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ABSTRACT

In mammals, cap-dependent translation of mRNAs is initiated by two distinct mechanisms: CBC-dependent translation (CT) and eIF4E-dependent translation (ET). Both translation initiation mechanisms share common features in driving cap-dependent translation; nevertheless, they can be distinguished from each other based on their molecular features and biological roles. CT is largely associated with mRNA surveillance, whereas ET is predominantly involved in the bulk of protein synthesis. However, several recent studies have demonstrated that CT and ET have similar roles in translational regulation. In a subset of mRNAs, CT preferentially drives the cap-dependent translation, as ET does, and ET is responsible for mRNA surveillance, as CT does. In this review, we summarize and compare the molecular features of CT and ET with a focus on the emerging roles of CT in translation.

INTRODUCTION

Eukaryotic transcripts synthesized by RNA polymerase II are sequentially and coordinately processed into mature messenger RNAs (mRNAs) through various nuclear events such as transcription, 5′-end capping, splicing, and 3′-end processing/polyadenylation (1). Early in transcription, the 5′-end of the primary transcript is covalently modified by the addition of a 7-methylguanosine cap, which co-transcriptionally occurs via nuclear capping enzyme (2,3). The 5′-cap structure is recognized by the nuclear cap-binding complex (CBC), composed of a heterodimer of cap-binding protein 80 (CBP80) and cap-binding protein 20 (CBP20) [also known as nuclear cap-binding protein 1 (NCBP1) and nuclear cap-binding protein 2 (NCBP2), respectively]. The CBC-bound pre-mRNA is further processed by a splicing machinery. As a consequence of splicing, a specialized protein complex named the exon junction complex (EJC), which consists of four core components (eIF4A3, MAGOH, Y14, and MLN51) and a number of auxiliary factors, is deposited approximately 20-24 nucleotides upstream of each exon-exon junction (4,5). In addition, the 3′-end of transcript is cleaved and polyadenylated. The 3′-poly(A) tail is recognized by nuclear poly(A)-binding protein 1 (PABPN1; also known as PABP2) (6). Mature mRNAs are exported from the nucleus to the cytoplasm only after the completion of proper mRNA processing in the nucleus, and they contain a 5′-cap bound by the CBC, 3′-poly(A) tail bound by PABPN1, and exon-exon junctions associated with EJCs. The mRNAs either being exported from the nucleus or completely exported via the nuclear pore complex serve as a template for translation in the cytoplasm.

In the cytoplasm, the 5′-cap directs cap-dependent translation via two distinct pathways: CBC-dependent translation (CT) and eukaryotic translation initiation factor

4E (eIF4E)-dependent translation (ET) (7). CT is believed to precede ET because CBC-bound mRNA is a precursor of eIF4E-bound mRNA (8). With respect to their functional roles, it is generally considered that CT is largely involved in mRNA quality control, whereas ET is in charge of the bulk of protein synthesis (7). However, recent studies have made it harder to define the functional boundary between CT and ET. Therefore, in this review, we describe the recent findings on CT and compare the molecular features of CT and ET with a focus on the emerging roles of CT in eukaryotic gene expression.

Molecular features of CT: similarities and differences between CT and ET

Eukaryotic translation initiation occurs through two distinct steps (Figure 1); the first is the formation of the 48S preinitiation complex (PIC) with codon-anticodon base pairing between the initiator tRNA and a start codon in the P site of a 40S ribosome (a small subunit of ribosome), and the second is the joining of a 60S ribosome (a large subunit of ribosome) to the PIC to form an elongation-competent 80S ribosome (9,10). To this end, the 40S ribosome should be physically attached to the cap-binding protein bound to the 5′-cap structure for efficient ribosome scanning through the 5′ untranslated region (5′UTR) to locate the start codon in the proper context. The physical association is mediated by a scaffold protein, which directly binds to the cap-binding protein and eIF3 complex (11). Notably, the eIF3 complex physically associates with the 40S ribosome and various translation initiation factors such as (i) eIF1 and eIF1A, which confer the fidelity of start codon selection (12,13), (ii) the ternary complex consisting of the eIF2 complex (composed of eIF2α, eIF2β, and eIF2γ), GTP, and methionine-charged initiator tRNA$_i$ (14), and (iii) eIF5, which stimulates the GTPase activity of eIF2γ and

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consequently leads to the conversion of GTP-bound eIF2 to GDP-bound eIF2 (9,10).

