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Translation initiation factors and their relevance in cancer

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Abstract

Deregulation of several translation initiation factors occurs in numerous types of cancers. Translation initiation factors are not merely ancillary players in cancer development and progression, but rather, they are key participants in cellular transformation and tumor development. In fact, the altered expression of translation initiation factors is involved in cancer cell survival, metastasis and tumor angiogenesis. Although the exact mechanisms remain to be fully characterized, translation initiation factors comprise novel targets for pharmacologic intervention. Here we review the most recently established roles of initiation factors in cancer development and progression, as well as unique methods used to study translational regulation.

Keywords

translational regulation; cancer; translation initiation factor; protein synthesis

Introduction

Protein synthesis is a costly biochemical process accounting for approximately 50% of the cell's energy, which is increased in cancer cells [1]. Much of protein synthesis regulation occurs at the step of mRNA translation initiation. Briefly, 40S ribosomal subunits bind eukaryotic initiation factors (eIFs) 1, 1A, 3, 5 and the eIF2/met-tRNAi/GTP ternary complex to form a 43S pre-initiation ribosome complex (PIC). The 43S ribosome, with a complex of three proteins that comprise eIF4F (eIF4E, eIF4G, eIF4A) binds the 5' m⁷GpppN "cap" and scans the mRNA for an in-context AUG initiation codon (Figure 1) [2]. Importantly, overexpression or increased activity of many initiation factors, including eIF3 and eIF4F, have been implicated in the etiology of many human cancers (Table 1) [3]. However, the exact role that increased levels or activity of initiation factors play in directing cancer physiological behavior remains poorly understood.

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Conflict of interest statement

The authors declare no conflicts of interest.

Mitogenic stimulation and signaling through the PI3K/Akt/mTORC1 pathway stimulates formation of the eIF4F complex, mRNA binding and translation initiation. Cellular stresses, such as amino acid deprivation and hypoxia, which are common in tumors, down-regulate mTORC1 activity, preventing formation of the eIF4F complex and downregulating protein synthesis. Select mRNAs containing special 5' untranslated regions (5'UTRs) with elements known as Internal Ribosome Entry Sites (IRESs) and upstream Open ReadinG Frames (uORFs) are capable of maintaining translation under these stress conditions. Many of the mRNAs containing these specialized translation elements are capable of translating under stress and encode transcription factors responsible for enabling the cell to survive or resolve the stress and restore normal protein synthesis. Studies have shown that these unconventional mechanisms of mRNA translation and hyperactivation of mTORC1 signaling are essential for cancer development, resistance and metastasis [4,5].

Translation initiation factors

Commanding initiation: eIF4E and the 4E-BPs

The cap-binding protein eIF4E has been considered in classic models to be a rate-limiting factor that mRNAs compete for, particularly mRNAs with long, structured 5'UTRs that limit their efficient translation initiation. However, a recent study has challenged this view, showing that cancer cells commandeer levels of eIF4E that are typically in excess of what is required for normal cell function and animal development [6]. Tissue culture studies, animal tumor models and human tissue samples all demonstrate that overexpression of eIF4E is important for transformation and drug resistance [7]. Overexpression of eIF4E promotes translational reprogramming enabling transcription, transport and translation of select mRNAs without strongly increasing overall protein synthesis. Many of these selectively translated mRNAs are involved in angiogenesis (VEGF-A), cell proliferation (c-myc), cell survival (Bcl-2) [8] and other aspects of oncogenesis. Many studies have focused on the selective translation of eIF4E-dependent mRNAs and the roles eIF4E, eIF4A and eIF4G in reprogramming the cell's translome towards malignancy and the metastatic state [9,10]. For example, experimental downregulation of either eIF4E or eIF4A inhibits melanoma proliferation, survival and invasion through translational downregulation of select mRNAs [11]. Several elements, both structural and sequence-specific, have been identified within the 5' and 3' UTRs of mRNAs that confer a requirement for higher levels of eIF4E [6]. Genome-wide mRNA polysome translation profiling analysis, ribosome foot printing analysis and CLIP sequencing have all been used to identify cis- and trans-acting mRNA elements that regulate selective mRNA translation [12]. The advantages and limitations of these techniques are described in Table 2.

