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Translational Control as a new paradigm of Cancer Etiology

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ABSTRACT

Work over the past two decades has significantly shown progress in understanding the link between translational control and tumorigenesis. Various signaling pathways confer qualitative and quantitative changes in mRNA translation in response to extracellular cues thereby altering the phosphorylation status and thus the activity of components of the translational machinery. Activation of certain key oncogenic pathways like PI3K-AKT-mTOR and Ras-MAP kinase result in rapid and dramatic reprogramming of protein translation leading to cellular transformation and tumor development. This review focusses on the nexus between cancer and translational control. This paradigm unravels a novel frontier in the multihit model of cancer etiology and presents eloquent promise for innovative cancer therapies. We emphasize the need to study the new era of research in signaling to translational machinery. We finally bring in light the recent advances in cancer drug designing tools e.g., compounds that potently and specifically target signaling to translational machinery.

Keywords: *Cancer, Extracellular, Malignant, Oncogene, Translation.*

I. INTRODUCTION

Cancer, medically known as malignant neoplasm is a generic term for a large group of diseases that can affect any part of the body involving unregulated cell growth. The defining characteristic of cancer cells is the rapid transformation of normal cells to abnormal cells that grow and divide uncontrollably beyond their usual boundaries, and then invade adjoining parts of the body thus spreading to other organs. Unlike regular cells, cancer cells do not experience any programmatic death and instead continue to grow and divide. This progression of changes on cellular and genetic level ultimately reprograms a cell to undergo uncontrolled cell division, resulting in a malignant mass [1].

Cancer affects many people irrespective of gender, age, or ethnicity and has no physical barriers within the body. There are more than 100 different types of cancer. This being the reason for the fact that cancer is the prime cause of death worldwide responsible for one in every eight deaths which accounts for 7.6 million deaths (around 13% of all deaths) in 2008 and the same is estimated to rise to over 13.1 million by 2030 [2].

II. GENES INVOLVED IN CANCER

In order for a normal cell to transform into a cancer cell, the genes that regulate cellular proliferation and differentiation must be altered [1]. There are three categories of genes that are involved in these changes which include those whose products [3]:

1) directly regulate cell proliferation (either promoting or inhibiting),

2) control programmed cell death or apoptosis, and

3) are involved in the repair of damaged DNA.

Depending on how they affect each process, these genes can be categorised into two broad categories: tumor suppressor genes (growth inhibitory) and proto-oncogenes (growth promoting).

2.1 Oncogenes are normal genes expressed at inappropriately high levels, or altered genes with novel properties. In each case, expression of these genes results in malignant phenotype of cancer cells. Oncogenes are in fact the mutant alleles of proto-oncogenes. Since mutation in a single allele of a proto-oncogene can cause cellular transformation, such mutations are considered dominant [1].

2.2 Tumor suppressor genes are genes that hamper cell survival, cell division, or other properties of cancer cells. Tumor suppressors are generally transcription factors that are activated by DNA damage or cellular stress. Tumor suppressor genes are often disabled by cancer-causing genetic changes. Tumor suppressor genes code for anti-proliferation signals and proteins that suppress cell growth and mitosis. Unlike proto-oncogenes, typically both alleles of a tumor suppressor gene must be altered for transformation to occur. Tumor suppressor genes may be further divided into two groups: promoters and caretakers. Promoters are the conventional tumor suppressors, which when mutated, directly lead to transformation by releasing the brakes on cellular proliferation e.g. p53 and Rb. Caretaker genes are accountable for processes that safeguard the integrity of the genome, such as those involved in DNA repair. Although caretaker genes do not control cell proliferation directly, cells with mutations in these genes have compromised ability to repair DNA damage and therefore are likely to acquire mutations in other genes, like proto-oncogenes, tumor suppressor genes and apoptosis controlling genes[4,5]

Oncogenes and tumor suppressor genes are exquisitely regulated at the translational level via specific regulatory elements in their mRNAs. Increases in cell mass (cell growth), that occurs largely in the G1 phase of the cell cycle, is imperative for accurate cell division. Global protein synthesis and ribosome biogenesis are dynamically and tightly regulated to meet the growth demands of a cell. Therefore, a crucial relationship exists between the cell cycle, ribosome biogenesis and translational control [6]. This balance is properly conserved in the cell through key checkpoints. For instance, down-regulation of ribosome formation and activity is necessitated during M phase to ensure proper cytokinesis. As such, it is evident that a translational program that interfaces with the cell-cycle machinery should ensure the translation of specific mRNAs at appropriate levels during each window of cell growth and division. Cancer cells display a broken balance between growth and cell division, leading to unrestrained elevations in protein synthesis and cell size [7].

