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Translational control of mRNAs by 3′-untranslated region binding proteins

Running title:

Translational control of mRNAs by 3′-UTR

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Summary

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. RNA binding proteins that bind to these *cis*-acting elements regulate 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.

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 have specific post-transcriptional regulation (9, 10).

The cap-dependent mRNA translation process is divided into three major steps: initiation, elongation and termination and 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 exemption, 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 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 interaction 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 PABPC1/eIF4G complex and stimulates translation (15). Hence, mRNA translation can be modulated by the cap binding protein complex. mRNA circularization 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.

Figure 2B. eIF4E is a cap binding protein that is the foundation of a translation initiation complex at the 5′-terminal cap structure (11, 12). 4E homologous protein (4EHP) is an eIF4E-related molecule that competitively and directly binds the cap structure. However, 4EHP represses translation because of weak affinity to eIF4G (16). 4EHP can be recruited by RBPs such as Bicoid (which binds to a specific *cis*-element in the 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.

Figure 2C. 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 translation 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 and species specific mechanisms for repression of translation. In *D. melanogaster*, after miRISC binds to an miRNA target site in an mRNA 3′-UTR, Ago2 represses translation by competing for eIF4E binding, which is similar to Cup (26).

Regulation of translation through the 43S translation initiation complex.

Figure 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, thereby 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 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).

HuD is a vertebrate neuron-specific mRNA 3′-UTR binding protein that stimulates translation initiation through its ability to bind eIF4A *in vitro* and in rat PC12 cells (32).

The gamma interferon activated inhibitor of translation (GAIT) complex consists of, 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 43S translation initiation complex recruitment. GAIT 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 *VEGF*. mRNA circularization is maintained during GAIT-mediated translation repression and is expected to contribute to the action of the 3′-UTR binding protein complex on 5′-terminal cap dependent translation initiation (33).

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 (34). 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 (35).

Emerging evidence indicates that base modifications, including inosine, N6-methyladenosine (m^6A), N1-methyladenosine, 5-methylcytosine, 5-hydroxymethylcytidine and pseudouridine, can modulate the fate of mRNA (36). Among these modifications, m^6A in 3′-UTRs promotes translation when recognized by YTH domain-containing family protein 1 (YTHDF1) (37). Similarly, methyltransferase like 3 (METTL3), a catalytic subunit of the m^6A methyltransferase complex, recognizes an un-methylated site of m^6A and promotes translation (38). 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 m^6A reader, competitively binds the same site and degrades mRNA (39). These complementary functions of m^6A readers could enable dynamic and precise regulation of gene expression.

Regulation of translation through 80S ribosome assembly.

Figure 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 43S initiation complex and assembly of the 80S ribosome (40).

Another example of 80S assembly inhibition by 3′-UTR is that of Pumilio-homology domain protein 6 protein (Puf6p)-mediated *ASH1* mRNA translation repression during mRNA transport in *Saccharomyces cerevisiae*. 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 translation repression of the *ASH1* mRNA. Intriguingly, Casein kinase 2 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. After mRNA localization, Src kinase mediated phosphorylation of ZBP1 restores *β-actin* mRNA translation (42).

Regulation of translation through elongation

Figure 2F. Phosphorylation-mediated regulation of translation through repression of

RBPs has a critical role during Transforming growth factor β (TGFβ)-induced epithelial-mesenchymal transition. 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" it 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 and thereby restores translation of target mRNAs (43). eEF1A dissociation-mediated translation 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.

Figure 2G. Many RBPs bound to 3′-UTRs of mRNAs induce mRNA degradation, although we do not discuss this in detail in this review. These RBPs include components of miRISCs, Bruno, and Smaug, and associate with the deadenylase complex, poly(A)-specific ribonuclease (PARN), the poly(A) ribonuclease 2 (PAN2)/PAN3

complex and the CCR4-NOT transcription complex (CNOT complex) to enhance deadenylation (10). Deadenylated short-A tailed (<25 nucleotide) mRNAs were selectively recognized and uridylated by TUT4/7. This oligo uridylation enhanced the further degradation of the mRNA body (45). Deadenylation is thought to dissociate PABP from the 3′-tail of mRNA and 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 translation efficiency in somatic cells (46, 47). When the poly (A) tail length is <20 nt, translation is repressed in most genes in somatic cells (47). Because PABP binds to poly(A)s of 20 nt, 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 translation efficiency are coupled in embryonic cells (46, 48). In *X. laevis* oocytes, 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 (49, 50). Maskin/CPEB complex-mediated translation

repression also functions in this state (23). 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), a 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, an mRNA quality control system (51). 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 (52). Similarly, translation termination induces the degradation of replication-dependent histone mRNAs and Staufen1-mediated mRNA decay (53, 54). 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 translation regulation and mRNA decay, mechanisms that are

closely involved with each other.

Perspectives

In the present review, we briefly introduced the mechanism of translation control by mRNA 3′-UTR binding proteins. Translation 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 translation 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 translation 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 dissociating 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 (55).

