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# eIF4E – from translation to transformation

Yaël Mamane[1], Emmanuel Petroulakis[1], Liwei Rong[1], Kaori Yoshida[1], Lian Wee Ler[1] and Nahum Sonenberg[1]*

[1]*Department of Biochemistry, McGill Cancer Centre, McGill University, 3655 Promenade Sir-William-Osler, Montreal, Quebec, Canada, H3G 1Y6*

**Over the years, studies have focused on the transcriptional regulation of oncogenesis. More recently, a growing emphasis has been placed on translational control. The Ras and Akt signal transduction pathways play a critical role in regulating mRNA translation and cellular transformation. The question arises: How might the Ras and Akt signaling pathways affect translation and mediate transformation? These pathways converge on a crucial effector of translation, the initiation factor eIF4E, which binds the 5′cap of mRNAs. This review focuses on the role of eIF4E in oncogenesis. eIF4E controls the translation of various malignancy-associated mRNAs which are involved in polyamine synthesis, cell cycle progression, activation of proto-oncogenes, angiogenesis, autocrine growth stimulation, cell survival, invasion and communication with the extracellular environment. eIF4E-mediated translational modulation of these mRNAs plays a pivotal role in both tumor formation and metastasis. Interestingly, eIF4E activity is implicated in mitosis, embryogenesis and in apoptosis. Finally, the finding that eIF4E is overexpressed in several human cancers makes it a prime target for anticancer therapies.**
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## Eukaryotic initiation factor 4E– eIF4E

Control of mRNA translation plays a critical role in cell growth, proliferation and differentiation. In eukaryotes, most mRNAs are translated in a cap-dependent manner. The cap structure $m^7$GpppN (where N is any nucleotide) is found at the 5′ terminus of all cellular eukaryotic mRNAs (except those in organelles) (reviewed in Gingras *et al*., 1999). A key player in the regulation of translation is the mRNA 5′ cap-binding protein eIF4E, which is the rate-limiting member of the eIF4F complex. This complex also consists of eIF4A, an ATP-dependent helicase, and a large scaffolding protein, eIF4G, which acts as a docking site for other proteins. An alternative mechanism of translation initiation is cap- and eIF4E-independent and requires an internal RNA structure termed Internal Ribosome Entry Site (IRES) to which the 40S subunit binds directly. Originally, this mode of translation initiation was identified in picornaviruses (Jang *et al*., 1988; Pelletier and Sonenberg, 1988), but subsequent studies revealed the presence of IRES-dependent cellular translation in mitosis and apoptosis (reviewed in Gingras *et al*., 1999; Holcik *et al*., 2000; Pyronnet and Sonenberg, 2001; Vagner *et al*., 2001; Gallego, 2002).

*Correspondence: N Sonenberg; E-mail: nahum.sonenberg@mcgill.ca

## Inhibitors of eIF4E: 4E-BPs

Assembly of the eIF4F complex is inhibited by a family of repressors termed the eIF4E-binding proteins (4E-BPs). The 4E-BPs (4E-BP1, 4E-BP2 and 4E-BP3) are small heat-stable proteins which inhibit cap-dependent translation (Pause *et al*., 1994; Poulin *et al*., 1998). Binding of the 4E-BPs to eIF4E is regulated by phosphorylation: hypophosphorylated 4E-BPs interact strongly with eIF4E, whereas the hyperphosphorylated forms bind weakly (reviewed in Gingras *et al*., 1999). Extracellular stimuli such as growth factors, hormones, mitogens, amino acids, cytokines and G-protein-coupled receptor agonists induce 4E-BP phosphorylation and thus, it's released from eIF4E (reviewed in (Gingras *et al*., 1999).