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III. CANCEROUS TRANSLATION MACHINERY

One of the most regulated steps in translation is Initiation [8]. During initiation, various key checkpoints are coordinated by a plethora of distinct initiation factors that control not only the translation of specific mRNA but also the rate at which mRNA translation occurs. Briefly, Eukaryotic initiation factor 4E (eIF4E) binds the 5′-terminal 7-methylguanosine cap of cellular mRNAs, that brings the mRNA to the eIF4F translation initiation complex, which then scans the mRNA in 5′-3′ direction from the cap. This requires the unwinding of RNA secondary structure to reveal the translation initiation codon and allow mRNA translation. 4E-BP1, an eIF4E binding partner, binds to eIF4E and prevents its assembly into the eIF4F complex thereby inhibiting cap-dependent translation.

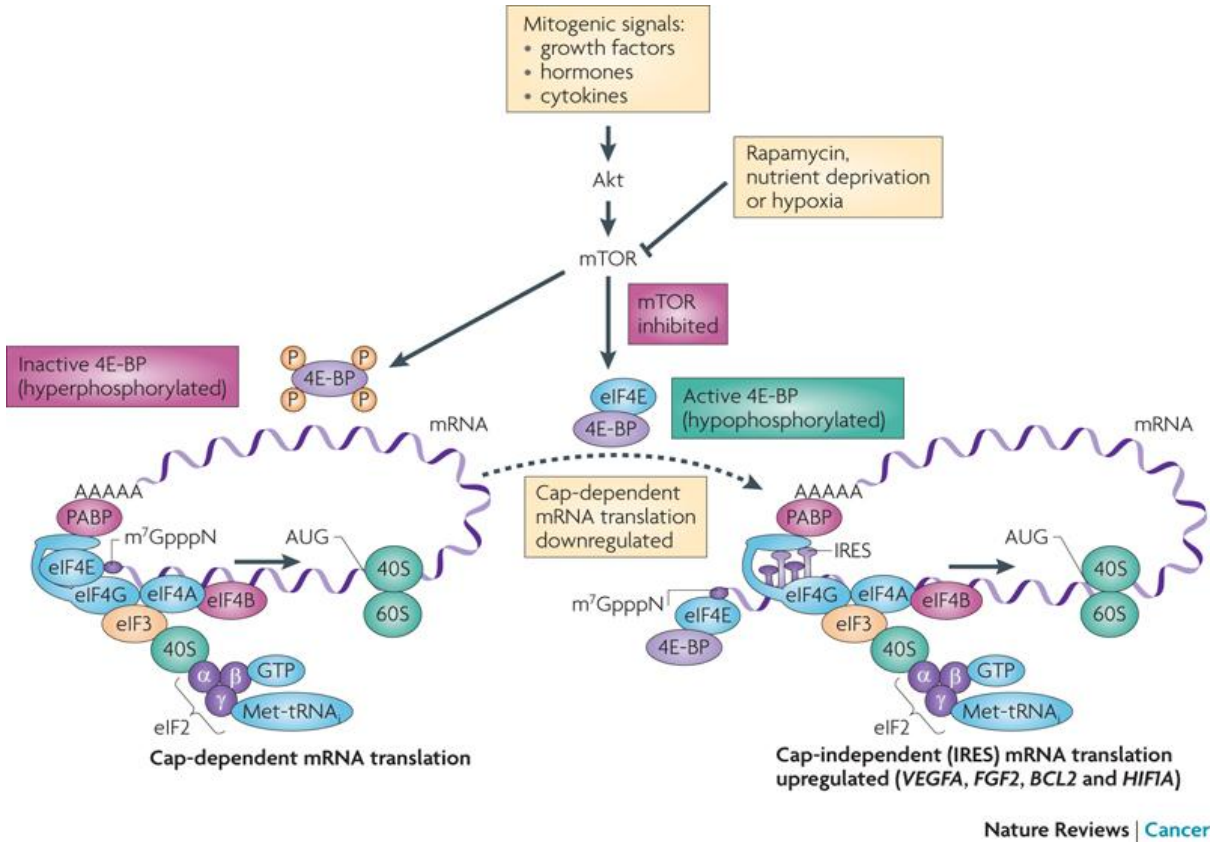

Fig 1: eIF4E/4E-BP as a switch between cap dependent and cap independent translation

