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Critical Reviews and Perspectives

Non-canonical mRNA translation initiation in cell stress and cancer

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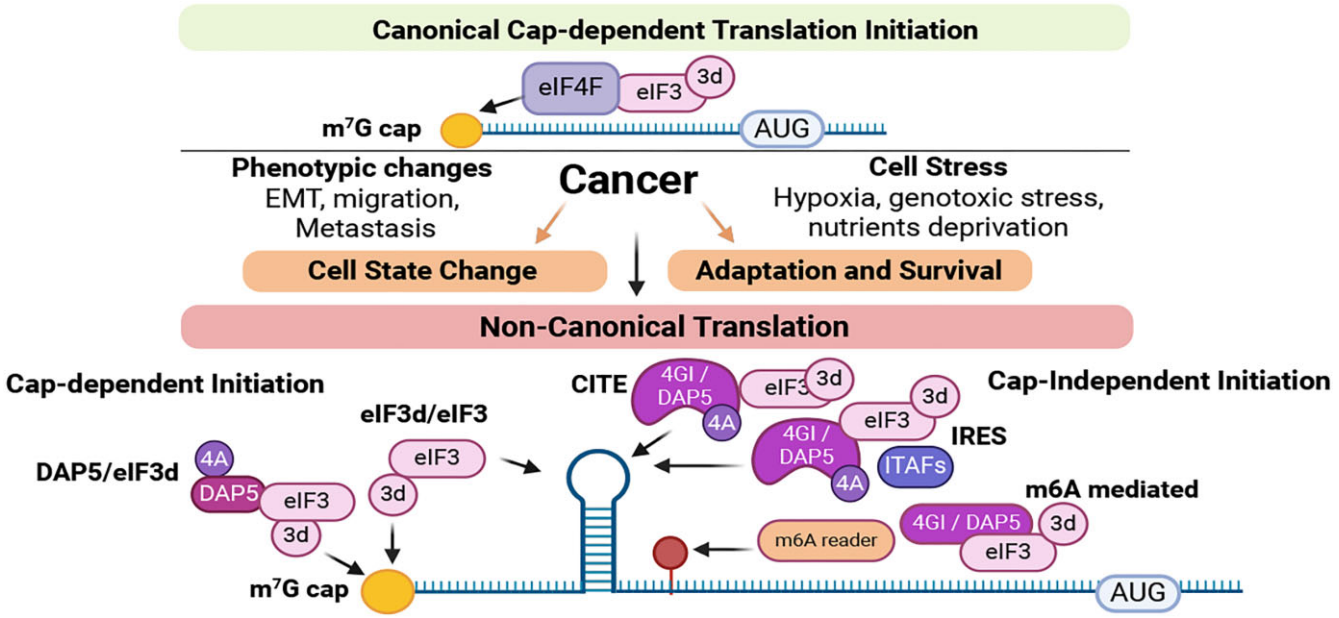
Abstract

The now well described canonical mRNA translation initiation mechanism of m^7G 'cap' recognition by cap-binding protein eIF4E and assembly of the canonical pre-initiation complex consisting of scaffolding protein eIF4G and RNA helicase eIF4A has historically been thought to describe all cellular mRNA translation. However, the past decade has seen the discovery of alternative mechanisms to canonical eIF4E mediated mRNA translation initiation. Studies have shown that non-canonical alternate mechanisms of cellular mRNA translation initiation, whether cap-dependent or independent, serve to provide selective translation of mRNAs under cell physiological and pathological stress conditions. These conditions typically involve the global downregulation of canonical eIF4E1/cap-mediated mRNA translation, and selective translational reprogramming of the cell proteome, as occurs in tumor development and malignant progression. Cancer cells must be able to maintain physiological plasticity to acquire a migratory phenotype, invade tissues, metastasize, survive and adapt to severe microenvironmental stress conditions that involve inhibition of canonical mRNA translation initiation. In this review we describe the emerging, important role of non-canonical, alternate mechanisms of mRNA translation initiation in cancer, particularly in adaptation to stresses and the phenotypic cell fate changes involved in malignant progression and metastasis. These alternate translation initiation mechanisms provide new targets for oncology therapeutics development.

Graphical abstract



Introduction: cancer cell stress survival and malignant progression must involve alternate mechanisms of translation initiation

Cancer is the second leading cause of death, the majority of which (two-thirds) is directly attributable to cancer cell metastasis (1,2). Metastasis is a multistep complex process by which tumor cells undergo multiple phenotypic and physiologic changes that profoundly alter cancer cell identity. Although cancer cells typically maintain a high level of protein synthesis, key events in cancer progression and metastasis involve the downregulation of canonical mRNA translation. For example, the loss of cancer cell adherence and the

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acquisition of a migratory and metastatic phenotype known as the epithelial to mesenchymal transition (EMT) (3,4), requires the cessation of cancer cell proliferation (5,6) and with it the downregulation of global eIF4E-mediated mRNA translation initiation (5,6). However, the downregulation of eIF4E-mediated mRNA translation is associated with the upregulation of selective translation of mRNAs that encode survival, cell stress, migration and EMT factors (7–12). Moreover, the tumor microenvironment (TME) presents a harsh setting consisting of oxygen deprivation (hypoxia) and nutrient deprivation due to poor tumor vascularization, and chronic inflammatory immune cell-mediated oxidative stress involving release of free radicals (12,13). Cancer cells attempt to mitigate these stresses in part through non-canonical mechanisms of selective mRNA translation (7). The cancer cell is typically also under stress as a result of its continuous high energetic requirements that serve the high level of protein synthesis needed to support near-constant cell proliferation. Normal cells direct approximately 20% of their energy requirements to protein synthesis, whereas the high level of mostly continuous protein synthesis in cancer cells accounts for up to 40% or more of the cancer cell's energy consumption (14).

The pivotal role played by transcriptional reprogramming and metabolic rewiring as fundamental adaptive mechanisms to tumor cell malignant progression and adaptation to stress have been well characterized (15). However, the contribution of translational reprogramming has only more recently been investigated. In this review, we focus on non-canonical, alternative translation initiation mechanisms that support cancer cell survival and metastasis, and which are often employed when canonical translation initiation is downregulated by cancer cell stress and survival responses, as well as during the process of cell invasion and metastasis.