## Upstream Effectors Of eIF4E: PI3K/Akt/mTOR

The phosphatidylinositol 3-kinase (PI3 K) mammalian Target of Rapamycin (mTOR) pathway is activated by growth factors, mitogens and hormones (Figure 1) (reviewed in Schmelzle and Hall, 2000; Gingras *et al*.,. 2001; Raught *et al*., 2001; Proud, 2002; Jacinto and Hall, 2003; Ruggero and Pandolfi, 2003). Activation of PI3 K initiates a cascade of events: The 3′-phosphoinositide-dependent kinase 1 (PDK1) activates AKT. Activated AKT phosphorylates TSC2, thereby rendering TSC1/TSC2 complex unstable and inactive. Rheb, a small G protein, is no longer inhibited by the GTPase activating protein (GAP) activity of TSC2 (Inoki *et al*., 2002; Potter *et al*., 2002). TSC1 and TSC2 are tumor suppressors, which are often mutated in tuberous sclerosis, a condition characterized by the emergence

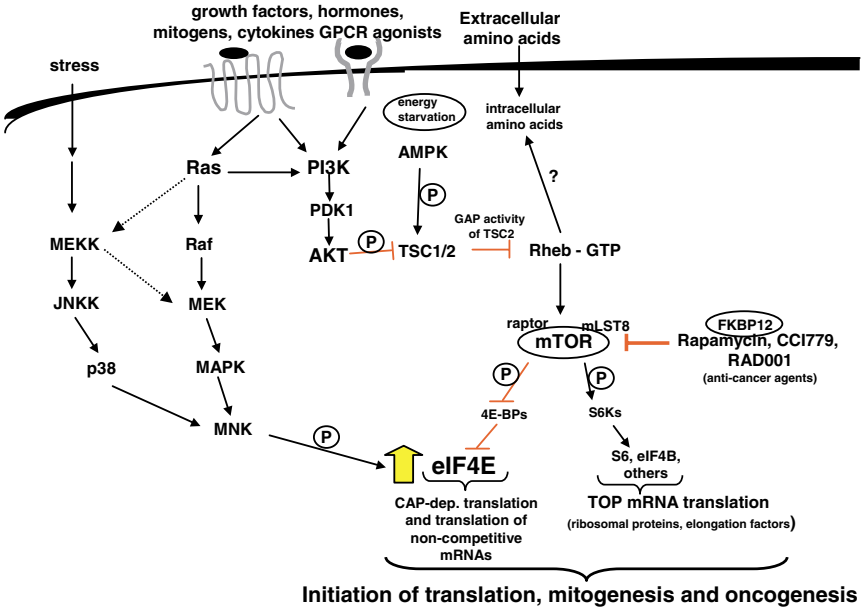


**Figure 1** The roads to eIF4E. The PI3K/AKT/mTOR pathway is activated by growth factors, mitogens and hormones. Nutrients (amino acids, glucose) also activate mTOR. Activation of PI3 K initiates a cascade of events: PDK1 activates AKT which phosphorylates TSC2, thereby rendering TSC1/TSC2 complex unstable and inactive. Rheb, the small G protein, is no longer inhibited by the GAP (GTPase-activating protein) activity of TSC2. The AMP-activated protein kinase (AMPK) also phosphorylates and enhances the activity of TSC2 under energy starvation. Through yet uncharacterized mechanisms, Rheb leads to activation of mTOR. mTOR, which consists of a large multi-protein complex contains two known partners, raptor and G$\beta$L, that promote the activation of the translational activator S6 K and the hierarchical phosphorylation the 4E-BPs. Hyperphosphorylated 4E-BPs release eIF4E, thereby allowing for cap-dependent translation to occur. Activated S6 K phosphorylates the ribosomal protein S6 and causes an increase in translation of 5'TOP containing mRNAs. Most TOP mRNAs encode components of the translation machinery such as ribosomal proteins, elongation factors and the poly (A) binding proteins. Rapamycin and its derivatives CCI-779 and RAD001 specifically interact the immunophilin FKBP12. This complex then binds and inhibits mTOR signaling to downstream targets. These compounds are currently being used in clinical trials as anticancer agents. Another signal transduction pathway, the Ras/Raf/ MAP kinase pathway, is also activated by growth factors and stress. Activation of Ras and MEKK leads to a cascade of events such as JNKK and MAPK activation which culminates in Mnk activation. Mnk phosphorylates eIF4E within the eIF4F complex and permits the recruitment of the ribosome to an mRNA at the initiation codon.The dashed lines indicate possible links.