The resulting multi-factor complex is called the 43S PIC (or the scanning complex) (9).

For ET, the 40S ribosome is attached to the 5′-cap structure via eIF4G, which directly binds to eIF4E (9,10) and the eIF3 complex (15,16). In the case of CT, a majority of mRNA-bound CBC recruits the 40S ribosome through physical interactions of a CT-specific factor, CBC-dependent translation initiation factor (CTIF) with CBP80 (17) and the eIF3 complex (18). However, an ET-specific factor, eIF4G also has an ability to bridge the CBC and the eIF3 complex, although there are some controversial reports (17-21). Intriguingly, eIF4G and CTIF serve as a binding platform for the eIF3 complex because they share an evolutionarily conserved domain called the middle domain of eukaryotic translation initiation factor 4G (MIF4G domain) with approximately 46% similarity (17,22,23). However, they directly bind to different subunits of the eIF3 complex to recruit the 40S ribosome to mRNA (eIF3c, eIF3d, and eIF3e for eIF4G and eIF3g for CTIF). Initial study of *in vitro* reconstitution experiments using purified eIF3 complex revealed that eIF3g is dispensable in eIF3 complex formation (24). However, a recent mass spectrometric analysis showed that eIF3g is located in close proximity to eIF3j (25), which is positioned at the decoding center of the 40S ribosome (26). In addition, a recent cryoelectron microscopic analysis of the mammalian 48S PIC revealed that eIF3g is relocated from the peripheral region of the 40S ribosome to the P site at its intersubunit face to promote efficient subunit joining (27). Therefore, eIF3g is thought to serve as a platform for the CT complex to easily access the start codon and consequently to assemble an elongation-competent 80S ribosome.

After attachment of the 40S ribosome to the cap structure, a scanning complex

scans for the start codon in the 5′ to 3′ direction along the 5′UTR. Efficient ribosome scanning requires an ATP-dependent DEAD-box RNA helicase for unwinding RNA secondary or tertiary structures in the 5′UTR (28). Interestingly, CT and ET exhibit different factor requirements for unwinding the secondary or tertiary structures. For ET, eIF4A1 or eIF4A2, which directly interacts with eIF4G, facilitates efficient unwinding (29-31). In contrast, the CT complex engages eIF4A3 through its interaction with CTIF (32). Accordingly, the downregulation of eIF4A3 but not eIF4A1 and eIF4A2 reduces the translational efficiency of CBP80-bound mRNAs harboring moderate secondary structures and blocks CT-associated mRNA quality control (32).

It should be noted that eIF4A itself has weak helicase activity (33,34) and thus requires a cofactor to efficiently unwind RNA secondary or tertiary structures in the 5′UTR. For ET, the binding of eIF4G to eIF4A1/2 converts eIF4A1/2 from a closed to an open conformation, promoting its helicase activity (31). In addition, the helicase activity of eIF4A1/2 is stimulated by eIF4B and eIF4H (28,35). However, it is not yet known what cellular factor(s) can modulate the helicase activity of eIF4A3 during CT. One plausible candidate is MLN51, a component of the EJC, as MLN51 has been found to enhance the helicase activity of eIF4A3 (36,37). As eIF4G does (28,31), it is also likely that CTIF could facilitate conformational change of eIF4A3 to promote the helicase activity.

After the scanning complex finally reaches the start codon, the 48S PIC undergoes drastic remodeling. eIF5 in association with the eIF3 complex stimulates the GTPase activity of eIF2γ of the eIF2 complex, converting eIF2-GTP to eIF2-GDP (14). Then, eIF5B (a ribosome-dependent GTPase) triggers the dissociation of eIF1, eIF1A, eIF2-GDP, eIF3, and eIF5 from the 40S ribosome and facilitates the joining of the 60S

ribosome (38-40). Subsequently, the GTPase activity of eIF5B is stimulated, releasing eIF5B from the ribosome. A majority of studies on the mechanism of this step have focused on ET, particularly by adopting *in vitro* reconstitution approaches. Considering that the overall initiation process of CT is similar to that of ET, it is possible that CT may follow a comparable route for 48S PIC assembly and subsequent 60S joining using canonical initiation factors as well as CT-specific factors such as CTIF and eIF4A3.