Canonical eIF4E-dependent mRNA translation initiation is crucial for sustaining overall protein synthesis

Canonical mRNA translation supports a wide variety of essential cellular metabolic functions, as well as facilitating the translation of mRNAs involved in cell proliferation (10,11,16,17). The rate-limiting step of canonical mRNA translation is typically at initiation, which is governed by the 5′ cap-binding complex known as eukaryotic initiation factor 4F (eIF4F) (17–19) (Figure 1). eIF4F is composed of the canonical cap-binding protein eIF4E, which is increased in expression with cellular transformation, the mRNA ATP-dependent helicase eIF4A, and the scaffolding protein eIF4GI, or a more minor family member eIF4GII, upon which much of the initiation complex assembles (19). eIF4E is regulated at several levels, including transcriptionally, by phosphorylation at serine 209 which imparts a poorly understood increase in the translation of certain oncogenic mRNAs that might involve facilitated nuclear export, and by sequestration by the eIF4E binding proteins (4E-BPs) (20). In the hypo-phosphorylated state, the 4E-BPs block the formation of the eIF4F complex by competing with eIF4GI and II for the binding of eIF4E, thereby impairing eIF4E interaction with the 5′ cap (19). However, with stimulation by mitogens, growth factors, nutrients, cytokines, and other physiological cell stimuli, the mechanistic target of rapamycin complex 1 (mTORC1) phosphorylates the 4E-BPs, causing the dissociation of 4E-BP from eIF4E and upregulation of canonical eIF4E-mediated mRNA translation (19). mTORC1 is also involved in regulating a number of other cell processes that are integrated with its control of protein synthesis, including cell proliferation and growth, lipid metabolism, catabolic status and other cellular processes (21,22).

eIF4F is joined by the multi-subunit factor eIF3, which is composed of twelve proteins (19,23). eIF3 has a number of functions, one of which is to recruit the 40S ribosome, eIF4F, and the ternary complex consisting of eIF2-GTP-Met-tRNAi to capped mRNAs to initiate translation (23). Following 40S ribosome subunit scanning to the initiation codon, the 60S ribosome subunit joins and generates an elongation-capable 80S ribosome, which involves hydrolysis of GTP on eIF2 and release of eIF2-GDP (24). The GDP on eIF2 must then be exchanged with GTP, by guanine exchange factor (GEF) eIF2B. The eIF2B-GDP to GTP exchange is a major control point in eukaryotic protein synthesis and responds to cell stress by downregulating GEF activity, particularly the Unfolded Protein Response (UPR) (24,25). In the UPR, any of four protein kinases phosphorylate the eIF2α subunit at Ser-51, raising its binding affinity for eIF2B, thereby competitively inhibiting eIF2B GEF activity and impairing translation initiation (24–26). The endoplasmic reticulum protein kinase PERK is most involved in inhibiting translation by the UPR (24,25).

In addition to its role as a general factor in canonical mRNA translation initiation, eIF3 also demonstrates selectivity for translation of specific mRNAs, conferred by several of its subunits with RNA binding activity (23,27). Among the eIF3 subunits, the best studied is eIF3d, which has been shown to promote the translation of specific mRNAs through its cap-binding activity (28–30).

Many types of cancer cells increase the expression of canonical eIF4E and hyper-phosphorylate the 4E-BPs (the major form is 4E-BP1), by increasing the activity of mTORC1 (31,32), thereby enhancing conventional eIF4E/cap-dependent translation. Increased expression of eIF4E and its availability correlates with decreased progression-free and overall survival (31,32).

mRNAs differ in their requirement for canonical eIF4E-mediated mRNA translation. mRNAs that possess long generally more structured 5′UTRs have an increased requirement for eIF4E, as do mRNAs with increased secondary structure close to the cap (33–35). There is considerable evidence that eIF4E levels differentially control translation of specific mRNAs (36–38). In this regard, studies have shown that oncogenic mRNAs can contain increased 5′ secondary structure, although many do not and yet also demonstrate a greater dependence on eIF4E (16). Consistent with this finding, mice made haplo-insufficient for eIF4E were shown to be physiologically normal but much more resistant to establishment of induced cancers, in accord with an increased requirement for eIF4E by oncogenic mRNAs but not necessarily due to increased 5′UTR secondary structure (39). Certain sequence motifs have been shown to be specifically responsible for an increased requirement for eIF4E, and although direct binding by eIF4E to these 5′UTR elements has not been demonstrated, it is likely that sequence specific mRNA binding proteins that interact with eIF4E may be involved (33).

Although eIF4E-mediated mRNA translation is centrally important it is clear that it is not the only mechanism by which mRNAs can initiate translation. For example, despite the near-complete sequestration of eIF4E by hypo-phosphorylated 4E-BPs in stressed cancer cells, or cells treated with mTORC1 inhibitors, mRNA translation is only partially impaired, with a large subset of capped mRNAs very effectively bypassing

