we present examples of RBP-mediated regulation of translation and we discuss their biological roles.

MOLECULAR MECHANISM OF CAP-DEPENDENT mRNA TRANSLATION BY 3'-UTR BINDING PROTEINS

In eukaryotes, most protein coding mRNAs have a 5'-terminal cap structure and a 3'-terminal poly-adenine. Histone mRNAs, however, are an exception, having a specific stem-loop structure in the 3'-terminal region (13). The cap structure acts as an anchor and is critical for translation initiation by the eukaryotic initiation complex (14). In eukaryotes, this cap-dependent translation initiation is implemented by two macromolecular complexes, namely, the eukaryotic initiation factor-4F (eIF4F) complex, consisting of eIF4E, eIF4G and eIF4A, and the 43S initiation complex, consisting of a 40S ribosome, eIF3, eIF1A, eIF2 and methionyl-tRNA (11, 12). The eIF4F complex connects the 5'- and 3'-termini of the mRNA via interactions with poly(A) binding protein (PABP) or histone stem-loop binding protein (SLBP) (13). This mRNA circularization plays a significant role in efficient translation, probably by accelerating ribosome recycling (Fig. 2A) (11, 12). In addition, eukaryotic release factor 3 (eRF3) directly binds to the PABP/eIF4G complex and stimulates translation (15). Hence, mRNA translation can be modulated by the cap-binding protein complex. The circularization of mRNA is also a significant molecular feature in the regulation of cap-dependent mRNA translation by 3'-UTR RBPs (11, 12).

## REGULATION OF TRANSLATION THROUGH THE CAP STRUCTURE (Fig. 2B)

The cap-binding protein, eIF4E, is the foundation of a translation initiation complex at the 5'-terminal cap structure (11, 12). In addition, the eIF4E-related molecule, 4E homologous protein (4EHP), competitively and directly binds the cap structure. However, 4EHP represses translation because of its weak affinity to eIF4G (16). 4EHP can be recruited by RBPs such as Bicoid (which binds to a specific *cis*-element in the
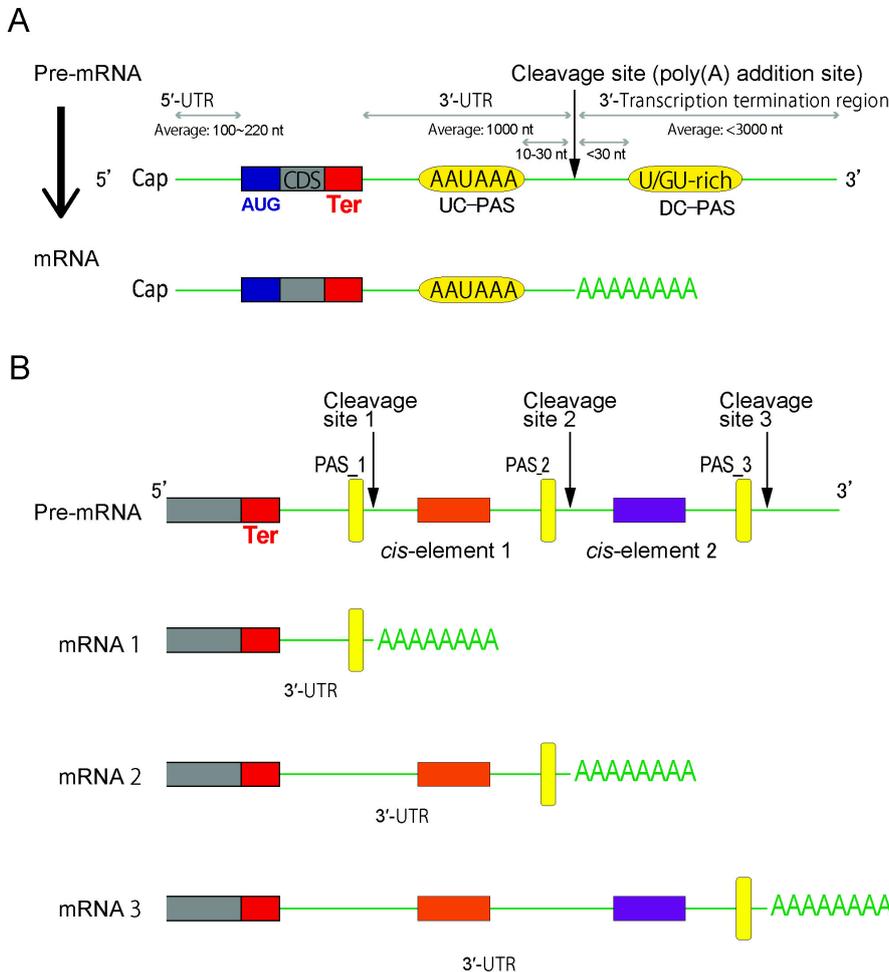
Fig. 1. mRNA processing generates 3'-UTR variants. (A) Schematic depictions of pre-mRNA and mature mRNA. UTR (untranslated region), CDS (protein coding sequence), UC-PAS (upstream core polyadenylation signal), DC-PAS (downstream core polyadenylation signal). (B) mRNA isoforms with alternative poly(A) additions.