In addition to the 5′-cap structure, the poly(A) tail is critical for efficient cap-dependent translation (41). During ET, cytoplasmic poly(A)-binding protein 1 (PABPC1; also known as PABP1) associates with the poly(A) tail of mRNAs and interacts with eIF4G via direct binding to the PAM1 motif in the N-terminus of eIF4G (42). This interaction enhances the efficiency of ET either by augmenting the cap-binding ability of eIF4E (43,44), which may lead to stable mRNA circularization (45), or by directly or indirectly facilitating the recruitment of the 60S ribosome to the 48S PIC (46). In addition, PABPC1 binds to eukaryotic polypeptide chain release factor 3 (eRF3), one of translation release factors that promotes translation termination (47,48). In contrast, there is no known CT-specific poly(A)-binding protein, and whether the poly(A) tail of CBC-bound mRNAs is involved in CT has not been confirmed. Notably, there is no characterized binding motif or domain within CBP80 and CTIF for binding to poly(A)-binding proteins (either PABPN1 or PABPC1). However, considering that PABPN1 forms a complex with the CBC but not with eIF4E (20) and that it is detected in actively translating polysomes (49), the possibility that PABPN1 may participate in CT cannot be completely ruled out.

CT vs. ET in nonsense-mediated mRNA decay

During mRNA processing in eukaryotic cells, premature termination codons (PTCs) can arise on mRNAs as a consequence of mutations in somatic cells, inaccurate transcription or splicing, or alternative splicing that leads to intron retention or inclusion of a PTC-containing exon (50). These aberrant mRNAs would express truncated polypeptides, the accumulation of which is potentially deleterious to the cells. Fortunately, eukaryotic cells have evolved several mRNA quality control pathways, which are typified by nonsense-mediated mRNA decay (NMD). The aberrant mRNAs harboring PTCs would be selectively recognized and rapidly degraded by the NMD pathway before truncated polypeptides are accumulated within the cells (7,51-53).

Efficient NMD requires at least a single round of translation to recognize the PTCs on mRNAs. NMD has long been considered to occur during CT because (i) CBC-bound mRNAs are precursors of eIF4E-bound mRNAs, (ii) the CBC can drive cap-dependent translation, and (iii) the majority of NMD occurs on CBC-bound mRNAs (7,8,20,49,54,55). Therefore, the traditional model of CT-coupled NMD can be described as follows: newly synthesized CBC-bound and EJC-deposited mRNAs are subject to the first round of translation during or after their export from the nucleus to the cytoplasm. The first round of translation would be predominantly mediated by the CBC rather than eIF4E because newly synthesized mRNAs have a 5′-end cap bound by the CBC. During the first round of CBC-mediated translation, an elongating 80S ribosome removes EJCs deposited 20-24 nucleotides upstream of exon-exon junctions after splicing. When the elongating 80S ribosome reaches a termination codon, eRF1 and eRF3 are recruited to the terminating ribosome along with UPF1 (a key NMD factor) and SMG1 kinase, forming the SMG1-UPF1-eRF1/3 (SURF) complex. The stability of the SURF complex is dependent on the presence or absence of EJCs

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downstream of the termination codon. The SURF complex would be unstable if there is

no EJC downstream of the termination codon; consequently, the termination codon

would be recognized as "normal", and the mRNA would be stable. On the other hand, if

EJC is present downstream of the termination codon, it interacts with the SURF

complex and induces complex remodeling; consequently, the termination codon would

be recognized as a "PTC", and the mRNA would be rapidly degraded via

exoribonucleolytic or endoribonucleolytic cleavage.

Recently, two separate studies claimed that NMD can occur on eIF4E-bound

mRNAs as well as CBC-bound mRNAs (56,57). To verify their hypothesis, they

examined the efficiency of NMD under conditions where ET is compromised. The

studies found that treatment of cells with 4EGI-1, a specific translational inhibitor,

which disrupts the interaction between eIF4E and eIF4G (58), and overexpression of

eIF4E-BP1, which competes with eIF4G for binding to eIF4E (59), suppressed the

NMD of PTC-containing mRNAs (e.g., β-globin and GPx1). Furthermore, the half-life

of PTC-containing mRNAs (e.g., β-globin, immunoglobulin μ, and TCRβ) was also

decreased in eIF4E-bound messenger ribonucleoproteins (mRNPs) as well as in CBP80-

bound mRNPs. In addition, eIF4E was found to be associated with UPF1 in an RNA-

dependent manner. Based on these observations, the authors proposed that both CBC-

bound and eIF4E-bound mRNAs are subject to NMD.

