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eIF4E Phosphorylation in Prostate Cancer[1,2]

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Abstract

Prostate cancer (PCa) progression involves a shift from endocrine to paracrine and eventually autocrine control resulting from alterations in molecular mechanisms in the cells. Deregulation of RNA translation is crucial for tumor cells to grow and proliferate; therefore, overactivation of the translation machinery is often observed in cancer. The two most important signal transduction pathways regulating PCa progression are PI3K/Akt/mTOR and Ras/MAPK. These two pathways converge on the eukaryotic translation initiation factor 4E (eIF4E) which binds to the protein scaffold eIF4G upon mechanistic target of rapamycin (mTOR) activation and is phosphorylated by the mitogen-activated protein kinase (MAPK) interacting protein kinases (Mnk1/2). This review describes the role of eIF4E in mRNA translation initiation mediated by its binding to the methylated 5′ terminal structure (m7G-cap) of many mRNAs, and the ability of many tumor cells to bypass this mechanism. Hormonal therapy and chemotherapy are two of the most prevalent therapies used in patients with advanced PCa, and studies have implicated a role for eIF4E phosphorylation in promoting resistance to both these therapies. It appears that eIF4E phosphorylation enhances the rate of translation of oncogene mRNAs to increase tumorigenicity.

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Introduction

Prostate cancer (PCa) development, growth and metastasis depends initially on androgens, therefore androgen deprivation therapy (ADT) is the first line of treatment for metastatic PCa. However, despite initial response the majority of these patients eventually relapse, giving rise to castration resistant prostate cancer (CRPC) [1]. Many factors play different roles in PCa progression to CRPC including: (i) chromosomal aberrations, with deletion of chromosomal segments and some amplifications [2], (ii) inactivating mutations in tumor suppressors, including the phosphatase and tensin homolog (PTEN) [3] and the p53 gene at around 30% of the cases [4], (iii) overexpression of oncogenes (or proto-oncogenes) such as epidermal growth factor receptor (EGFR) or MYC [5] and (iv) activation of cancer specific pathways decreasing apoptosis, increasing proliferation and affecting differentiation, such as those downstream of phosphatidylinositol 3-kinase (PI3K) and Ras [6].

There are three main causes for the increased expression of certain factors with PCa progression – (i) increased transcription, (ii) increased translation and (iii) decreased internalization and degradation. Among the various factors that contribute to the progression of PCa, one in particular shows increasing relevance, which is the deregulation of protein synthesis control [7]. Protein overexpression is

Abbreviations: eIF4E, eukaryotic translation initiation factor 4E; mTOR, mammalian target of rapamycin; PCa, prostate cancer; Mnk, mitogen activated protein kinase interacting protein kinase; ADT, androgen deprivation therapy; MAPK, mitogen-activated protein kinase; CRPC, castration resistant prostate cancer; PTEN, phosphatase and tensin homolog; EGFR, epidermal growth factor receptor; PI3K, phosphoinositide 3-kinase; eIF, eukaryotic initiation factor; IRES, internal ribosome entry site; ITAFs, IRES trans-acting factors; RAPTOR, regulatory associated protein or mTOR; PRAS40, 40 kDa pro-rich Akt substrate; RICTOR, rapamycin insensitive companion of mTOR; PROTOR, protein observer of RICTOR; mSIN1, mammalian stress-activated map kinase-interacting protein 1; Rheb, Ras homolog enriched in brain; 4EBP1, eukaryotic translation initiation factor 4E binding protein 1; PIN, prostate intraepithelial neoplasia; MEK, mitogen-activated protein kinase kinase; SRPK, Ser/Arg (SR)-rich protein kinase; BPH, benign prostate hyperplasia; TOP, 5′-Terminal OligoPyrimidine; LARP1, La-related protein 1; MTA1, metastasis associated protein; HSP, heat shock protein; FKBP12, FK506 binding protein 12; MTC, medullary thyroid carcinoma; EMT, epithelial mesenchymal transition; CYP17A, cytochrome P450 17A1.

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commonly observed in cancer, conferring its ability to increase proliferation or decrease apoptosis rapidly. Expressions of several proteins have been linked with oncogenesis, such as Myc, Ras and Cyclin D1. To increase protein expression, cancer cells alter the cellular translational machinery, a case in point is ErbB3, a member of the EGFR family of receptor tyrosine kinases (RTK), which shows no change at the mRNA level between normal prostate and prostate cancer, but display significantly higher protein expression in PCa compared to normal prostate [8]. In this review, we will discuss the role of mRNA translation mechanisms in the progression of prostate cancer to a castration resistant state.

Mechanisms of mRNA Translation Initiation

Translation of proteins in eukaryotes occurs in three phases: initiation, elongation and termination. Initiation is usually the phase implicated in cancer development and progression [9]. During initiation, several eukaryotic initiation factors (eIFs) bring together the first transfer RNA (tRNA), the small ribosomal subunit (40S) and the mRNA. This pre-initiation complex scans the 5' untranslated region (5'UTR) in the 5′ to 3′ direction of the mRNA with the methionyl tRNA specialized for initiation (Met-tRNAi) in search of the startcodon, usually (but not always) AUG [9]. Once the start codon is recognized, the eIFs are separated from the complex and the large ribosomal subunit (60S) joins the complex to form the elongation competent 80S ribosome.