3'-UTR of *caudal* mRNA) and the Pumilio/Nanos/Brat complex (which binds to a specific *cis*-element in the 3'-UTR of *hunchback* mRNA) during *Drosophila melanogaster* development (17, 18). Mammalian 4EHP also has the ability to suppress translation via the same mechanisms (19, 20). On the other hand, 4EHP can augment translation during hypoxia in human U87MG glioblastoma cells (21). The transcription factor, hypoxia-Inducible Factor 2α (HIF-2α), can bind both DNA and RNA and forms a complex with RBM4 on the 3'-UTRs of a subset of mRNAs including *FGFR* mRNA. The HIF-2α/RBM4 complex then recruits 4EHP to stimulate translation. eIF4A, but not eIF4G, is present in this complex (21).

REGULATION OF TRANSLATION THROUGH THE eIF4E-eIF4G STRUCTURE (Fig. 2C)

The interaction between eIF4E and eIF4G is required for mRNA circularization and the initiation of cap-dependent

translation (11, 12). *D. melanogaster* Cup, *Xenopus laevis* Maskin, mammalian Neuroguidin (NGD) and mammalian cytoplasmic fragile X mental retardation protein (FMRP) interacting protein 1 (CYFIP1) bind eIF4E competitively with eIF4G and repress translation. These translational repressors are recruited to mRNAs through specific 3'-UTR binding proteins, namely, Cup/Bruno, Cup/Smaug, Maskin/cytoplasmic polyadenylation element binding protein (CPEB), NGD/CPEB, and CYFIP1/FMRP (22-25).