Mitogenic signals such as growth factors, hormones and cytokines activate the protein kinase Akt, which in turn leads to the phosphorylation and activation of mTOR (mammalian target of rapamycin), the kinase component of mTOR complex 1 (mTORC1). Activated mTOR phosphorylates and inactivates 4E-BP1 abrogating its interaction with eIF4E. Free eIF4E binds eIF4G and promotes cap-dependent translation [9]. Downregulation of mTOR activity by physiological stresses such as nutrient deprivation, hypoxia, and the drug rapamycin, results in

hypophosphorylated (activated) 4E-BP1 that competes with eIF4G for binding to eIF4E, thereby preventing cap-dependent translation. The 4E-BP-eIF4E complex can remain bound to the m^7GpppN cap, aiding the inhibition of cap-dependent mRNA translation owing to blockade of the 5′ end of Mrna [10]. Elevated levels of hypo-phosphorylated 4E-BPs, together with elevated levels of eIF4G, can thus function as a physiological switch, as seen in certain locally advanced cancers, impairing the initiation of translation on cap-dependent mRNAs but facilitating translation of dual mechanism mRNAs as they also contain an internal ribosome entry site (IRES) to which eIF4G may bind directly [11,12].

This tightly regulated process of translation initiation eventually contributes to the overall amplitude of the specific protein in the cell [13]. Genes encoding Initiation Factors (e.g., eIF3, eIF4G, eIF4E, eIF5A2) have been reported to be amplified in a wide variety of human cancers and regulate specific steps of translation initiation including the initiator Met-tRNAi binding and ribosome–mRNA interaction. The genetic loci of eIF4E and eIF4G, two important initiation factors responsible for cap-dependent translation, were originally found overexpressed in squamous cell lung carcinoma and breast cancer. Furthermore, overexpression and gene amplification of eIF5A2, which promotes the formation of the first peptide bond, has been implicated in ovarian cancer as well as in other tumors including lung cancer, breast cancer and hepatocellular carcinoma [14]. The genetic imbalances of the initiation factors described above have been reported to affect the overall expression levels of their mRNA and/or protein.

IV. CROSSTALK OF ONCOGENIC SIGNALLING PATHWAYS AND SPECIFIC TRANSLATIONAL COMPONENTS

Work over the last decade is in concert with the paradigm that deregulation of translational control is a common mechanism by which different oncogenic pathways (e.g., PI3K, Myc, and Ras) facilitate tumor development and cellular transformation. In normal cells, these pathways act as sensors of energy, nutrient availability, stress, as well as growth factor signals, and integrate these inputs to direct control gene expression at the translational level and ribosome production [15]. One of the prime reasons for this cross talk is the coupling of these external cues with the execution of cell survival, cell growth, division etc; which are directly related to protein synthesis. Importantly, all these signals when hyperactivated become oncogenic. The oncogenic signals directly regulate the expression and activity of specific translational components. Remarkable examples include the PI3K-AKT-mTOR and Ras-MAPK signal transduction cascades, as well as transcriptional programs governed by oncogenic Myc. Oncogenic stimuli such as PI3K-AKT-mTOR, Ras and Myc enhance protein synthesis by synchronizing the regulation of ribosome biogenesis, translation initiation, and translation elongation. The conventional PI3K-AKT-mTOR signalling pathway facilitates ribosome biogenesis via both elevated rRNA synthesis and amplified ribosomal protein production. This signalling pathway stimulates the rate limiting step of translation i.e. translation initiation

primarily through mTORC1-dependent hyperactivation of eIF4E and thus cap dependent translation. In the absence of such signalling, hypophosphorylated 4E-BPs bind to and inhibit eIF4E, abrogating its ability to interact with eIF4G [16-18].