eIF4E function is regulated by its availability, which in turn is controlled by the eIF4E binding proteins (4E-BPs), which are mTORC1-regulated repressor proteins that competitively bind eIF4E, blocking its interaction with eIF4G, thereby preventing eIF4E-mediated cap-dependent mRNA translation. mTORC1 hyperphosphorylates the 4E-BPs causing the release of eIF4E for translation initiation and restoration of protein synthesis. Hyperactivated mTORC1 is a hallmark of cancer cells and promotes transformation, cell proliferation, survival and metastasis [13–15]. The loss of 4E-BP1 (or overexpression of

eIF4E) confers resistance to chemotherapeutic agents and accelerates tumorigenesis in mice [15], although high levels of 4E-BP1 in prostate cancer are associated with resistance to PI3K inhibitors [16].

eIF4E is phosphorylated by kinases Mnk1/2 at S209 via the MAPK/ERK/MNK pathway. eIF4E S209 phosphorylation is important for the EMT (Epithelial to Mesenchymal Transition), cancer cell survival and metastasis, likely by promoting selective mRNA translation [17]. Increased expression of eIF4E and S209 phosphorylation may also promote tumor initiation by cancer stem cells (CSCs) [18]. Higher levels of eIF4E were shown to increase selective translation of TGF- β and Wnt/ β -catenin mRNAs that are critical for the oncogenic process [19,20]. Therefore, translational control via eIF4E availability acts as a convergence point for signaling of many oncogenic pathways to promote tumorigenesis.

The cap connection: eIF4G

eIF4G is a large protein, ~180 kDa, typically described as a scaffolding protein because of its interactions with eIF4E, eIF4A, the 43S PIC, MNKs and poly A binding protein (PABP), among other functions. Further, eIF4G has been associated with a switch from cap-dependent to cap-independent mRNA translation initiation during stress conditions [Supple Ref 8]. Overexpression of eIF4G is strongly associated with malignant transformation of immortalized cells in tissue culture, as well as advanced stage breast cancer and metastasis in patients. It is also highly overexpressed in inflammatory breast cancer (IBC) and cancer cells with a high proliferative index (Table 1) [Supple Ref 9] [21,22]. Genomic amplification of eIF4G occurs in ~30% of squamous cell lung cancers [Supple Ref 10].

The cap disconnection: DAP5

The eIF4G1 homolog DAP5 (NAT1, eIF4G2, p97) lacks binding sites for eIF4E and PABP, and has a number of interesting properties that underlie its role in cancer. DAP5 has been primarily studied in tissue culture where it promotes alternative translation of mRNAs that utilize cap-independent mechanisms, typically by IRES elements. Some of these mRNAs are specifically translated during cancer cell invasion and metastasis, as well as survival (anti-apoptosis), and include Bcl-2, Apaf-1, cIAP1, CDK1 and p53 [23,24]. Recent studies, including ribosomal and polysomal profiling in embryonic stem cells, have shown that DAP5 is involved in the translation of proteins required for cell differentiation [25,26]. Nevertheless, the exact mechanism of action and the role of DAP5 *in vivo* in cancer remains to be understood.

Unwinding complexity: RNA helicase eIF4A and ancillary factors

Overexpression of the abundant isoform eIF4A1 is observed in primary hepatocellular carcinoma (HCC), cervical cancer and some melanomas [Supple Ref 11, 12] whereas its activity is increased in some other cancer types, possibly by increased mTOR activity (Figure 1). mRNAs that translationally benefit from increased levels or activity of eIF4A are involved in cell proliferation, cell cycle progression, cell survival and angiogenesis. Studies have shown that increased levels of eIF4A are required for T-cell acute lymphoblastic leukemia (T-ALL) development and leukemia maintenance, through a translationally controlled mechanism [27].

eIF4B and eIF4H assist in eIF4A-mediated mRNA secondary structure unwinding which facilitates 40S ribosome subunit binding and scanning. The mitotic kinase MELK (Maternal Embryonic Leucine zipper Kinase) can phosphorylate eIF4B, which promotes proliferation of highly malignant breast cancer cells [Supple Ref 15]. Reduced expression of eIF4B selectively represses translation of many mRNAs, including the apoptosis inhibitor Bcl-2 [28]. eIF4H is reportedly up-regulated in lung adenocarcinomas where it may confer resistance to chemotherapy while increasing translation of mRNAs involved in cell growth and survival [29].