Many RNA binding proteins involved in translation control and/or mRNA degradation have additional roles in alternative pre-mRNA splicing, alternative poly(A) addition and other mRNA processing events (56). In addition, translation control analysis using plasmid vector based reporter assays must consider the possibility of

unexpected/undesired transcription from all regions of the circular plasmid DNA and unexpected mRNA processing. Hence, *in vitro* reconstituted translation experiments should also be performed in addition to cell and/or animal based analysis.

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Figure legends

Figure 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) addition.

Figure 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.

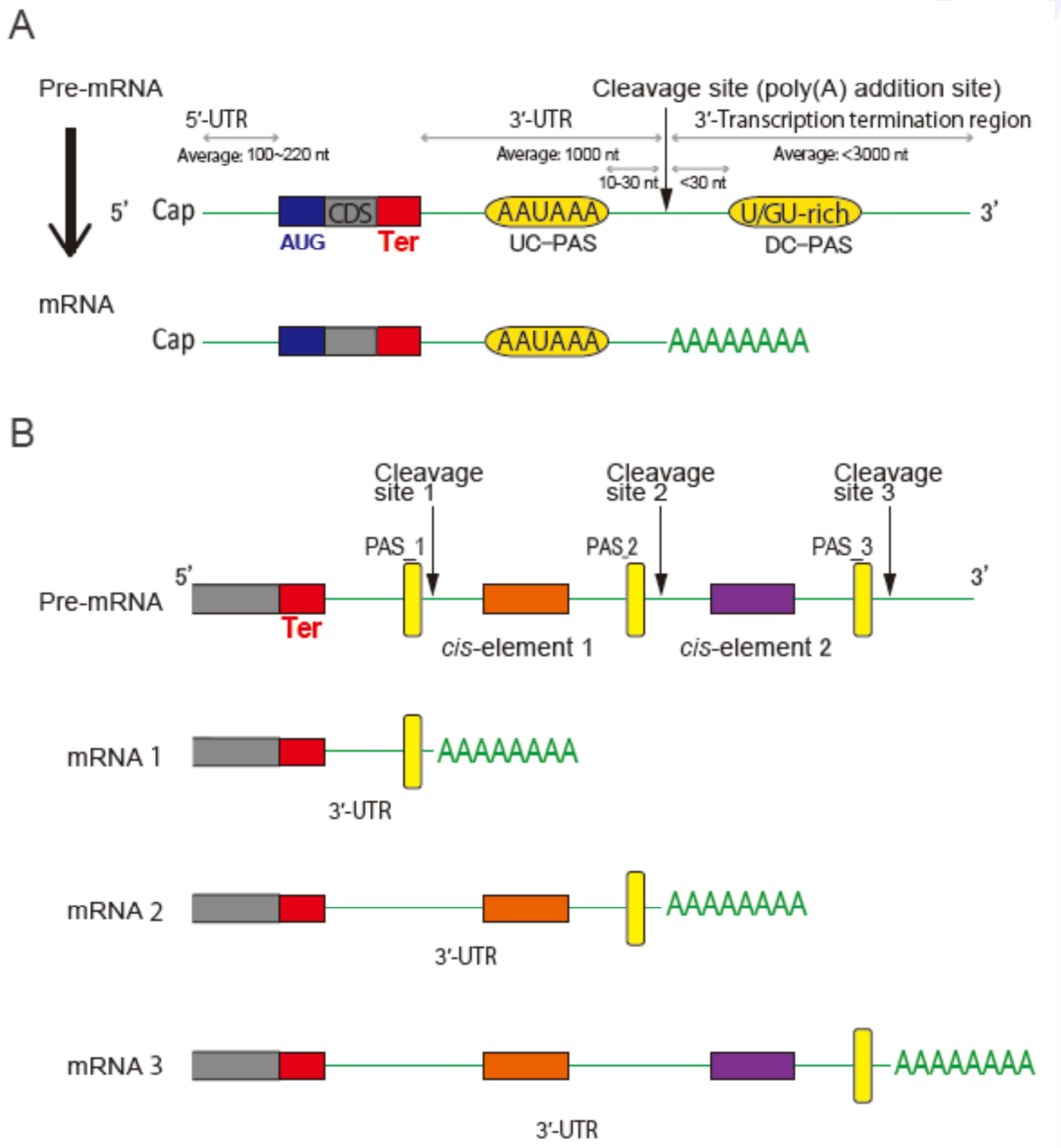
D. Regulation of translation through the 43S translation initiation complex.

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.