microRNAs (miRNAs) are small RNA molecules consisting of 21-24 nucleotides that form microRNA-induced silencing complexes (miRISCs) with Argonaute (Ago) proteins and repress translation. Ago proteins have isoform specific mechanisms for repression of translation. In *D. melanogaster*, after miRISC binds to a miRNA target site in an mRNA 3'-UTR, Ago2 represses translation by competing for eIF4E binding, which is similar to Cup (26).
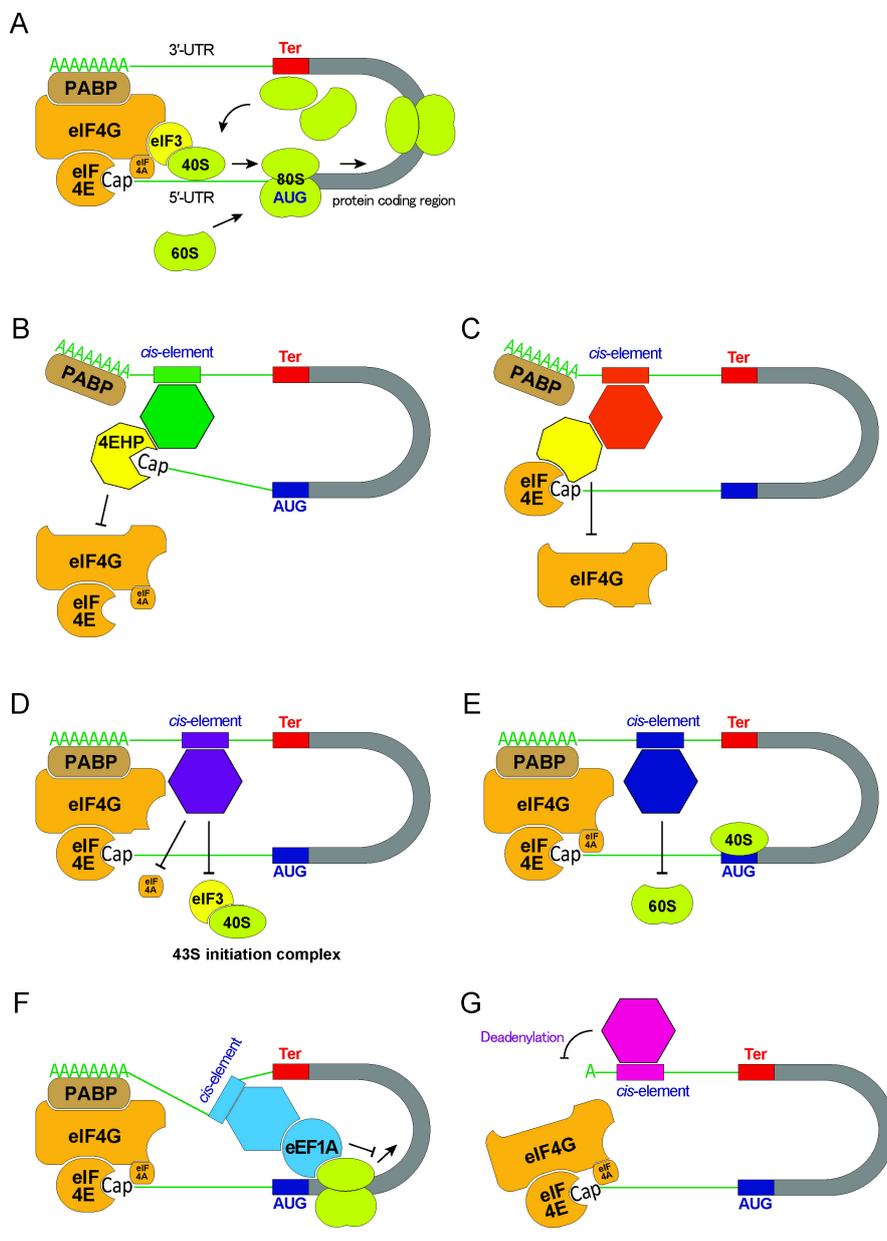
Fig. 2. Translational control by 3'-UTR binding proteins. (A) Schematic depiction of circularized mRNA translation. (B) Regulation of translation through the cap structure. (C) Regulation of translation through the eIF4E-eIF4G complex. (D) Regulation of translation through the 43S translation initiation complex. (E) Regulation of translation through the 80S ribosome assembly. (F) Regulation of translation through translation elongation. (G) Regulation of translation through the poly(A) tail.

REGULATION OF TRANSLATION THROUGH THE 43S TRANSLATION INITIATION COMPLEX (Fig. 2D)

In contrast to *D. melanogaster* Ago2, *D. melanogaster* Ago1 and vertebrate Ago2 repress translation by interfering with the assembly of a functional eIF4F complex. This occurs through the displacement of eIF4A (in vertebrate eIF4A1 and eIF4A2) from the mRNA, leading to the functional suppression of the 43S initiation complex (27, 28). A conflicting model of vertebrate Ago2 action has been proposed. In this model, the

vertebrate Ago-associated CCR4-NOT complex recruits eIF4A2. The eIF4A2 would then inhibit translation initiation by preventing the recruitment of active eIF4A1 (29). Further investigations are necessary to verify these models (30, 31). In addition, these Ago isoforms are expected to affect mRNA circularization through complex formation with trinucleotide repeat-containing protein 6 (TNRC6), which has the ability to repress translation (30, 31).

The gamma interferon-activated inhibitor of translation (GAIT) complex consists of a ribosomal protein L13a (rpL13a),

glyceraldehyde-3-phosphate dehydrogenase (GAPDH), glutamyl-prolyl-tRNA synthetase (EPRS), and NS1-associated protein-1 (NSAP1), and represses translation initiation by inhibiting recruitment of the 43S translation initiation complex. The GAIT complex recognizes specific stem-loop structure elements and, in response to interferon-γ, forms on a subset of 3′-UTR elements of mRNAs, including those of *ceruloplasmin* and *vascular endothelial growth factor* (*VEGF*). mRNA circularization is maintained during GAIT-mediated repression of translation and is expected to contribute to the action of the 3′-UTR binding protein complex on 5′-terminal cap-dependent translation initiation (32).