Bringing the pieces together: eIF3, a complex player in human cancer

Although the exact mechanism(s) by which the largest and most complex initiation factor, eIF3 (~800 kDa), affects cancer malignancy is still being elucidated, growing evidence suggests that eIF3 plays a critical role in human cancer and may be an actionable target for drug development. eIF3 is essential for recruiting translation factors and 40S ribosome subunits to the mRNA (Figure 1). Ten of the thirteen eIF3 protein subunits (eIF3a - m) have been linked to human cancers (Table 1), many by overexpression (a, b, c, h or i) [30] and possibly by direct interaction with certain cancer-related mRNAs [31]. In fact, silencing eIF3a reverses the malignant phenotype of human lung and breast cancer cell lines [32], and downregulates the CDK inhibitor p27(Kip1) [33]. A recent study suggests that eIF3b may be required for the proliferation of human osteosarcoma cells, acting by regulating tumor necrosis factor receptor superfamily member 21 (TNFRSF21), which activates the NF- κ B pathway [34]. eIF3c also interacts with and impairs the function of the tumor suppressor proteins schwannomin and merlin [35], promotes cell proliferation of primary hepatocellular carcinoma (HCC) cells [Supple Ref 22] and is overexpressed in gliomas [36]. eIF3d is associated with several types of cancers (Table 1), including bladder, glioblastoma, prostate and breast [Supple Ref 23]. Silencing eIF3d impairs cancer cell proliferation and invasion by suppressing Wnt/ β -catenin signaling and CDK1 [37,38] [Supple Ref 24]. It was recently demonstrated that eIF3d is a highly specialized cap binding protein, at least for the oncogenic transcription factor c-JUN [39].

Among other cancers, colorectal and HCC are associated with higher levels of eIF3h and eIF3i (Table 1). eIF3h is amplified in a variety of human carcinomas and may be a target of the anti-cancer agent harmine-derived beta-carboline, CM16 [40]. Overexpression of eIF3f was recently shown to suppress Akt and ERK signaling, increase p53 protein levels and inhibit clusterin protein expression, which promotes cancer cell proliferation and reduces chemosensitivity [41]. The remaining subunits of eIF3 (g, j, k, l and m) are the least studied in cancer development. Recent findings suggest the nuclear redistribution of eIF3g might play a role in the development and progression of breast cancer cells [Supple Ref 29], and is involved in DNA degradation during apoptosis [Supple Ref 30].

Coming together: the joining of ribosome subunits, and the roles of eIF2 and eIF2B

eIF2 is a complex of three proteins, α , β , and γ , which carry the initiating methionyl-tRNA and GTP. GTP hydrolysis on eIF2 promotes initiation codon recognition. The released eIF2-GDP must be recycled back to eIF2-GTP for initiation to occur, which is mediated by eIF2B, a multifunctional GEF (Guanine Exchange Factor). Phosphorylation of the α -subunit

of eIF2 at S51 prevents GDP-to-GTP exchange by increasing the affinity of eIF2B for eIF2-GDP, thereby blocking protein synthesis. Recent studies suggest that prolonged eIF2 α phosphorylation can promote cell survival, transformation and drug resistance, while in contrast, other studies suggest that eIF2 α phosphorylation can trigger apoptosis [Supple Ref 37 and 38], which may be cell and tumor-type specific. A recent study showed that embryonic stem cells (ESCs) have high levels of constitutive eIF2 α phosphorylation, which increases translation of uORF-containing mRNAs encoding cellular pluripotency factors [42]. This may also occur in cancer stem cells (CSCs) that promote metastasis and recurrence. Further, eIF2B is involved in the cell's ability to adapt to prolonged activation of the integrated stress response (ISR)/unfolded protein response (UPR) [43]. A small molecule inhibitor of the ISR (ISRIB) enhances the eIF2B GEF activity, rendering cells insensitive to translational inhibition by eIF2 α phosphorylation. In cancer cells, eIF2B-mediated translational reprogramming protects cancer cells from apoptosis [44,45].