4.1 PI3K-AKT-mTOR pathway

One of the best-studied examples of oncogenic signalling pathways that affect translational control is the PI3K-AKT-mTOR pathway, which directly regulates translation initiation via activation of the kinase mammalian target of rapamycin complex 1 (mTORC1). The PI3K-AKT-mTOR pathway is considered as one of the most commonly mutated pathways in cancer [19]. mTORC1 phosphorylates ribosomal protein S6 kinase 1/2 (S6K1/2) and the eIF4E-binding proteins (4E-BPs). S6K1/2 are ribosomal protein S6 kinases that affect the efficiency of translation initiation and elongation.

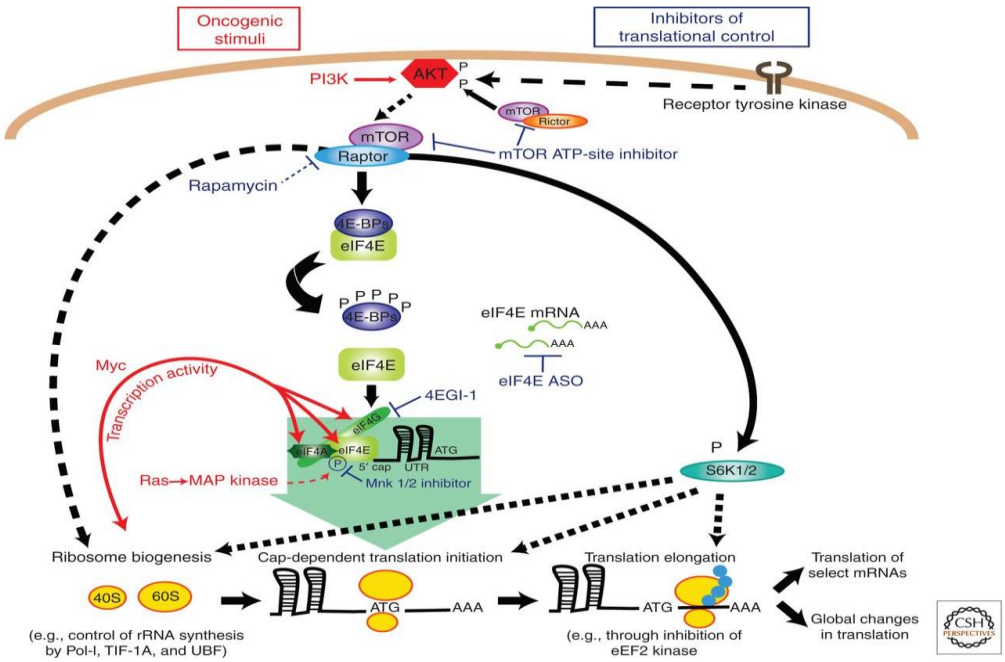

Fig 2: Oncogenic signals regulating each stage of translation
(adapted from Cold Spring Harbor Perspectives in Biology)

Phosphorylation of 4E-BPs at canonical sites leads to a conformational change that frees eIF4E, which, with the aid of other eukaryotic initiation factors ultimately recruits the 40S ribosomal subunit to the 5′ cap of mRNAs during translation initiation.

Initiation is considered as the rate-limiting step of cap dependent translation and eIF4E is regarded the key factor in controlling this step. This deduction in the availability of eIF4E is in part based on the fact that eIF4E activity is highly governed at both the mRNA and protein level. At the mRNA level, eIF4E is up-regulated by various transcription factors including the oncogene Myc. At the translational level, eIF4E activity is also regulated through phosphorylation by the MAP kinase targets MNK1/2 at serine 209 in addition to inhibitory interactions with 4E-BPs. This tight regulation of eIF4E activity provides a robust mechanism for cells to change translation initiation in response to different stimuli, including growth factor and oncogenic signalling [20,21].