Fig.1


A
Pre-mRNA
Cleavage site (poly(A) addition site)
5'-UTR
Average: 100~220 nt
3'-UTR
Average: 1000 nt
10-30 nt
<30 nt
3'-Transcription termination region
Average: <3000 nt
5'
Cap
CDS
AUG
Ter
AAUAAA
UC-PAS
U/GU-rich
DC-PAS
3'
mRNA
Cap
AAUAAA
AAAAAAAA
B
Cleavage site 1
Cleavage site 2
Cleavage site 3
PAS_1
PAS_2
PAS_3
5'
Pre-mRNA
Ter
3'
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3'-UTR
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3'-UTR
mRNA 3
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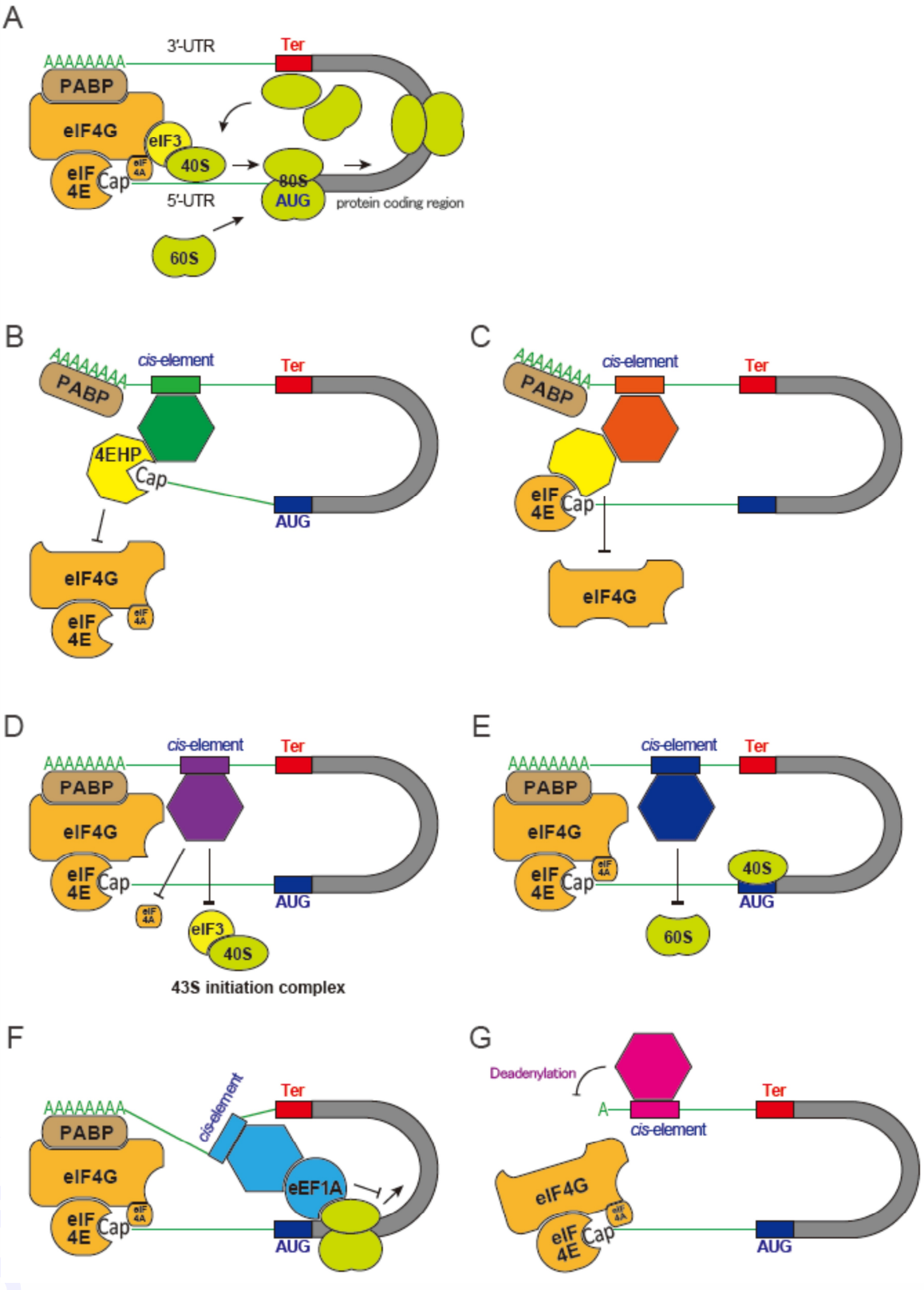
3'-UTR

Fig.2


A
3'-UTR
Ter
PABP
eIF4G
eIF3
40S
eIF 4E
Cap
80S
AUG
protein coding region
5'-UTR
60S
B
cis-element
Ter
PABP
4EHP
Cap
AUG
eIF4G
eIF 4E
C
cis-element
Ter
PABP
eIF 4E
Cap
eIF4G
D
cis-element
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PABP
eIF4G
eIF 4E
Cap
AUG
eIF3
40S
43S initiation complex
E
cis-element
Ter
PABP
eIF4G
eIF 4E
Cap
40S
AUG
60S
F
cis-element
Ter
PABP
eIF4G
eIF 4E
Cap
eEF1A
AUG
G
Deadenylation
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