Recruiting other initiator factors: eIF5A, eIF5B, eIF6, and PABP

eIF5A consists of two highly related isoforms (eIF5A1 and 2) that promote peptide bond formation by initiating 80S ribosomes [3] and translation elongation [46]. eIF5A1 is overexpressed in lung adenocarcinomas and BCR-ABL-positive leukemia [Supple Ref 40]. eIF5A1 and 2 are also the only proteins known to be hypusinated, where an amino-butyl residue is added to lysine [47]. The more poorly studied eIF5A2 protein is expressed at low levels if at all in normal cells, but is strongly overexpressed by gene amplification, often with PIK3CA, in human ovarian, brain, testicular and colorectal cancers (Table 1).

Translation initiation factor eIF6 is an anti-association factor. It binds to the 60S subunit and prevents its association with 40S ribosomal subunits in the absence of mRNA.

Phosphorylation of eIF6 releases 60S ribosomal subunits, allowing for functional formation of 80S ribosomes [2]. eIF6 is up-regulated in abundance and activity in many human cancers, the latter by protein kinase C (PKC) β II phosphorylation on S235 [48]. However, the role of eIF6 in tumorigenesis is complex and incompletely understood. In a B-cell lymphoma animal model, reduced expression of eIF6 is associated with longer survival and prevention of myc-mediated lymphomagenesis, consistent with eIF6 overexpression in human lymphomas and many solid tumors [Supple Ref 61]. Over-expression of eIF6 in transformed cell lines markedly increases cell migration and invasion, possibly by regulating proteins that control tumor cell motility such as cdc42 [49].

It is debatable whether PABP should be considered a translation factor, but nevertheless, it promotes translation initiation by binding the poly (A) tail of mRNA and eIF4G and stimulates translation initiation. However, the role of PABP in cancer development is not clear. PABP is overexpressed in high grade HCC tissues, and its silencing reduces cancer cell proliferation. Independent of a direct translation factor interaction, PABP interaction with AGO2, which is involved in RNA-mediated gene silencing, has been reported to enhance miRNA inhibition of tumor suppressor genes [Supple Ref 63].

Concluding remarks and perspectives

Although detailed mechanisms by which certain translation initiation factors are involved in human cancer remain to be understood, there is no doubt they function as drivers and not just passengers in the oncogenic process. As reviewed here and by others, deregulation or altered expression of certain translation factors can promote cancer development and its progression, often acting on tumor cell survival, growth factor-independent proliferation, hypoxia responses, neo-vascularization, evasion of apoptosis and the response of tumor cells to their microenvironment, generally through selective mRNA translation. Strong progress has been made using genome-wide translation technologies to study the translome in cancer, providing evidence for altered translational control in development, progression and metastasis of human cancers, as well as enabling identification of new targets for drug development. Understanding the detailed roles of translation initiation factors in cancer offers the opportunity for improving actual therapeutic benefit in human cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1|. Overview of key steps in mRNA translation initiation.

The 40S ribosomal subunit interacts with eIF1, eIF1A, eIF3, eIF5 and the ternary complex (eIF2/GTP/Met-tRNA_i) forming the 43S pre-initiation complex. The assembly of the eIF4F complex (eIF4G, eIF4E and eIF4A) on the m⁷GpppN “cap” facilitates the recruitment of the 43S PIC to the mRNA via eIF4G-eIF3 interaction. The interaction of PABP with the scaffolding protein eIF4G might promote the circularization of the mRNA, at least for some part of initiation. eIF4A, a helicase, unwinds the mRNA, with single strand RNA binding protein eIF4B. The eIF4E-mRNA cap complex with eIF4G-eIF3, comprise the 48S ribosomal complex, which progressively searches for the translation initiation codon (typically an AUG). AUG recognition is promoted by hydrolysis of GTP bound to eIF2, an essential step for stable 60S ribosomal subunit recruitment and formation of an active 80S ribosome to initiate protein synthesis. eIF5A promotes peptide bond formation and translation elongation. The inactive eIF2-GDP is recycled to active eIF2-GTP by GTP recycling factor eIF2B.