Although the data are compelling, several key issues should be carefully

considered. First, considering that CBC-bound mRNA is a precursor of eIF4E-bound

mRNA, it is likely that a majority of the first round of translation may be predominantly

mediated by the CBC rather than eIF4E. Therefore, it should be clearly determined

whether the observed reduction in the level and half-life of eIF4E-bound NMD

substrates simply reflects the reduction in the level and half-life of CBC-bound NMD substrates. Second, although 4EGI-1 was originally reported as a specific compound that inhibits ET (58), several subsequent studies have reported additional 4EGI-1 targets besides the interaction between eIF4E and eIF4G (60,61). Notably, it has been reported that treatment of cells with 4EGI-1 in relatively low concentrations strongly inhibited translation without significant changes in eIF4F levels; on the other hand, 4EGI-1 treatment increased the association of the 5′-cap with ribosomal complexes containing the phosphorylated (inactive) form of eIF2 (60). This effect would inhibit the efficiency of both CT and ET. Third, CBC-bound mRNPs but not eIF4E-containing mRNPs contain detectable amounts of EJCs, which are critical for stimulating the NMD of PTC-containing mRNAs (8,17,20,32,49,62). Therefore, as mentioned earlier, the rapid degradation of NMD substrates in eIF4E-containing mRNPs would reflect the rapid degradation of NMD substrates in CBC-containing mRNPs. However, another equally plausible explanation is that CBC-bound NMD substrates may be predominantly subject to EJC-dependent NMD, whereas eIF4E-bound NMD substrates may be subject to EJC-independent NMD. Fourth, the replacement of the CBC by eIF4E occurs in a translation-independent manner (55). Therefore, even before the complete termination of CT, CBC would be replaced by eIF4E, suggesting the possibility of a transient interaction between eIF4E and UPF1.

Recently, two independent studies revealed that mammalian target of rapamycin complex 1 (mTORC1), which specifically controls ET efficiency by phosphorylating eIF4E-BP (63), can modulate the efficiency of NMD (64,65). One study demonstrated that insulin treatment increased the interaction between UPF1 and eIF4E-bound PTC-containing mRNAs and augmented eIF4E-associated NMD, which

was blocked by treatment with rapamycin (a selective inhibitor of mTORC1) (65). On the other hand, another study reported that rapamycin treatment promoted the NMD of a subset of mRNAs, probably by blocking the replacement of CBC by eIF4E (64). Therefore, it would be interesting to determine whether there are CT-specific or ET-specific NMD substrates depending on cellular conditions.

Replication-dependent histone mRNAs are largely translated via CT

Histone genes are essential as structural and functional units for packaging genomic DNA into chromatin to sustain genomic integrity and for regulating transcriptional activity, respectively (66,67). In particular, the expression of replication-dependent histone (RDH) genes is tightly controlled during the cell cycle. Upon entry into the S phase, the levels of RDH mRNAs increase by approximately 35-fold at the transcriptional level (68). Newly synthesized RDH transcripts are processed into mature RDH mRNAs with the aid of (i) U7 small nuclear ribonucleoprotein (U7 snRNP), which interacts with histone downstream element (HDE), (ii) stem-loop binding protein (SLBP), which directly binds to the histone stem-loop (HSL) located in the 3′UTR, and (iii) a 3′-end cleavage complex containing cleavage and polyadenylation specificity factor subunit 73 (CPSF73), CPSF100, and symplekin (69,70). The site between the HSL (recognized by SLBP) and the HDE (base-paired with U7 snRNA) is cleaved by CPSF73 and further trimmed by ERI1, a 3′-to-5′ exonuclease. The resulting RDH mRNAs, which have a HSL instead of a poly(A) tail, are exported from the nucleus to the cytoplasm for translation. On the other hand, at the end of S phase or under genotoxic stresses, actively translating RDH mRNAs are rapidly degraded via hyperphosphorylation of UPF1, which recruits various mRNA degradation factors to

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RDH mRNAs (70-72).