of multi-systemic benign tumors (hamartomas) (reviewed in Marygold and Leevers, 2002; Kwiatkowski, 2003). The AMP-activated protein kinase (AMPK) also phosphorylates and enhances the activity of TSC2 under energy starvation (Inoki *et al*., 2003b). Rheb leads to activation of mTOR through an unknown mechanism (reviewed in Inoki *et al*., 2003a; Manning and Cantley, 2003; Tee *et al*., 2003). Nutrients (amino acids, glucose) also activate mTOR (reviewed in Proud, 2004). mTOR is a member of the phosphatidylinositol kinase-related protein kinase (PIKK) family. Although the C-terminal region of TOR possesses high homology to lipid kinases, it acts as a serine/threonine protein kinase (reviewed in Schmelzle and Hall, 2000; Gingras *et al*., 2001; Raught *et al*., 2001; Proud, 2002; Jacinto and Hall, 2003; Ruggero and Pandolfi, 2003)). mTOR, which is part of a complex of approximately 1 megadaltons, contains two other known partners, raptor and G$\beta$L, that promote the phosphorylation and activation of the translational activator S6K and the hierarchical phosphorylation the 4E-BPs (Hara *et al*., 2002; Kim *et al*., 2002; Loewith *et al*., 2002; Jacinto and Hall, 2003; Kim *et al*., 2003; Ruggero and Pandolfi, 2003; Kim and Sabatini, 2004). Hyperphosphorylated 4E-BPs are released from eIF4E, therefore stimulating cap-dependent translation. Activated S6K phosphorylates the ribosomal protein S6 and eIF4B and correlates with an increase in translation of 5′ terminal oligopyrimidine tract (5′TOP) containing mRNAs. Most TOP mRNAs encode components of the translation machinery such as ribosomal proteins, elongation factors and the poly (A) binding protein (Jefferies and Thomas, 1996; Meyuhas *et al*., 1996; Meyuhas, 2000).

TOR proteins (TOR1 and TOR2) were initially discovered in yeast during a screen for rapamycin-resistant mutants (Heitman *et al*., 1991; Cafferkey *et al*., 1993; Kunz *et al*., 1993; Helliwell *et al*., 1994; Lorenz and Heitman, 1995). TOR was later cloned in fungi, plants, worms, flies and mammals, and is known as FKBP12-rapamycin-associated protein (FRAP), rapamycin and FKBP12 target (RAFT) or rapamycin target (RAPT) (Brown *et al*., 1994; Chiu *et al*., 1994; Sabatini *et al*., 1994; Cruz *et al*., 1999; Oldham *et al*., 2000; Zhang *et al*., 2000; Long *et al*., 2002; Menand *et al*., 2002). Rapamycin and its derivatives CCI-779 (Wyeth-Ayerst) and RAD001 (Novartis) specifically interact the immunophilin FK506-binding protein-12 (FKBP12). This complex binds and inhibits mTOR signaling to downstream targets (Figure 1). These compounds have generated considerable excitement

in both the clinical and basic cancer research communities since they exhibit potent activity against several tumor cell types (reviewed in (Mita *et al*., 2003; Houghton and Huang, 2004)). Since rapamycin inhibits cap-dependent translation but does not affect IRES-activated translation, it is an attractive agent for anticancer therapies.

## Early findings: eIF4E transforms cells

Earlier studies implicated eIF4E in cellular transformation and oncogenesis. Since eIF4E levels are relatively low in cells compared to other translation initiation factors (Hiremath *et al*., 1985; Duncan *et al*., 1987), it was hypothesized that overexpression of eIF4E could lead to the deregulation of translational and cellular homeostasis. Stable expression of eIF4E in NIH3T3 and CHO cells enhances cellular proliferation, induces a transformed morphology (spindle-shape, refractile cells) and promotes growth in soft agar (Lazaris-Karatzas *et al*., 1990). Microinjection of eIF4E into NIH3T3 also causes cells to enter into S phase (Smith *et al*., 1991). Reduction of eIF4E expression in CREF cells leads to a decrease in global translation rates, an increase in cellular division times, a reversal of the transformed morphology and decreased growth in soft agar (De Benedetti *et al*., 1991; Rinker-Schaeffer *et al*., 1993; Graff *et al*., 1995). eIF4E exerts a mitogenic and oncogenic effect through the activation of the Ras signaling pathway (Lazaris-Karatzas *et al*., 1992). Furthermore, eIF4E cooperates with v-Myc and E1A to immortalize rat embryo fibroblasts (Lazaris-Karatzas and Sonenberg, 1992). Finally, partial reversion of the eIF4E-induced transformed phenotype is achieved by the overexpression of eIF4E binding proteins, 4E-BP1 and 4E-BP2 (Rousseau *et al*., 1996a; Polunovsky *et al*., 2000; Li *et al*., 2002b).