Table 1|

Differential expression of certain eIFs and regulatory factors in human tumor specimens

Protein	Differential expression	Cancer entity and references*
eIF4E	Up	Breast cancer [1] Endometrial [2] Head & neck [3] Bladder [4] Cervical [5] Prostate [6]
eIF4G	Up	Nasopharyngeal carcinoma [7] Breast [8,9] Squamous cell lung [10]
eIF4A1	Up	HCC [11] Melanoma [12]
eIF4A2	Down	Breast [13] Lung [14]
eIF4B	Up	Breast [15]
eIF4H	Up	Lung [16]
eIF3a	Up	Colorectal, Gastric, Breast, Cervical, Lung, Oral cavity squamous [17]
eIF3b	Up	Bladder, Colon [18] Prostate [19]
eIF3c	Up	Testicular seminoma [20] Glioma [21] Liver [22]
eIF3d	Up	Prostate [23] Breast [24]
eIF3e	Down	Breast [25] Colon [26] Lung [27]
eIF3f	Down	Melanoma [28] Pancreatic [28]
eIF3g	Up	Breast [29] Bladder [30]
eIF3h	Up	Breast [31] HCC [32] Lung [33] Colon [34]
eIF3i	Up	Head & neck [35] HCC [35] Colon [36]
eIF3m	Up	Colon [20]
eIF2 α	Increased phosphorylation	Oropharyngeal carcinoma [37,38]
eIF2B	Increased activity	Melanoma [39]
eIF5A1/2	Up	Increased hypusination in BCR-Abl leukemia [40]
eIF5A2	Up	Urinary bladder [41] Ovarian [42] Colorectal [43] HCC [40] Lung [40]
eIF6	Up	Colorectal [44] Leukemia & lymphoma [44] Head & neck [45] Ovarian serous [46]

Protein	Differential expression	Cancer entity and references*
eIF1	Up	HCC [47]
4E-BP1	Down	Reduced survival in cancer [1]
	Up	Reduced tumor grade in breast cancer [1] Locally advanced breast cancer [8] Ovarian [48]
PABP	Up	Liver [49]

* References listed in Supplementary Information

Table 2|**Methods to study the translome**

Methods	Advantages	Disadvantages
Polysomal profiling	<ul style="list-style-type: none"> • Measures ribosome density on mRNAs for accurate measurement of translation efficiency • Enables identification of proteins associated with initiation complexes and/or ribosomes • Can assess global and specific changes in the translome • Discovery of novel regulatory elements in mRNAs 	<ul style="list-style-type: none"> • Labor intensive and requires a large amount of starting material • High chance of RNA degradation • Does not provide individual nucleotide resolution • Requires specialized and expensive equipment
Ribosomal profiling	<ul style="list-style-type: none"> • Quantitatively identify mRNA associated with ribosomes • Capabilities of examining initiation, elongation, or termination 	<ul style="list-style-type: none"> • Labor intensive • Requires meticulous expertise in bioinformatics analysis • Requires a large amount of starting material
Ribosome-affinity purification	<ul style="list-style-type: none"> • Does not require a large amount of starting material • Can be used to study the translome of quiescent cells • Quick and robust technique 	<ul style="list-style-type: none"> • Requires the tagging of ribosomes • Does not provide a high resolution translational map • Cannot discriminate between number of bound ribosomes
CLIP techniques	<ul style="list-style-type: none"> • Unique method that map direct RNA–protein interactions site using UV cross-linking • Individual-nucleotide-resolution • Can be performed on any tissue type 	<ul style="list-style-type: none"> • Labor intensive and technically challenging • Availability of specific antibodies • Require meticulous and expertise in bioinformatics analysis • May lead to the identification of artificial interactions