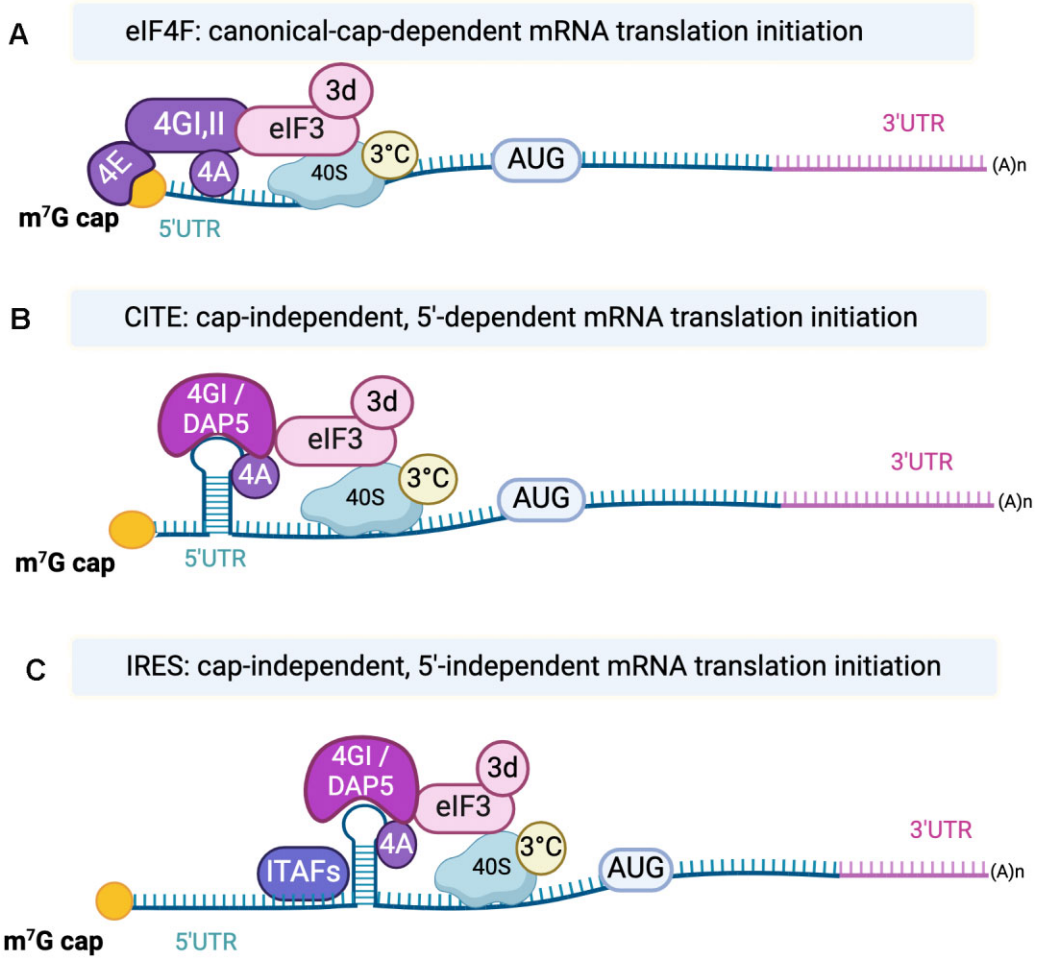

Figure 1. Canonical translation initiation is mediated by the m^{7}GTP cap and eIF4E, and cap/eIF4E-independent translation initiation mechanisms are mediated by CITE and IRES mechanisms. (**A**) Canonical cap/eIF4E-dependent translation initiation involves recognition of the m^{7}GTP cap by eIF4E in association with eIF4GI or II and eIF4A (the eIF4F complex). eIF3 interacts with eIF4GI or II which in turn recruits the 40S ribosome subunit and the ternary complex (3°C) consisting of eIF2-GTP-Met-tRNAi to form the pre-initiation complex (PIC). Following 40S ribosome subunit scanning to the initiation codon (AUG), the 60S ribosome subunit joins (not shown). (**B**) CITE cap/eIF4E-independent but 5′UTR dependent translation involves structural elements or modifications in the 5′UTR that are thought to bind directly to certain translation initiation factors that contain RNA binding motifs such as eIF4GI, II, or III, and/or eIF3, without the need for eIF4E and cap interaction, but in close proximity to the cap. (**C**) Cellular IRES-mediated mRNA translation initiation is thought to involve stable secondary hairpin structures anywhere in the mRNA (although generally in the 5′UTR) that can directly recruit the 40S small ribosomal subunit in the absence of cap and eIF4E interaction. IRES-mediated initiation typically requires interaction with IRES trans-acting factors (ITAFs), and either eIF4GI, eIF4GII or eIF4GIII (DAP5/*eIF4G2*), eIF3 and often eIF4A. DAP5 in particular has been shown to assist in cellular IRES-mediated mRNA translation. The Figure was partly generated using Biorender under the agreement number UO26MCB80P (www.Biorender.com).

the loss of canonical eIF4E-mediated mRNA translation initiation, as observed during tumor hypoxia and nutrient deprivation, or inhibition of mTORC1 by a rapalog drug (40–43). Remarkably, as much as 20-40% of protein synthesis activity typically remains (28,44–47). The large reservoir of mRNA translation despite mTORC1 inhibition and eIF4E sequestration is particularly surprising, as mTORC1 activity is involved in maintaining the activity or availability of translation factors in addition to eIF4E. For instance, mTORC1 activates S6K that acts on eIF4A, eEF2, eIF3 and other translation factors (48–50). Thus, while poorly understood, there must be other mechanisms of mRNA translation that account for the high level of eIF4E/mTORC1-independent mRNA translation in cancer cells under stress. These mRNAs may have differential requirements for certain components of the canonical translation machinery.

Mechanisms of non-canonical, alternate mRNA translation initiation

Given the frequent exposure of cancer cells to physiological and pathological stress conditions, non-canonical alternate mRNA translation initiation 'escape' mechanisms are essential to bypass the requirement for eIF4E and mTORC1 activity. Such alternate initiation mechanisms are vital to translate mRNAs that encode cell survival factors and orchestrate phenotypic changes in cell identity. These mechanisms are reviewed below (Figure 1). They include: (i) non-canonical eIF4E-independent Internal Ribosome Entry Site (IRES)-mediated translation of a small number, perhaps 5%, of cellular mRNAs; (ii) cap-dependent but eIF4E-independent mechanisms of cellular mRNA translation initiation that utilize eIF4E paralogs, or an alternate cap-binding protein known as eIF3d and (iii) cap-independent translation en-

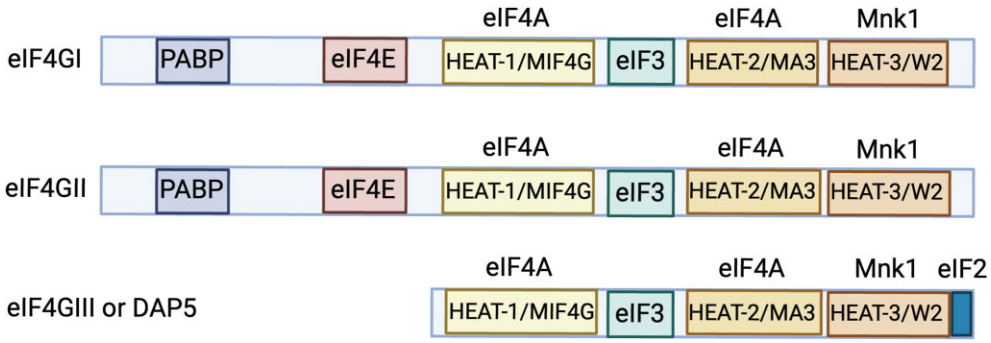

Figure 2. eIF4G family member proteins. Shown are the three human eIF4G proteins. eIF4GI protein (*eIF4G1* gene) contains binding domains for Poly(A)-Binding Protein (PABP), eIF4E, two binding sites for eIF4A, three HEAT motifs (flexible helix-turn-helix anti-parallel α-helices), an eIF3 binding site, an MA3 protein binding domain (α-helical repeats), and a W2 protein binding domain (two invariant tryptophan amino acids and α-helices). eIF4GII protein (*eIF4G3* gene) is highly homologous to eIF4GI but is typically expressed only in low amounts in most cells, and eIF4GIII protein also known as DAP5 (*eIF4G2* gene) which is about 65% homologous to eIF4GI and lacks PABP and eIF4E interaction sites. The Figure was partly generated using Biorender under the agreement number TZ26DM9P6S (www.Biorender.com).

hancer (CITE)-mediated binding of translation initiation factors to the 5′ untranslated region (5′UTR).