## eIF4E and the translation of malignancy-associated proteins

eIF4E is expressed at low level and is the least abundant initiation factor in most cell types (Hiremath *et al*., 1985; Duncan *et al*., 1987). This suggests that cap-bearing mRNAs 'compete' for the available eIF4E and thus eIF4F in order to become efficiently translated (Lodish, 1974; Rhoads *et al*., 1993; Zimmer *et al*., 2000). mRNAs with short, unstructured, 5'UTR are considered to be 'competitive' since they are less dependent on the unwinding activity of the eIF4F complex. In contrast, the GC-rich region of mRNAs with highly structured 5'UTRs are translated less efficiently. Consistent with this model, overexpression of eIF4E results in enhanced translation of mRNAs containing extensive secondary structure in their 5' UTR (Koromilas *et al*., 1992). Less competitive mRNAs encode for growth-promoting gene products such as cyclin D1, c-myc, VEGF (reviewed in De Benedetti and Harris, 1999; Zimmer *et al*., 2000; Graff and Zimmer, 2003).

### *Ornithine decarboxylase – ODC*

ODC mRNA contains a GC-rich 5'UTR, rendering it poorly translated (Grens and Scheffler, 1990; Manzella and Blackshear, 1990). Overexpression of eIF4E in cells leads to a 30-fold increase in ODC protein levels, as well, depletion of eIF4E using anti-sense RNA suppressed ODC mRNA translation in the eIF4E-overexpressing cells (Shantz and Pegg, 1994, 1999; Graff *et al*., 1997).

Polyamines are ubiquitous cellular components that are involved in normal and neoplastic growth. Polyamine biosynthesis is tightly regulated in mammalian cells by the activities of two key decarboxylases, ornithine- and S-adenosylmethionine decarboxylase. Polyamines are essential for growth, differentiation, survival and mediate cellular transformation (reviewed in Shantz and Pegg, 1999; Schipper and Verhofstad, 2002; Hillary and Pegg, 2003). Overexpression of ODC transforms NIH 3T3 cells (Moshier *et al*., 1993; Auvinen *et al*., 1997). Transgenic expression of polyamine biosynthetic enzymes, such as ODC and S-adenosylmethionine decarboxylase in mice, causes skin cancer (reviewed in Pegg *et al*., 2003). Also, both intracellular polyamine concentrations and ODC activity are increased in colorectal cancer tissue and in premalignant polyps (reviewed in Wallace and Caslake, 2001). The polyamine pathway is also implicated in carcinogenesis and tumor progression of breast cancer (Manni, 2002). Thus, the polyamine synthetic pathway is considered to be an anticancer target (reviewed in Davidson *et al*., 1999; Manni, 2002; Thomas *et al*., 2002; Seiler, 2003; Thomas and Thomas, 2003). Since eIF4E directly regulates ODC mRNA translation, targeting both eIF4E and ODC may serve as an important target for anticancer therapy.