After the reading frame for the protein is determined, the elongation phase starts recruiting aminoacylated tRNAs to the first binding site, adding amino acids in a chain regulated by eukaryotic elongation factors (eEFs), binding them by peptide bonds until a stop codon is recognized and the synthesis is terminated, releasing the 60S ribosome from the complex and dissociating it into its subunits to be recycled into another round of protein synthesis (Figure 1*A*). All steps of protein synthesis are strictly regulated but a large part of the translational control is observed in the initiation step [10].

Eukaryotic mRNA translation initiation starts with the binding of the eukaryotic initiation factor 4E (eIF4E) to the mRNA 5′-cap

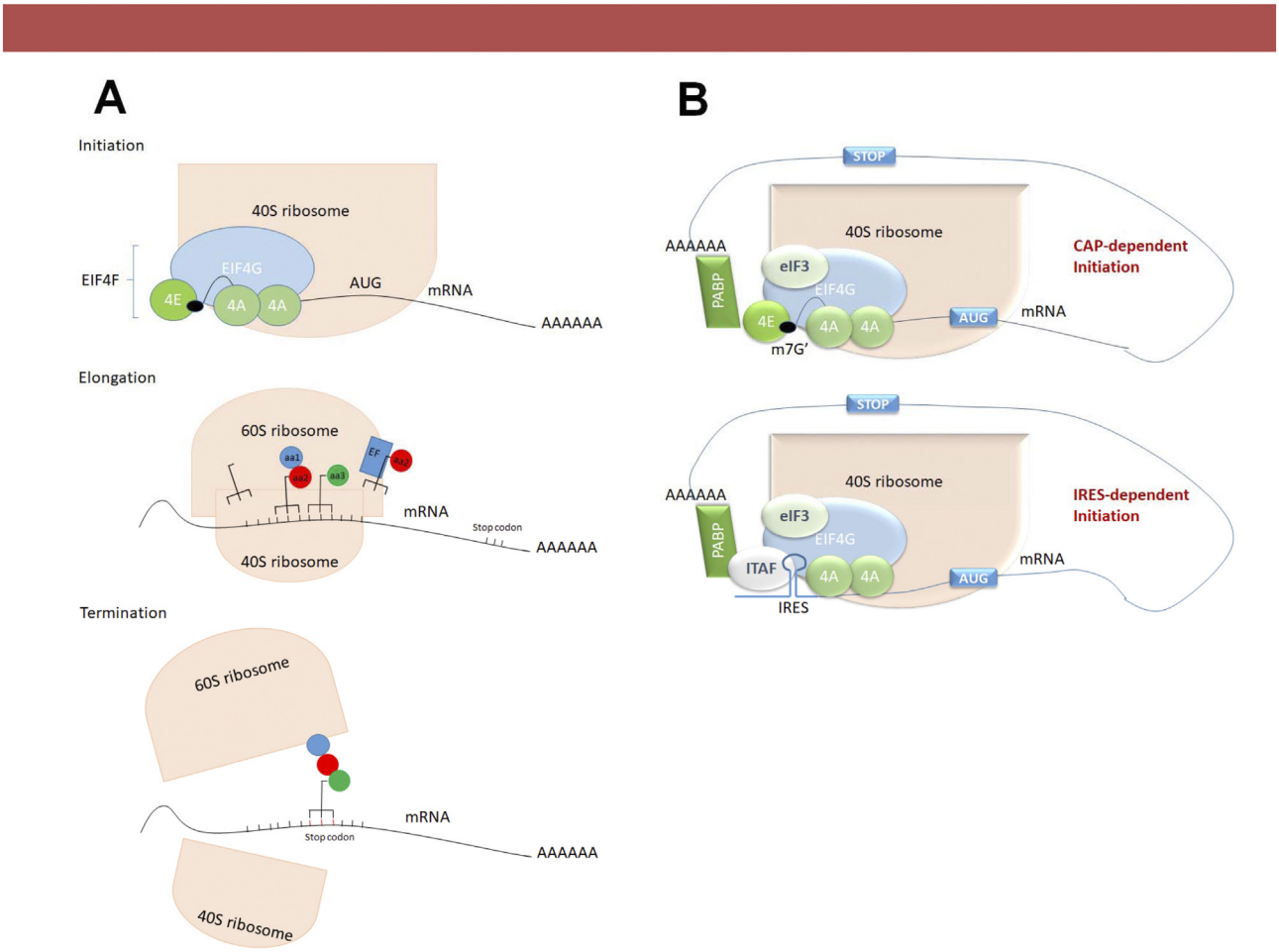

Figure 1. (A) Steps of eukaryotic protein translation. At initiation, the eukaryotic translation initiation complex eIF4F, bound to the small ribosomal subunit 40S scans the messenger RNA (mRNA) for the start codon, when then the big ribosomal 60S subunit binds the complex to initiate translation. At Elongation, amynoacylated transfer RNAs (tRNA) bring together amino acids to be bound together by eukaryotic elongation factors (eEFs) through peptide bonds forming a chain. In the termination phase, the stop codon is read by the complex, releasing the large ribosomal subunit and terminating synthesis. (B) Protein translation initiation mechanisms. Cap-dependent initiation takes place with binding of the eIF4E to the m7G 5′ PCa of the mRNA and bringing together all proteins to form the eIF4F protein translation initiation complex. Alternatively, Cap-independent translation, or translation initiation by internal ribosomal entry site (IRES) does not need the mRNA PCa binding to eIF4E, utilizing a group of proteins named IRES trans-activating factors (ITAFs).