Cap and eIF4E-independent IRES-mediated mRNA translation

Among the cap and eIF4E-independent mechanisms of translation initiation, IRES-dependent translation is the most extensively investigated. IRESs were initially identified in viral mRNAs that are not capped (51). Viruses exploit IRESs to commandeer the cellular translation initiation machinery, simultaneously inhibiting cellular eIF4E-dependent mRNA translation while promoting the translation of viral proteins in a cap-independent manner (51–53). The distinctive feature of viral IRESs lies in their capacity to facilitate ribosome assembly and initiate translation independently of an mRNA 5′ cap, and in fact, independent of a free 5′ mRNA end (51,54). In contrast, cellular IRES containing mRNAs, like all cellular mRNAs, are capped and can use canonical cap-dependent initiation in the absence of stress. However, these mRNAs switch to IRES-dependent but cap-independent mRNA translation when mTORC1/eIF4E directed translation is inhibited, as under hypoxic or genotoxic stress, or during the EMT when mTORC1 and eIF4E are inhibited (55). The mechanism(s) by which a cellular mRNA IRES guides ribosome assembly and selection of an open reading frame (ORF) for translation initiation remains a subject of ongoing research. It is well established that viral IRESs typically consist of stable hairpin structures that can directly bind either the 40S ribosome, eIF4G family members, or initiation factor eIF3, which in addition to commandeering other host cell factors known as Internal Trans-acting Factors (ITAFs), direct the ribosome to a specific ORF (56,57). However, cellular IRESs are much more poorly understood than viral IRESs. If there are any rules for cellular IRESs, it is that they typically contain GC-rich and highly structured sequences that can serve as docking sites for non-canonical 40S ribosome loading promoted by ITAFs (55,58). IRESs are often embedded in long 5′UTRs that may also contain one or more upstream ORFS (uORFs). Strong 5′UTR secondary structure and uORFs are impediments to canonical eIF4E/cap-dependent mRNA translation initiation at a downstream ORF (55,58). It is important to note that while IRESs play a significant role in alternate translation initiation, particularly when eIF4E and mTORC1 have been inhibited during cell stress, IRES-dependent cellular mRNA translation corresponds to only a small number of cellular mRNAs (59). IRES-mediated translation therefore cannot account for the 20-40% of persistent protein synthesis observed despite inhibition of eIF4E and mTORC1 activity. This suggests that other non-IRES, non-canonical mechanisms of translation initiation must be significantly involved when canonical translation is downregulated during oncogenic stress and oncogenesis.

Cap and eIF4E-independent CITE-mediated mRNA translation

CITEs constitute a second non-canonical alternate mRNA translation initiation mechanism. CITEs were originally described in plant virus mRNAs (60), but have now also been discovered in a small number of animal cell mRNAs (61,62). While a mechanistic understanding is still emerging, CITEs bind certain translation initiation factors that possess RNA binding motifs, including eIF4GI, eIF4GII, eIF4GIII (DAP5/*eIF4G2*), eIF4E and eIF3, as well as 40S ribosome subunits (61,63). CITEs function in a cap-independent manner, similar to IRESs, but unlike IRESs, CITEs require a free 5′ end that can direct translation initiation from the 5′UTR but in a cap-independent manner (61). CITEs have been described at the mRNA level as comprising stem-loops, pseudoknots, and other RNA secondary/tertiary structures, but they remain poorly described with little common identity other than the need for a secondary structure and an exposed 5′ end (55,61). Recent evidence indicates that at least for some CITEs, for example in the Hsp70 mRNA 5′UTR during heat shock, modification by N^6-methyladenosine (m^6A) provides a recognition site that bypasses the cap to promote direct binding and translation initiation by eIF3 (64).

Cap-dependent but eIF4E-independent mRNA translation—a principal role for DAP5/eIF4G2

eIF4G consist of three family members, eIF4GI (*eIF4G1* gene), the scaffolding of factor eIF4F, eIF4GII (*eIF4G3* gene) and eIF4GIII (*eIF4G2* gene), also known as DAP5, Nat1 and p97 (65–68) (Figure 2). DAP5 shares 65% homology with eIF4GI but lacks the N-terminal third of eIF4GI, and therefore retains eIF4A and eIF3 interaction, but lacks the eIF4E and Poly(A)-binding protein (PABP) interaction sites (65,68). DAP5/*eIF4G2* enters into a 43S pre-initiation complex (PIC)