4.2 The 4E-BPs/eIF4E axis

The 4E-BPs/eIF4E axis is the most well-characterized nodes in translation control and cancer. For instance, eIF4E gene amplification has been reported in human head, neck and breast cancer specimens. eIF4E is also found overexpressed in a wide variety of tumors. The oncogenic potential of eIF4E has been well recapitulated both in vitro and in vivo. Research based evidence reveal that overexpression of eIF4E is sufficient to induce transformation of human epithelial cells and immortalized murine fibroblasts[22,23]. Constitutive expression of eIF4E in a mouse model that mimics the human oncogenic lesion results in increased cancer susceptibility. Moreover, eIF4E transgenic mice develops lymphomas, lung carcinomas, angiosarcomas, and hepatoma. Also, in vivo overexpression of eIF4E couples with c-Myc to drive lymphomagenesis in part through a mechanism by which eIF4E overcomes Myc-induced apoptosis, a cellular barrier to tumor formation. This has been confirmed by using an adoptive transfer method in vivo, which shows that phosphorylated eIF4E contributes to Myc-induced tumorigenesis largely by suppressing apoptosis[24-26]. Furthermore, it has recently been demonstrated that the loss of 4E-BP1 function by silencing its expression induces Epithelial to Mesenchymal Transition followed by generation of cell migratory and invasive capabilities as well as metastasis in breast and colon cancer models [27].

4.3 Ras-MAP kinase signaling

In addition to PI3K-AKT-mTOR pathway, Ras-MAP kinase signalling elevates eIF4E activation via phosphorylation at serine 209. Myc promotes protein synthesis by upregulating the transcription of multiple translational components including eIF4E mRNA. It has been well documented that the Ras/MAPK pathway shows crosstalk with PI3K/mTOR pathway at various steps to modulate translation. Besides its role upstream of mTORC1, MAPK phosphorylates some additional components of the translational machinery, such as eIF4B in vitro and in vivo[28]. eIF4B facilitates the RNA-helicase activity of eIF4A [29] and eIF4B phosphorylation has been found to increase its interaction with eIF3[30]. This interaction corresponds with increased translation rates and also is in agreement with the finding that phosphorylated eIF4B promotes cap-dependent translation in vivo [30]. S6Ks can also regulate eIF4B phosphorylation, which explains the biphasic pattern of eIF4B phosphorylation as observed in response to certain mitogenic signals.

Together, these oncogenic stimuli modulate the multiple stages of translation to drive both selective changes in the translation of specific mRNAs and global changes in protein synthesis as well.

V. CLINICAL- "TRANSLATIONAL" APPROACHES

Multiple approaches are in trial to therapeutically target the translational apparatus including rapamycin, ATP-active site inhibitors of mTOR, 4EGI-1, and eIF4E antisense oligonucleotides (ASO) MNK1/2 kinase inhibitors[31]. The eIF4E oncogene, which is often overexpressed in human cancer, represents an attractive and promising target for rational drug design. Now a days, several approaches are being pursued to therapeutically target eIF4E, but the most direct of these is the use of antisense oligonucleotides (ASOs) that bind specifically to eIF4E mRNA and degrade it by RNase H. The eIF4E-ASO is also being tested in combination with chemotherapy in new phase I/II clinical trials of metastatic prostate and lung cancer[32]. Additional attempts to inhibit eIF4E have focused on abrogating its ability to interact with eIF4G which is dependent on an eIF4G Y(X)4LΦ motif, in which X is variable and Φ is any hydrophobic residue[33]. High-throughput screens for search of inhibitors that could inhibit eIF4E from binding to the Y(X)4LΦ motif unravelled 4EGI-1 as a candidate compound which is both a cytostatic and cytotoxic agent acting across multiple cell lines. Currently, indirect approaches are proving particularly effective to target oncogenic eIF4E activity [34]. For instance, inhibiting the mTOR kinase holds tremendous impetus. Characterizations of recently developed mTOR ATP-site inhibitors in vitro and in vivo have shown pronounced efficacy than allosteric mTOR inhibitors (rapalogs) [35,36]. In line with these studies, PP2A has been extensively used in preclinical trial for AKT-driven lymphomagenesis[26]. Altogether, these findings strongly reinforce that the therapeutic potency of ATP-site inhibitors may be associated with their ability to inhibit mTORC1-dependent 4E-BP phosphorylation and eIF4E oncogenic activity[26]. Notably, INK128, a more potent derivative of PP242 and several other ATP-site inhibitors, are currently in phase I/II clinical trials in patients with advanced hematological malignancies and solid tumors [37,38].

VI. CONCLUDING REMARKS

Modulation of the translational landscape appears to be a cricial factor in tumor formation associated with overactivation of signal transduction pathways. The review highlights the importance of cap-dependent mRNA translation in cancer progression suggesting that the deregulation in translational control may represent a mechanism for drug resistance. We discuss studies that provide novel insights into the biological research and clinical relevance of translational regulation in metastatic progression and therapy.

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