### *Cyclin D1*

The progression of mammalian cells through G1 phase of the cell cycle is governed by the D-type cyclins (D1, D2, D3). These proteins are induced at the beginning of the G1 phase and associate with serine/threonine cyclin-dependent kinases to form activated holoenzymes. Cyclin D1 expression is increased in several human cancers (colorectal and mammary adenocarcinomas, mantle cell lymphomas, oral squamous cell carcinomas and pancreatic tumors) (Wang *et al*., 1994; Guo *et al*., 2003; Hui *et al*., 2003; Miyamoto *et al*., 2003), as well as in several cancer cell lines (hematopoeitic lineage) (Matsumura *et al*., 1999) (reviewed in (Johnson and Walker, 1999; Diehl, 2002; Graff and Zimmer, 2003; Park and Lee, 2003; Polsky and Cordon-Cardo, 2003; Stacey 2003). Interestingly, both cyclin D1 and polyamines are required for entry into S phase and their increased expression has been linked to transformation (reviewed in De Benedetti and Harris, 1999). eIF4E overexpression leads to an increase in cyclin D1 protein (Rosenwald *et al*., 1993a; Rosenwald *et al*., 1995). eIF4E enhances the transport of the cyclin D1 mRNA from the nucleus (Rosenwald *et al*., 1995; Rousseau *et al*., 1996b; Lai and Borden, 2000; Topisirovic *et al*., 2003).

*c-myc*

The translation of the c-Myc mRNA is normally repressed in B cells unless stimulated by mitogens or growth factors (Rosenwald *et al*., 1993b). Deletion mutations in the c-myc 5'UTR, which are present in several Burkitt lymphomas (resulting from translocation of the c-myc gene), result in enhanced translation of the c-Myc mRNA (Saito *et al*., 1983; Darveau *et al*., 1985; Parkin *et al*., 1988; Carter *et al*., 1999; Willis, 1999). c-myc is implicated in several biological processes such as cell growth, proliferation and apoptosis (reviewed in Gartel and Shchors, 2003; Hermeking, 2003; Levens, 2003; Pelengaris and Khan, 2003). c-Myc is expressed ubiquitously during embryogenesis and in post-developmental tissues with a high proliferative capacity. c-myc also inhibits terminal differentiation of most cell types and sensitizes cells to growth factor withdrawal-induced apoptosis (reviewed in Morrish and Hockenbery, 2003; Morrish *et al*., 2003). Activated oncogenic c-myc plays a critical role in the progression of Burkitt's lymphoma, its expression is elevated or deregulated in a wide range of other human cancers and is associated with aggressive tumors with poor prognosis (reviewed in Gartel and Shchors, 2003; Hermeking, 2003; Levens, 2003; Pelengaris and Khan, 2003).

*VEGF and FGF*

eIF4E overexpression results in a dramatic increase in the secretion of vascular endothelial growth factor (VEGF) without affecting mRNA levels (Kevil *et al*., 1996). VEGF mRNA in eIF4E-transfected cells is associated with the heavy polysomes indicating that increased VEGF expression is achieved through its translational upregulation (Kevil *et al*., 1996). Similarly, fibroblast growth factor-2 (FGF-2) mRNA is also loaded onto heavy polysomes in cells overexpressing eIF4E, leading to increased secretion of FGF-2 (Kevil *et al*., 1995). The formation of new blood vessels from pre-existing ones is a well-controlled process (reviewed in Ruegg and Mariotti 2003; Tonini *et al*., 2003), and plays a role in the pathophysiology of many diseases such as cancer and vascular disorders. It is fairly well established that tumor growth and metastasis are angiogenesis-dependent. Both VEGF and FGF-2 are key regulators of angiogenesis and are implicated in enhancing tumor progression (reviewed in Boudreau and Myers, 2003; Detillieux *et al*., 2003; Ferrara *et al*., 2003; Shinkaruk *et al*., 2003; Streit and Detmar 2003). Currently, several VEGF inhibitors which inhibit VEGF and VEGF receptor production or VEGF–VEGFR interactions are undergoing clinical testing in several malignancies (Shepherd, 2001; Zogakis and Libutti, 2001; Ribatti *et al*., 2002, 2003; Bisacchi *et al*., 2003).

Finally, increased eIF4E expression in cells regulates the translation of several other proteins involved in autocrine growth stimulation (PDGF, IGF2), cell survival (Bcl-2, Bcl-xL), invasion (MMP-9) and communication with the extracellular environment (NMDA) (reviewed in De Benedetti and Harris, 1999; Zimmer *et al*., 2000; Graff and Zimmer, 2003). Thus, the eIF4E-mediated translational modulation of these malignancy-associated mRNAs plays a pivotal role in both tumor formation and metastasis. Further investigations into the mRNAs which are strongly dependent on high eIF4E expression for efficient translation will lead to a better understanding of how eIF4E promotes transformation (Figure 1).