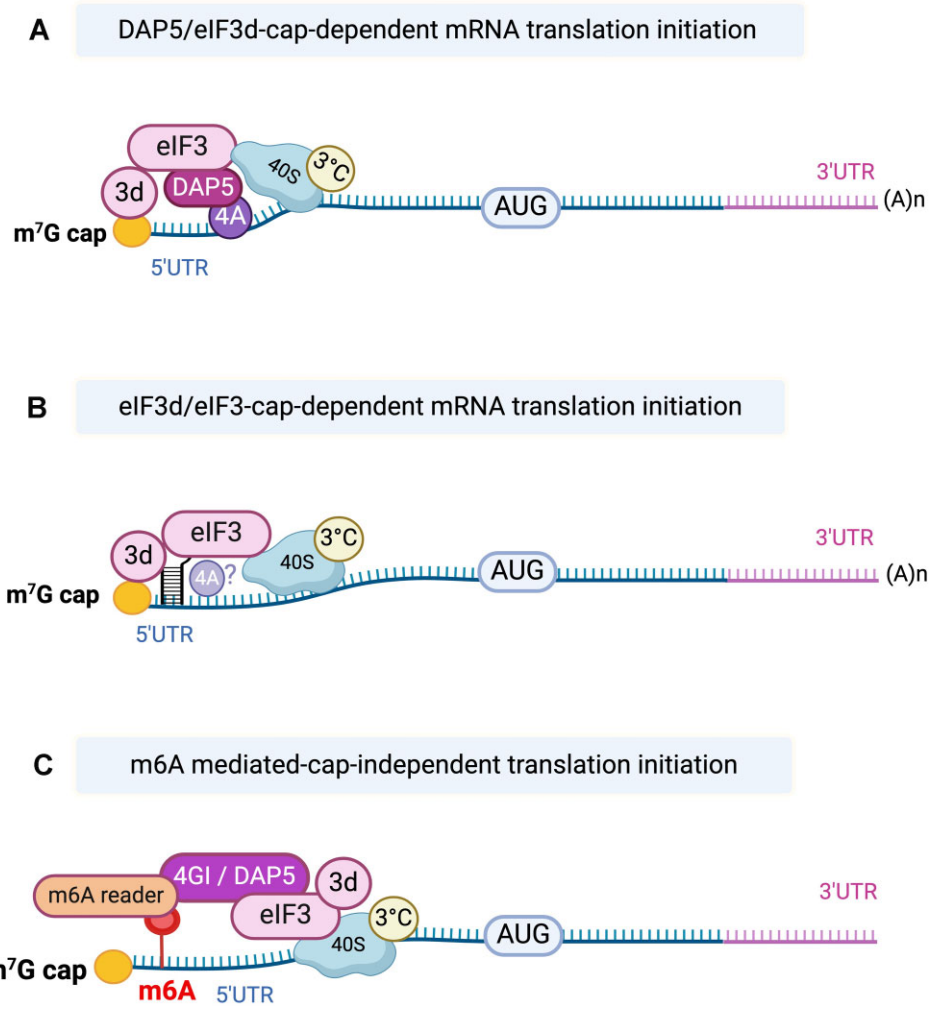

Figure 3. Non-canonical eIF3 and/or DAP5-dependent mRNA translation initiation mechanisms. (**A**) DAP5/eIF3d non-canonical cap-dependent but eIF4E-independent mRNA translation initiation involves recognition of the cap by eIF3d/DAP5 complexes that recruit eIF4A, eIF3, the 40S ribosome, and eIF2-GTP-Met-tRNAi ternary complex (3ºC) as an alternate form of the PIC. 40S ribosome subunit scanning, joining of the 60S ribosome subunit at the AUG are thought to be the same as canonical eIF4F-mediated initiation. (**B**) eIF3d/eIF3 non-canonical cap-dependent but eIF4E-independent mRNA translation,. This mechanism involves a specialized 5′ hairpin structure adjacent to the cap and cap-binding by eIF3d, presumably in association with the eIF3 complex, recruitment of the 40S ribosome subunit and the ternary complex. Given the absence of an eIF4G paralog, the recruitment of eIF4A remains uncertain. (**C**) m^6A mediated cap-independent mRNA translation initiation involves recruitment of eIF3 to m^6A marks in the 5′UTR. eIF3 in turn recruits the 40S ribosome and the ternary complex. The figure was partly generated using Biorender under the agreement number VC26ML5TN0 (www.Biorender.com).

with 40S ribosome subunits and eIF3, but without eIF4E (69) (Figure 3). Since eIF4GI and DAP5 share considerable structural similarity regarding their eIF3 binding sites, they likely compete for eIF3 interaction. This is supported by studies showing that mTORC1 inhibition reduces eIF4GI-eIF3 complex formation while increasing that of DAP5–eIF3 complexes (70). eIF4GII, which can also form an eIF4F complex, is generally expressed at a low level in most cells, whereas eIF4GI and DAP5 are expressed at similarly high levels (71). Early on it was readily recognized that because DAP5 cannot bind eIF4E, it can participate in cellular IRES-mediated mRNA translation, including under stress conditions that occur in cancer cells, including endoplasmic reticulum (ER) stress responses.

Interestingly, the *eIF4G2* mRNA encodes DAP5 from a non-canonical GUG initiation codon which is highly conserved among species (72), and non-AUG initiation reportedly provides resistance to certain stress responses that downregulate translation (73). This is consistent with the reported role of DAP5 in mediating stress-related mRNA translation, described below. DAP5 protein also binds translation initiation factor eIF2 (via eIF2β) considerably more strongly than does eIF4GI (74). In addition to eIF4E sequestration by the 4E-BPs the partial inactivation of eIF2 through phosphorylation of its α-subunit at Ser-51 decreases the availability of eIF2 (16,19,75). The preferential interaction of DAP5 with eIF2 would be expected to increase eIF2 availability for DAP5-dependent mRNAs, thereby favoring DAP5-mediated mRNA translation. Moreover, stress conditions that inhibit eIF4E/mTORC1-dependent mRNA translation initiation also promote increased expression levels of DAP5 (45,74), and increased interaction of DAP5 with eIF3 (70). Collectively, these findings implicate DAP5 in specialized stress-mediated, eIF4E/mTORC1-independent mRNA translation.

Cap and eIF4E-independent mRNA translation in cancer cell survival, stress repsonses and metastasis

Both IRES and CITE-mediated mRNA translation mechanisms direct cap- and eIF4E-independent translation to promote cancer cell survival, malignant progression, adaptation to stress responses, and tumor-directed angiogenesis. What is not clear is whether different cancer cell types and different stress conditions select one mechanism over another, since at least some mRNAs appear to utilize both mechanisms. As described earlier, there is evidence that cap and eIF4E-independent mechanisms may be promoted by stress-mediated mTORC1 inhibition.

There is considerable evidence for IRES-mediated mRNA translation during oncogenic transformation, adaptation to cell stress, and malignant progression. For example, the mRNAs for the *MYC* oncogene, *APAF1* (apoptotic peptidase activating factor 1), and *BAG1* (BCL2-associated athanogene 1), which are involved in cell oncogenic transformation and survival, are all reportedly translated by IRESs during stress (55,59). Hypoxia-inducible factor 1α (HIF1α) which orchestrates the hypoxia response and promotes cancer cell survival during oxygen limitation, can also use an IRES for translation of its mRNA under hypoxic conditions (76). The angiogenic *VEGFA* mRNA, which can translate via canonical eIF4E/mTORC1 mediated cap-dependent translation in normoxic cells, has been shown to switch to the use of its 5′UTR embedded IRES under hypoxic conditions (77), as does oncogenic *FGF2* and *FGF9* mRNA translation (78,79). In fact, there is evidence for two independent IRESs in the 5′ UTR of the *VEGFA* mRNA, possibly controlled by different factors, which likely supports translation initiation under different stress conditions (80). Similarly, lymphangiogenic *VEGFC* mRNA uses an IRES to promote lymphangiogenic metastatic spread under hypoxic conditions (81). However, in most published examples of IRES-mediated cellular mRNA translation involved in oncogenesis, of which these are just a few, the translation factors that direct IRES activity have not been established. It has been shown that for the *HIF1α*, *FGF9*, and *p53* mRNAs, DAP5 or eIF4GI can bind the 5′UTR and promote mRNA translation in a cap-independent manner (63). Whether the translation of these mRNAs by DAP5 or eIF4GI occurs through an IRES or CITE has not been fully established.