RDH mRNAs are unique in their structure because they lack a poly(A) tail but instead have a conserved HSL at their 3′UTR. In the case of canonical mRNAs, the interaction between PABPC1 and eIF4G triggers mRNA circularization for efficient translation. Similarly, the circularization of RDH mRNAs has been proposed to be mediated by an indirect interaction between SLBP and eIF4G via SLBP-interacting protein 1 (SLIP1), suggesting a possible role of ET in the translation of RDH mRNAs (73). However, this view was recently challenged by two reports demonstrating that the degradation of RDH mRNAs largely occurs on CBC-bound RDH mRNAs (32,74). Considering that (i) RDH mRNA degradation requires translation (75,76) and (ii) SLIP1-mediated RDH mRNA circularization increases the ET of RDH mRNAs (73), the eIF4E-bound RDH mRNPs are expected to be subject to rapid decay. In contrast, the authors found that a majority of RDH mRNA degradation occurs on CBC-bound RDH mRNAs depending on the direct association between CTIF and SLBP (74). Downregulation of a CT-specific factor, either CTIF or eIF4A3, was found to increase the abundance of RDH mRNAs. Furthermore, overexpression of eIF4E-BP1 or eIF4E-T did not affect the levels of RDH mRNAs. These observations support that the majority of RDH mRNAs are translated via CT instead of ET. Although the two studies described above have conflicting results, the findings indicated that at least a subset of mRNAs (e.g. RDH mRNAs) may preferentially use CT instead of ET for protein synthesis and mRNA degradation.

Differential regulation of CT and ET under stress conditions

Eukaryotic cap-dependent translation is regulated at various steps under certain

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conditions such as oxidative stress, hypoxia, viral infection, apoptosis, nutrient

starvation, differentiation, and development (77,78). Under stress conditions, two main

factors involved in translation initiation are posttranslationally regulated:

phosphorylation of eIF2α (Figure 2) and eIF4E-BP (Figure 3). GTP-bound eIF2

associates with the initiator tRNA (14). After establishment of the 48S PIC onto the

start codon, eIF5 stimulates the conversion of eIF2-GTP to eIF2-GDP, which is released

from the ribosome after the joining of the 60S ribosome (38-40). The released eIF2-

GDP binds to eIF2B, which is an eIF2-specific guanosine exchange factor (GEF), and is

converted to eIF2-GTP for recycling (14). However, under stress conditions, several

eIF2-specific kinases are activated and phosphorylate Ser51 in eIF2α, which include

PERK (ER stress), PKR (double-stranded RNA upon viral infection), HRI (heme

deficiency), and GCN2 (amino acid starvation) (14,77-79). The phosphorylated eIF2

complex sequesters eIF2B, leading to a decrease in the amount of available eIF2-GTP

and shutdown of translation. Therefore, both CT and ET can be blocked by eIF2α

phosphorylation as both types of translation require a functionally active eIF2 complex

(Figure 2).

In addition to eIF2α, the phosphorylation status of eIF4E-BP is changed in

response to intrinsic or extrinsic stresses. eIF4E-BP competes with eIF4G for binding to

eIF4E (59). Under normal or actively growing conditions, active mTORC1

phosphorylates eIF4E-BP, leading to the decreased binding of eIF4E-BP to eIF4E and

consequently resulting in an increase in ET efficiency (59,63). However, under stress

conditions, eIF4E-BP becomes hypophosphorylated and strongly binds to eIF4E,

resulting in the inhibition of ET. Therefore, eIF4E-BP is an ET-specific translation

regulator, and CT is insensitive to eIF4E-BP activity (Figure 3).