During female embryonic development in *D. melanogaster*, translation of *mls2* mRNA is prevented by the Sex-lethal (SXL)/upstream of N-ras (UNR) complex formed on a specific *cis*-acting element in the 3′-UTR of *mls2* mRNA. The SXL/UNR complex inhibits the recruitment of the 43S translation initiation complex by maintaining mRNA circularization (33). In addition, SXL binds to the 5′-UTR of *mls2* mRNA and represses initiation codon scanning by the 43S initiation complex in an upstream open reading frame (uORF)-dependent manner (34).

Emerging evidence indicates that base modifications, including inosine, N6-methyladenosine (m⁶A), N1-methyladenosine, 5-methylcytosine, 5-hydroxymethylcytidine, and pseudouridine, can modulate the fate of mRNA (35). Among these modifications, m⁶A in 3′-UTRs promotes translation when recognized by YTH domain-containing family protein 1 (YTHDF1) (36). Similarly, methyltransferase like 3 (METTL3), a catalytic subunit of the m⁶A methyltransferase complex, recognizes an un-methylated site of m⁶A and promotes translation (37). Although the precise mechanism needs to be elucidated, both YTHDF1 and METTL3 form a complex with components of the 43S translation initiation complex. Intriguingly, YTHDF2, another m⁶A decoder, competitively binds the same site and degrades mRNA (38). These complementary functions of m⁶A decoders could enable dynamic and precise regulation of gene expression.

REGULATION OF TRANSLATION THROUGH 80S RIBOSOME ASSEMBLY (Fig. 2E)

During the differentiation of erythrocytes, the heterogeneous nuclear ribonucleic protein K (hnRNPK)/hnRNPE1 complex associates with a specific *cis*-acting element in the 3′-UTR of *15-lipoxygenase* mRNA. The hnRNPK/hnRNPE1 complex represses translation by inhibiting 60S ribosome binding to the 43S initiation complex and assembly of the 80S ribosome (39).

Translational repression during mRNA targeting coupled to local translation is essential for spatial restriction of protein production (40). In *Saccharomyces cerevisiae*, *ASH1* mRNA, which encodes a repressor of mating-type switching, localizes to the tip of daughter cell. Translation of localizing *ASH1* mRNA is silenced by Pumilio-homology domain protein 6

protein (Puf6p). Puf6p prevent assembly of 80S ribosomes on *ASH1* mRNA. Puf6p recognizes a *cis*-acting element in the 3′-UTR of *ASH1* mRNA and binds yeast eIF5B. eIF5B is an essential component of 80S ribosome assembly; therefore, this RNA-dependent interaction is essential for translational repression of the *ASH1* mRNA. Intriguingly, casein kinase 2 (CK2)-mediated phosphorylation of Puf6p restores *ASH1* mRNA translation after mRNA localization (41).

In mammals, Z-DNA-binding protein 1 (ZBP1) represses *β-actin* mRNA translation through the inhibition of 80S assembly before its localization to the leading edge of cell migration. After mRNA localization, Src kinase-mediated phosphorylation of ZBP1 restores *β-actin* mRNA translation (42).

REGULATION OF TRANSLATION THROUGH ELONGATION (Fig. 2F)

Phosphorylation-mediated regulation of translation through repression of RBPs plays a critical checkpoint coordinating the expression of transforming growth factor β (TGFβ)-induced epithelial-mesenchymal transition (EMT) transcripts in tumorigenesis and metastatic progression. The hnRNPE1/eukaryotic elongation factor 1A (eEF1A) complex forms on specific *cis*-acting elements in the 3′-UTR of *disabled-2* mRNA and *interleukin-like EMT inducer* (ILEI) mRNA. The hnRNPE1/eEF1A complex represses translation by associating with the translating 80S ribosome to "stall" on mRNA by preventing eEF1A dissociation from the 80S ribosome. Akt2, which is activated by TGFβ signaling, mediates phosphorylation of hnRNPE1 and induces hnRNPE1 dissociation from mRNA, thereby restoring translation of target mRNAs. Importantly, attenuation of hnRNP E1 expression induced EMT and enabled cells to form metastatic lesions *in vivo* (43).

eEF1A dissociation-mediated translational repression is also used by *Caenorhabditis elegans gld-1* mRNA. The FBF-1 (nematode Pumilio)/CSR-1 (Ago isoform)/EFT-3 (nematode eEF1) complex forms on a specific *cis*-acting element in the 3′-UTR of *gld-1* mRNA and represses translation (44).