There is also evidence that inflammatory cytokines can trigger cancer cell stress signaling responses that promote non-canonical, IRES mechanisms of mRNA translation. For example, inflammatory IL-1β stimulates Early Growth Response-2 (*EGR-2*) mRNA translation. EGR-2 is a transcription regulatory protein associated with tumor expression and improved overall survival (82). The *EGR-2* mRNA was found to utilize an IL-1β-responsive IRES (83). In another example, macrophage inflammatory cytokines were found to stimulate the translation of tumor cell *CYP24a1* mRNA through an IRES-mediated mechanism (84). CYP24a1 is a cytochrome P450 vitamin D3 hydroxylase that promotes the degradation of the active form of Vitamin D3 which impairs oncogenic pathways, and as such can function as a tumor promoter.

In other interesting examples, increased translation of the Laminin B1 (*LAMB1*) mRNA during EMT invasion and metastasis in hepatocellular carcinoma reportedly uses an IRES (85). Platelet derived growth factor (PDGF) was shown to enhance *LAMB1* IRES activity increasing the cytoplasmic localization of the IRES transacting factor La during EMT, which is not impacted by eIF4E silencing (85). Nevertheless, one study suggests that cellular IRES-mediated mRNA translation, at least under hypoxic conditions, is actually quite low and is unlikely to play a primary role in the expression levels of the encoded proteins (86), although only a small subset of mRNAs was examined.

Some mRNAs have been shown to be translated in a cap and eIF4E-independent, but DAP5-dependent manner. These mRNAs include IRES-containing survival mRNAs encoding XIAP, c-AIP/BIRC2, HIAP2, BCL2 and others that can promote cancer cell resistance to apoptosis (87–92). In addition, DAP5 was found to promote the translation of circular RNAs that occur naturally (93,94), in an m^6A-dependent manner through interaction with m^6A reader proteins FMR1, IGFBP2 and PRRCA (95,96).

There is also evidence that DAP5 can promote the translation initiation of cellular stress-related mRNAs involved in oncogenesis through a CITE-mediated mechanism. DAP5 was found to bind directly to the 5′UTRs of *HIF1α*, *FGF9* and *p53* mRNAs and promote cap-independent translation that required a free 5′ end (63). In addition, DAP5 was found to bind to the 5′UTR and promote the translation of cyclin-dependent kinase 1 (CDK1) mRNA, which is a driver of cancer cell proliferation (88). Another study found that the *APAF1* mRNA can translate using a CITE mechanism with no cap-recognition requirement rather than an IRES in response to etoposide treatment (97). Whether the *APAF1, HIF1α*, *FGF9* and *p53* mRNA 5′UTRs can function as either an IRES or a CITE depending on the type of stress involved (genotoxic or hypoxic, for example) has not been investigated, as both IRES and CITE activities have been reported.

Yet another potential CITE mechanism involves a novel form of translational regulation of the *HIF1α* mRNA by DAP5 during hypoxia. Prolyl hydroxylase domain protein 2 (PHD2) is an oxygen sensor that hydroxylates and causes the degradation of the HIF1α protein when oxygen levels are normal (47). DAP5 was found to prevent *PHD2* mRNA translation by binding to eIF2 on the mRNA through the eIF2β subunit, blocking translation of its mRNA in hypoxic cells, and increasing *HIF1α* mRNA translation (47), which interestingly, is also dependent on DAP5 (63).

Cap-dependent but eIF4E-independent mRNA translation in cancer cell survival, stress responses and metastasis

The terminal progression of apoptosis and the induction of EMT in cancer cell invasion and metastasis are two cell phenotypic changes in which eIF4E-independent but cap-dependent alternate mechanisms of mRNA translation have been shown to be important. Stress-induced apoptosis involves the inhibition of canonical mRNA translation and selective mRNA translational reprogramming. Translation reprogramming participates in apoptosis, and includes the assembly of alternate non-canonical initiation complexes that are resistant to normal, non-stress regulatory signals. Apoptosis involves the caspase-mediated cleavage of certain translation initiation factors that participate in the mRNA binding step of initiation, particularly *eIF4G2*/DAP5, eIF4GI and PABP.

The role of DAP5/eIF4G2

DAP5 was initially described as a 97 kDa translation factor that undergoes cleavage to an 86 kDa form during apoptosis, which then promotes the increased translation of certain pro-apoptotic proteins such as XIAP and APAF-1 (66,91,98,99). In contrast, other studies have concluded that DAP5-mediated mRNA translation prevents apoptosis, as shown in response to genotoxic chemotherapy and DAP5-dependent translation of anti-apoptotic *BCL2* and *CDK1* mRNAs, for instance (100), and in response to anoikis during metastasis (101). It is likely that cleavage of DAP5 renders it a pro-apoptotic rather than anti-apoptotic specific translation initiation factor. It is noteworthy that while it was suggested that DAP5 and its 86 kDa form promote IRES-mediated mRNA translation, these conclusions were based on eIF4E independence, not cap independence. Indeed, many attributions to 'cap-independent' translation actually demonstrated eIF4E independence, as other cap-binding protein-mediated mechanisms of translation initiation apart from eIF4E were not known at the time. Interestingly, the type of stress also impacts whether eIF4G factors are targeted for caspase cleavage and/or degradation. For instance, oxidative stress results in rapid degradation of eIF4GI and II which have PEST domains and are degraded by the proteasome, whereas DAP5/*eIF4G2*/eIF4GIII does not and is long-lived during oxidative stress, where it reprograms mRNA translation to promote cell survival (101,102).

While DAP5, like the eIF4GI and II interacts with translation initiation factor eIF3, unlike eIF4GI and II proteins, DAP5 was found to be able to be directly crosslinked to eIF3d (28), which was shown to have 5′ cap recognition activity (29). DAP5 interaction with eIF3d, as a component of eIF3, participates in eIF4E-independent but cap-dependent translation of up to 20% of cancer cell mRNAs (28,45) (Figure 3). DAP5/eIF3d-dependent mRNA translation corresponds to a specific subset of cellular mRNAs largely encoding survival, EMT, cell migration, invasion, metastasis, and DNA repair functions (28,45). It was noted that the DAP5/eIF3d complex functions to program selective mRNA translation, particularly in situations where cellular stress conditions result in the inhibition of eIF4E, as when mTORC1 activity is downregulated. Reduced eIF4E availability also allows increased cap-binding by eIF3d, which based on qualitative studies, appears to be weaker than that of eIF4E (28,103).

eIF3d cap binding is reported to be reduced or prevented by casein kinase II phosphorylation at S528 and S529 near its cap binding pocket (104,105). It should be noted that the mechanism by which eIF3d binds to the m^7G cap is still emerging. Structural analysis suggests that eIF3d phosphorylation establishes an 'RNA gate' that blocks the m^7G binding pocket (29). Thus, eIF3d cap binding may involve the interaction of the entire eIF3 complex with mRNA prior to cap interaction, with subsequent eIF3d dephosphorylation and cap binding (105). Given the complexity of eIF3d cap interaction, there is not yet a direct quantitative comparison of cap binding affinity (K_d) by eIF3d compared to eIF4E.