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In comparison with ET, CT is relatively insensitive to certain environmental stresses, and this can be demonstrated by translational regulation during hypoxia, a condition in which cells or tissues have low oxygen levels. Global translation is regulated during hypoxic stresses at two independent stages: (i) eIF2α phosphorylation at the early stage (acute/moderate hypoxia) and (ii) eIF4E-BP hypophosphorylation and eIF4E sequestration into the nucleus or the cytoplasmic processing bodies at the late stage (prolonged hypoxia) (80-83). The former induces the global shutdown of protein synthesis by targeting both CT and ET, whereas the latter blocks ET but not CT. Accordingly, acute hypoxia inhibits NMD (84), whereas prolonged hypoxia does not affect NMD even though ET is markedly compromised (85). The relative resistance of CT to environmental stresses is further demonstrated by translational regulation under serum starved conditions, in which mTORC1 is inactivated and the amount of hypophosphorylated eIF4E-BP is elevated. Under these conditions, ET efficiency is drastically reduced. However, CT-coupled NMD remains efficient (86). Taken together, CT could support the translation of a subset of mRNAs under stress conditions when ET is compromised.

CONCLUSION REMARKS

CT and ET have long been considered to be largely involved in mRNA quality control and the bulk of protein synthesis, respectively. However, recent studies have reassessed their roles in translation initiation, revealing that both CT and ET are functionally interchangeable. Although definitive conclusions are difficult given the contradictory data, the following general conclusions can be made:

(i) NMD occurs during CT or ET; however, NMD is predominantly coupled to CT.

(ii) CT instead of ET is preferred in the protein synthesis of a subset of mRNAs. In other words, CT can drive multiple rounds of translation of a subset of mRNAs, similar to ET (17,87-89).

(iii) In comparison with ET, CT is relatively resistant to intrinsic or extrinsic stresses.

In this context, future studies should elucidate the molecular features of CT, identify mRNAs that are specific to CT or ET, and evaluate CT- or ET-specific NMD.

ACKNOWLEDGEMENTS

FIGURE LEGENDS

Figure 1. Mechanistic comparison of CBC-dependent translation (CT) and eIF4E-dependent translation (ET). The details are described in the text.

Figure 2. Translational control mediated by eIF2α phosphorylation under stress conditions. The details are described in the text.

Figure 3. Translational control under prolonged hypoxic conditions. The details are described in the text.

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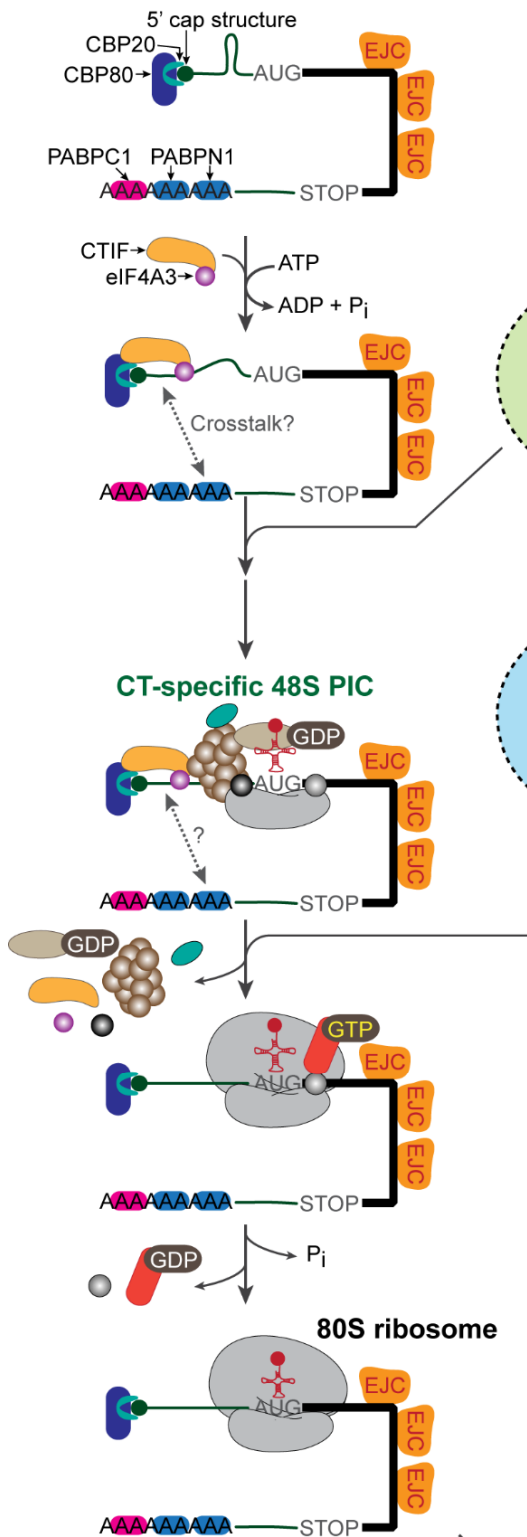78. Gebauer F and Hentze MW (2004) Molecular mechanisms of translational