REGULATION OF TRANSLATION THROUGH THE POLY(A) TAIL (Fig. 2G)

Many RBPs bound to 3′-UTRs of mRNAs induce mRNA degradation, although we do not discuss this in detail in this review (10). These RBPs associate with the deadenylase complex (e.g. poly(A)-specific ribonuclease (PARN), the poly(A) ribonuclease 2 (PAN2)/PAN3 complex and the carbon catabolite repression 4 (CCR4)−negative on TATA-less (NOT) complex) to enhance deadenylation (45). The terminal uridylyl transferases, TUT4 and TUT7, selectively recognize and catalyze uridylation of deadenylated mRNAs with short A-tails (< 25 nucleotides). This oligo uridylation enhanced the further degradation of the mRNA body (46).

Deadenylation is thought to dissociate PABP from the 3′-tail

of mRNA and to disrupt mRNA circularization, thereby repressing translation. However, recent studies demonstrated that median poly(A) lengths are about 60-100 nucleotides (nt), which is shorter than the 150-200 nt thought to be typical of mammalian poly(A) tails. Poly(A) lengths of > 20 nt are not correlated with translational efficiency in somatic cells (47, 48). When the poly (A) tail length is < 20 nt, translation is repressed in most genes in somatic cells (48). Because PABP binds to poly(A)s of 20 nt lengths, one PABP molecule might be sufficient to support mRNA circularization and poly(A)-dependent efficient translation.

In contrast to somatic cells, poly(A) tail length and translational efficiency are coupled in embryonic cells (47, 49). In *X. laevis* oocytes, cytoplasmic polyadenylation element binding protein (CPEB) binds specific cis-acting elements in the 3′-UTRs of mRNAs encoding cell cycle-related proteins, such as cyclin B. CPEB recruits PARN deadenylase and short poly(A) mRNAs are stabilized before oocyte maturation (50, 51). The stimulation of oocyte maturation induces CPEB phosphorylation and promotes the association of cleavage and polyadenylation specificity factor (CPSF) and Germ Line Development 2 (GLD-2), poly (A) polymerase. Poly(A) elongation then augments translation of target mRNAs.

REGULATION OF mRNA DECAY THROUGH TRANSLATION

As mentioned above, the 3′-UTR plays a key role in translational control. However, reciprocally, translation also regulates 3′-UTR-mediated mRNA decay. For instance, when exon-junction complexes are bound to the 3′-UTR, premature translation termination is recognized, and the mRNA is degraded by the nonsense-mediated mRNA decay pathway which acts as an mRNA quality control system (52). Normal translation termination codon recognition also stimulates mRNA degradation of inflammation-related mRNAs containing a specific stem-loop in the 3′-UTR. In this case, the stem-loop is recognized by Regnase-1, an endonuclease (53). Similarly, translational termination induces the degradation of replication-dependent histone mRNAs and Staufen1-mediated mRNA decay (54, 55). An RNA helicase called Up frame shift 1 (UPF1) is required for the translation-dependent mRNA decay systems described above. Taken together, 3′-UTRs can act bi-directionally in translational regulation and mRNA decay − mechanisms that are closely involved with each other.

PERSPECTIVES

In the present review, we briefly introduced the mechanism of translational control by mRNA 3′-UTR-binding proteins. Translational control is recognized as an essential regulatory mechanism of gene expression in various biological processes. For example, interferon-γ production from T-cells is regulated by translational control coupled with glycolysis. GAPDH, an

enzyme essential for glycolysis, also acts as an RBP that directly binds to a cis-acting element in the 3′-UTR of the interferon-γ mRNA and acts as a translational repressor in inactive T cells. T cell activation drastically alters the metabolic status of T cells, with aerobic glycolysis promoted over oxidative phosphorylation, and GAPDH can dissociate from the interferon-γ mRNA to function as an aerobic glycolysis enzyme. In this situation, GAPDH no longer represses the translation of interferon-γ mRNA, leading to an increase in interferon-γ production (56).

Many RBPs involved in translational control and/or mRNA degradation have additional roles in alternative pre-mRNA splicing, alternative poly(A) addition and other mRNA processing events (57). In addition, analysis of translational control using plasmid vector-based reporter assays must consider the possibility of unexpected/undesired transcription from all regions of the circular plasmid DNA and unexpected processing of mRNA. Hence, *in vitro* reconstituted translation experiments should also be performed in addition to cell and/or animal-based analysis.

CONFLICTS OF INTEREST

The authors have no conflicting financial interests.

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