It was found that DAP5 and eIF3d are increased in expression in cancer and non-transformed cells by exposure of cells to the cytokine tumor growth factor β (TGFβ) (45,103), which promotes EMT and metastasis. eIF3d is also often overexpressed in many cancers (106), which increases the ability to form a DAP5/eIF3d cap-initiation complex. This is particularly notable, as TGFβ which promotes EMT, also increases 4E-BP1 levels (107), which in turn downregulates conventional eIF4E-mediated cap-dependent mRNA translation. Thus, TGFβ orchestrates a DAP5/eIF3d alternate translation program by both decreasing canonical eIF4E mediated mRNA translation and increasing non-canonical DAP5/eIF3d mediated translation.

Non-canonical cap-dependent eIF4E-independent mRNA translation by DAP5/eIF3d has been shown to unify translational reprogramming, integrating mediation of cell stress responses with most aspects of the later stages of the EMT, including the increased expression of extracellular matrix metalloproteases (MMPs), increased expression of integrin proteins that disrupt cell-cell adhesion, increased cell migration proteins, and increased resistance to apoptosis during cancer cell migration (anoikis), all of which involve downregulation of mTORC1 activity and sequestration of eIF4E by the 4E-BPs (8,45,71). In fact, TGFβ which promotes the EMT in cancer cells, also downregulates mTORC1 activity while inducing increased expression of DAP5/eIF3d which selectively translates mRNAs involved in establishing the EMT phenotype, such as EMT transcription factor mRNAs encoding SNAIL1, SNAIL2, ZEB1, TWIST1, MMPs and integrins. Thus, DAP5/eIF3d induction and non-canonical mRNA translation are integral to TGFβ-mediated EMT and cancer cell survival and metastasis.

Other non-canonical but cap-dependent mRNA translation mechanisms are also involved in the EMT but are less well understood. For instance, transcription/translation regulatory protein Y-box binding factor (YB1) has been shown to activate *SNAIL1* mRNA translation in the EMT in a cap-dependent manner (108,109), whereas eIF3e, a subunit of eIF3, prevents TGFβ induction of the EMT (110,111). eIF3e may be downregulated in breast, endometrial, and other cancers, thereby promoting an EMT and malignant progression through a mechanism that reduces E-cadherin and HIF2α levels, but is not well understood (111,112). Additional studies are needed to understand how the YB1, DAP5/eIF3d, eIF3e and eIF4E cap-dependent non-canonical translation initiation mechanisms are integrated in the EMT.

eIF3d dependent but DAP5-independent mRNA translation

In addition to its ability to promote cap-dependent mRNA translation in a complex with DAP5, eIF3d has been shown to function without DAP5 to direct cap-dependent mRNA translation of certain cellular mRNAs, particularly in cells under stress (29,104–106) (Figure 3). While eIF3d may function to promote cap-dependent mRNA translation as a component of eIF3, which would bring in the pre-initiation complex consisting minimally of eIF4A, ternary complex and 40S ribosome subunits, other potential mechanisms are also beginning to emerge which need to be investigated more thoroughly. It should be pointed out that even in the absence of an understanding of a specific molecular mechanism, eIF3d subunit deletion studies showed that it is required for the selective translation of certain mRNAs, as in its requirement for translation of mitochondrial electron transport chain mRNAs (113).

eIF3d can mediate alternate translation initiation in several ways. Given the potentially weaker cap-binding activity of eIF3d compared to eIF4E, increased eIF3d abundance itself may promote greater non-canonical specialized mRNA translation. While the data are indirect, eIF3d has been shown

to be significantly increased in expression in a number of human cancers, which is associated with increased cancer cell proliferation (106). These data suggest a potential link between eIF3d levels, increased tumorigenesis, and eIF3d-mediated non-canonical mRNA translation, with or without DAP5 association, which has not been investigated. In addition, while eIF3d is phosphorylated at S528/S529 under homeostatic conditions which reduces cap-binding activity, under stress conditions such as glucose deprivation or chronic ER stress, eIF3d is dephosphorylated, which increases its competitive cap-binding activity (104,105). At least for certain mRNAs such as *cJUN*, eIF3d binding is attributed to interaction with a specific stem-loop structure (27) or an m^6A-modified 5′UTR (64). Dephosphorylated eIF3d was found to be essential for the ability of cells to survive persistent ER stress, a hallmark of cancer cells, through mRNA translation adaptation (105). Dephosphorylation of eIF3d during chronic ER stress promotes translation of the ALKBH5 demethylase, which reduces m^6A methylation of the ATF4 mRNA and increases its translation. This in turn is linked to increased levels of GCN2, eIF2α phosphorylation and bypass of uORF translation as a chronic ER stress adaptation necessary for cell survival. While bypass of uORFs may be important for the survival of chronic ER stress, at a mechanistic level of understanding, how increased eIF3d cap interaction promotes selective translation of ER stress mitigating mRNAs needs to be further investigated.

It was also shown that mTORC1 inhibition with 4E-BP sequestration of eIF4E promotes eIF3d-mediated selective translation of mRNAs involved in a switch from a proliferative to a non-proliferative migratory cell phenotype (114). None of the eIF4G proteins appears to be required in this form of eIF3d translational reprogramming. Rather, it is suggested that eIF3d interaction with mRNA binding proteins such as heterogeneous nuclear ribonucleoproteins hnRNPK and hnRNPF may form a translation initiation complex with eIF3d (114). Similarly, studies have identified RNA binding protein RNA-binding motif, single-stranded-interacting protein 1 (RBMS1) as a direct binding partner of eIF3d, presumably as a component of eIF3, which provides yet another non-canonical mechanism by which eIF3d participates in mRNA translation initiation (115). Interestingly, the eIF3l subunit of eIF3 has also been shown to have cap-binding activity (116), although studies have not yet demonstrated a cap-dependent translation function for eIF3l, nor explored a role in cancer and stress mediated translation.

