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Translation initiation factors and their relevance in cancer

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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.

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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′ ^{m7}GpppN '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.

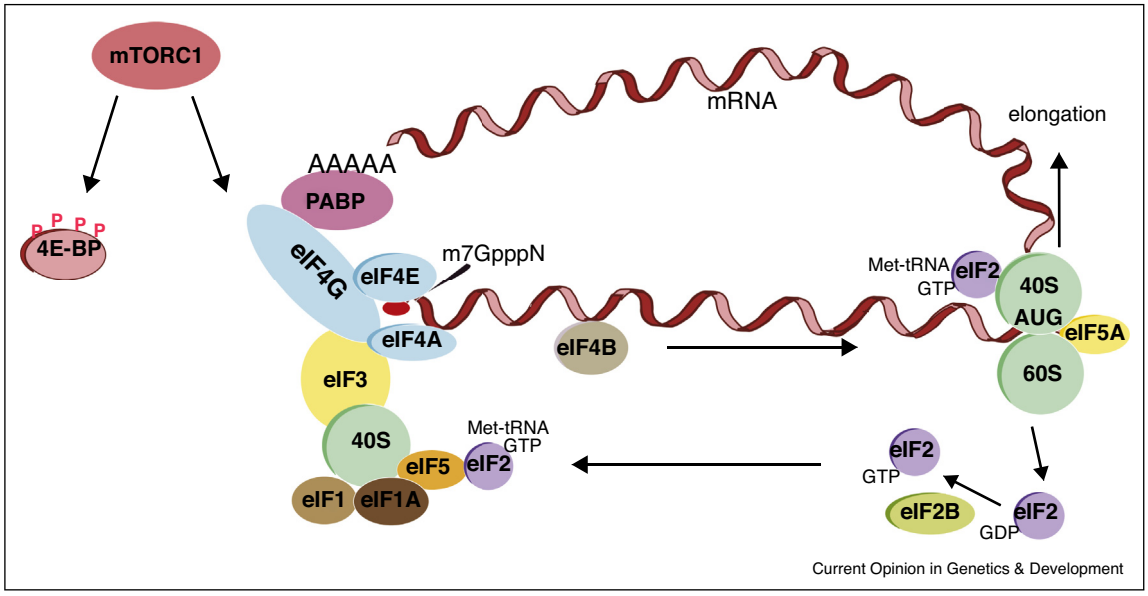
Mitogenic stimulation and signaling through the PI3K/Akt/mTORC1 pathway stimulates formation of the eIF4F complex, mRNA binding and translation initiation. Cellular stresses, such as amino acid deprivation and hypoxia, which are common in tumors, down-regulate mTORC1 activity, preventing formation of 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 translatome towards malignancy and the metastatic state [9,10]. For example, experimental downregulation of

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-tRNAi) forming the 43S pre-initiation complex. The assembly of the eIF4F complex (eIF4G, eIF4E and eIF4A) on the m^7GpppN '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.

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-acting and trans-acting 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 [13,14•,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