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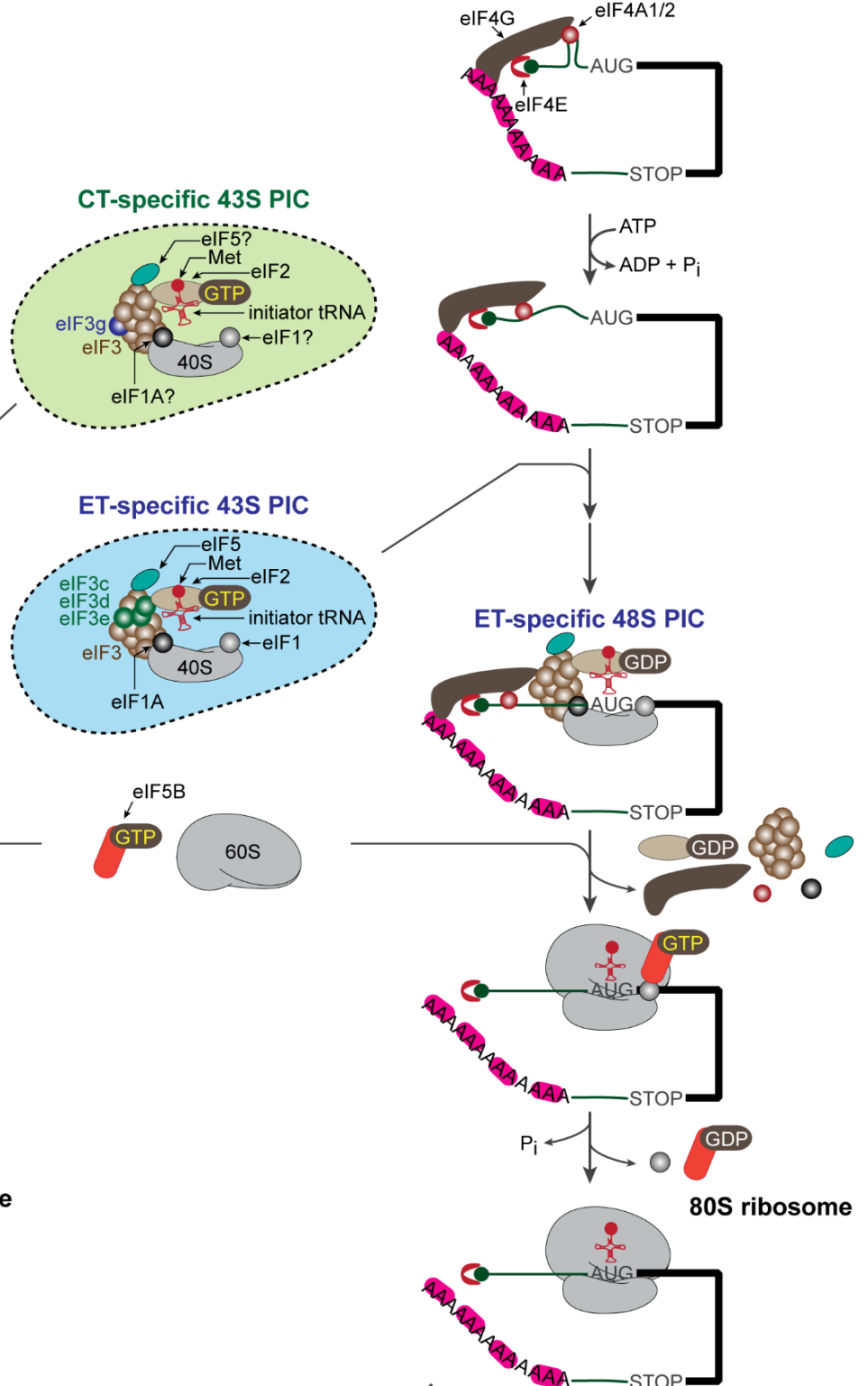
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Figure 1