Noncanonical cap-dependent mRNA translation initiation—a potential role for eIF4E paralogs

In addition to canonical eIF4E (also known as eIF4E1), mammalian cells also encode two other paralogs known as eIF4E2 or 4EHP (4E homologous protein), and eIF4E3 which have been implicated in cell stress and/or cancer cell-specific mRNA translation (117,118). While 4EHP has been the subject of considerable investigation, the function of eIF4E3 has not been explored by many investigators. Unlike eIF4E1 and 3, 4EHP cannot bind to the N-terminus of eIF4GI or II but does interact with the 4E-BPs (117–123). Consequently, as numerous studies have established in multiple biological systems, 4E-HP generally acts as an inhibitor of canonical eIF4E1/cap-dependent mRNA translation initiation (117–123). While 4EHP is expressed at lower levels than eIF4E, it is reported to be recruited to specific mRNAs by mRNA specific binding proteins that enforce 4EHP cap interaction and thereby selective mRNA translation inhibition (118,122,124–127). In mammalian cells, 4EHP directly binds the GIGYF1 and 2 proteins (Grb10 interacting GYF protein), particularly GIGYF2 which is involved in downregulation of ∼30% of overall protein synthesis (123,128,129).

A role for 4EHP in cancer and cell stress specific mRNA translation arose from reports that 4EHP can promote translation by forming a hypoxia-induced complex with eIF4GII, rather than eIF4GI to which it cannot bind (130,131). Studies indicated that the 4EHP/eIF4GII complex interacts with RNA binding motif protein 4 (RBPM4) and HIF2α to promote non-canonical selective cap-dependent translation of hypoxia-induced mRNAs by binding to the 3′UTR of hypoxia element containing mRNAs (130,132). This group also reported that the hypoxia induced 4EHP/eIF4GII/HIF1α/RBM4 complex drives hypoxia-dependent tumor growth in xenotransplant mouse models of tumorigenesis (133). However, there is some question as to how important the 4EHP/eIF4GII/HIF1α/RBM4 complex is for selective translation of hypoxia response mRNAs. Using high resolution polysome profiling techniques, it has subsequently been found that hypoxia results in a high level of alternative transcriptional start site (TSS) selection of many of the hypoxia response mRNAs (134). Indeed, studies have found that alterations in TSS during hypoxia and other forms of cell stress in breast cancer cells are a remarkably common way to alter 5′UTR length and secondary structure complexity that is often not appreciated, thereby promoting efficient translation initiation despite mTOR inhibition (135). The widespread change in alternate TSS was found to be largely, but possibly not entirely responsible for the selective translation of hypoxia response and cancer cell plasticity mRNAs (135). These data are consistent with the finding that METTL16 promotes lung tumor growth by binding and sequestering 4EHP from mRNA caps, thereby promoting oncogenic mRNA translation (136). Moreover, it was reported that hypoxia induces increased levels of eIF4E1 and selective canonical cap-dependent translation of hypoxia induced mRNAs (137). Which of the different reported mechanisms of hypoxia mediated selective mRNA translation prevail, and under which contexts, remains to be determined.

eIF4E3 is typically poorly expressed and has weak (10-40 fold reduced) cap binding activity due to an unconventional cap binding domain (138,139). However, it does interact with eIF4GI and III, and does not interact with the 4E-BPs (117,122,123,126,138,140). eIF4E3 has been found to play a role in cell stress and cancer-selective mRNA translation. At issue is that some studies demonstrate inhibition of mRNA translation initiation associated with tumor suppression activity (138,139), whereas others demonstrate strong canonical eIF4F-type mRNA translation initiation activity (122,140). eIF4E1 that lacks Ser-209 phosphorylation was associated with increased levels of eIF4E3 (141). Correspondingly, overexpression of eIF4E3 in cancer cells was shown to downregulate mRNAs dependent on eIF4E1, which was explained by competitively blocking canonical eIF4E-mediated mRNA nuclear export and translation initiation which more selectively targets oncogenic and survival mRNAs (138,139). However, changes in mRNA translation profiles with overexpression of eIF4E3 were quite small compared to more pronounced tran-

scriptional start site alterations (141). Moreover, biochemical and translational analysis indicates that eIF4E3 can enter into an eIF4F-type complex that can direct cap-dependent mRNA translation initiation (122,140). Importantly, because eIF4E3 does not interact with the 4E-BPs, the eIF4E3/eIF4F complex is independent of mTORC1 inhibition and inhibition of eIF4E1-mediated canonical mRNA translation (140). These studies instead suggest that eIF4E3 may function as a classical eIF4F partner in cap-dependent mRNA translation, but one which is particularly active when mTORC1 activity is downregulated during cell stress and during oncogenesis.

Summary

It is likely that additional non-canonical alternate mechanisms of eIF4E-independent mRNA translation, both cap-dependent and cap-independent, will continue to emerge as studies have now begun to focus on this important area of research. There is now a growing understanding that mRNA translation initiation can be highly specialized for certain mRNAs and that mRNAs can use different translation mechanisms in different contexts. Translation initiation can be guided by novel cap-binding proteins, specific RNA secondary structures, RNA motifs, covalent modifications such as m^6A, and alternate scaffolding proteins. All of these mechanisms provide assembly of translation initiation complexes, as well as inherent RNA binding properties of canonical translation initiation factors including some of the eIF3 factor proteins. It makes good sense that there would be a variety of non-canonical mechanisms to support specialized mRNA translation under different stresses even for the same mRNAs, and for the different cell phenotypes involved in oncogenesis and tumorigenesis, which are impacted by many of these different stresses. Importantly, specialized and novel translation initiation mechanisms offer new opportunities for therapeutics development that may provide lower toxicity with higher precision than targeting the canonical translation initiation mechanism. That mRNA translation presents real opportunities for development of translation-specific cancer therapeutics is now well established. This has been shown by the clinical introduction of experimental antisense oligonucleotide and small molecule inhibitors of eIF4E and eIF4A that are reasonably well tolerated (16,17,48,142). The development of new translation-specific inhibitors that target non-canonical metastasis and cancer cell stress-specific mRNA translation mechanisms could extend the reach of current therapeutics for more effective treatment of metastatic disease.

Some key outstanding questions

- How do different physiological stimuli determine which of the different stress-mediated non-canonical mRNA translation mechanisms will be used?
- What designates recognition and binding for translation factors in CITE-mediated mRNA translation initiation?
- What is the molecular mechanism for cellular IRES element function?
- Which cell mRNAs originally determined to utilize an IRES based on eIF4E-independence are actually translated in a cap-dependent manner by eIF4G2/DAP5-eIF3d?
- Does eIF3d-mediated cap-dependent mRNA translation typically involve the entire eIF3 complex, or are other mRNA binding factors involved?
- How does the DAP5/eIF3d complex specify mRNA selectivity?
- Do eIF4E2/4E-HP and eIF4E3 participate dually in opposite functions depending on cell, metabolic and cell stress contexts?

Data availability

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Conflict of interest statement

None declared.

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