CBC-dependent translation initiation
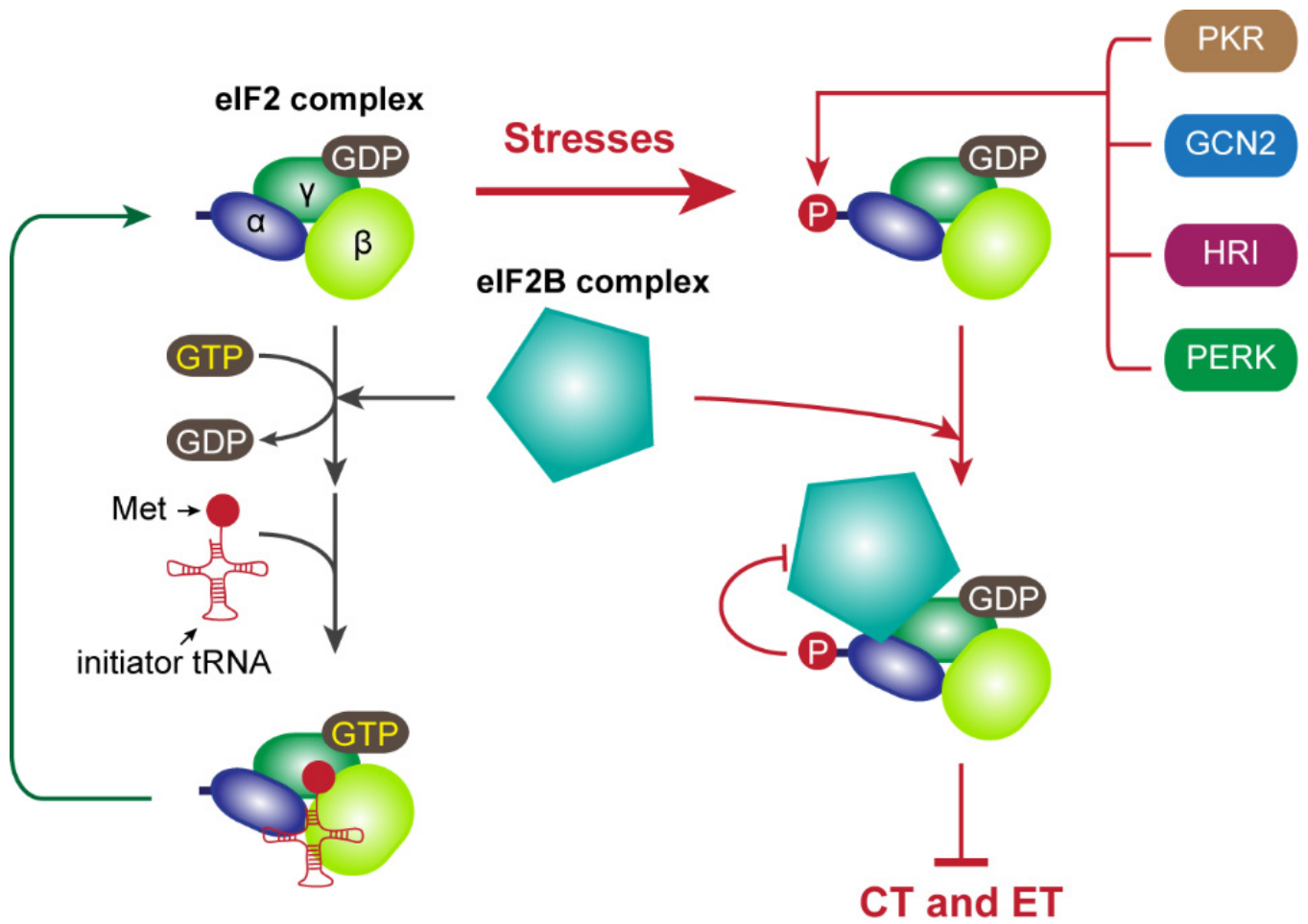
eIF4E-dependent translation initiation

CT-specific 43S PIC

ET-specific 43S PIC

CT-specific 48S PIC

ET-specific 48S PIC

80S ribosome

80S ribosome

Translation elongation

Figure 2

Figure 3