## eIF4E And The Ras/Map Kinase Pathway

Growth factors and stress activate the Ras/Raf/ MAP kinase pathway which regulates normal cell growth and malignant transformation (Figure 1). Mutations in the *ras* genes or alterations in signaling components such as Raf and MAP kinases are commonly found in human tumors (reviewed in Downward, 2003; Malumbres and Barbacid, 2003).

Several lines of evidence implicate the Ras/MAP kinase pathway in eIF4E phosphorylation (Figure 1). Phosphorylation of eIF4E is increased in *ras* or *src*-transformed cells (Frederickson *et al*., 1991; Rinker-Schaeffer *et al*., 1992). Also, Ras signaling activates Mnk, which phosphorylates eIF4E on Ser209 (Pyronnet *et al*., 1999; Pyronnet, 2000). Translational regulation also occurs at this level where eIF4G recruits Mnk which phosphorylates eIF4E within the eIF4F complex and permits the recruitment of the ribosome to an mRNA (reviewed in Gingras *et al*., 1999; Hershey and Merrick, 2000) (Figure 1). eIF4E phosphorylation on Ser209 is critical for growth and development of *Drosophila* (Lachance *et al*., 2002). The amount of phosphorylated eIF4E available is also important for efficient ODC translation in ras-activated cells (Shantz, 2004). A recent study by Shantz (2004) has demonstrated that the Ras/MAP kinase pathway is required for the induction of ODC activity. Oxidative stresses, which activate the MAP kinases (MEKK), also increase eIF4E phosphorylation in vascular cells (Duncan *et al*., 2003).

Recent evidence suggests that the Ras and AKT signaling pathways lead to cellular transformation by enhancing the translation of specific mRNAs (Rajasekhar *et al*., 2003). Rajasekhar *et al*. performed an elegant study in which they used glial progenitor cells prepared from transgenic mice which were induced to form glioblastoma by the activation of the Ras and AKT pathways. In this study, the Ras and/or AKT pathways were also downregulated using treatment with small molecules that inhibit one or more components of the pathways. Gene expression profiling using microarray chips was performed to examine alterations in gene expression patterns after the inhibition or activation of the Ras and AKT pathways (Rajasekhar *et al*., 2003). Surprisingly, relatively modest changes in gene expression profiles were seen when using total cellular RNA. However, dramatic changes in the recruitment of some RNAs to ribosomes were seen in response to Ras/AKT activation. Therefore, alterations in the Ras and AKT signaling pathways profoundly affect the recruitment of mRNAs to polysomes. These mRNAs generally

encode for proteins that are known to function in cell growth and proliferation, and are implicated in tumorigenesis. This effect is regulated in part by eIF4E (Lasko, 2003; Prendergast, 2003; Rajasekhar *et al*., 2003).

## eIF4E and embryogenesis/reproduction

Regulation of mRNA translation is also crucial for the control of gene expression during development. Studies in zebrafish implicate eIF4E in oogenesis, gastrulation and erythropoiesis (Klein and Melton, 1994; Curtis *et al*., 1995; Fahrenkrug *et al*., 1999). The differential expression of eIF4E during zebrafish embryogenesis suggests that eIF4E may act as a tissue-specific translation enhancer (Fahrenkrug *et al*., 1999). A role for eIF4E in spermatogenesis in *C. elegans* has also been proposed since elevated levels of eIF4E have been detected in germ granules (Amiri *et al*., 2001). Finally, Cormier *et al*. demonstrated that the dissociation of eIF4E from 4E-BP and subsequent degradation of 4E-BP, following fertilization of sea urchin eggs, led to an increase in cap-dependent translation. This is critical for the first mitotic division of sea urchin embryos (Cormier *et al*., 2001; Salaun *et al*., 2003).

## eIF4E and apoptosis

eIF4E also mediates cell survival and apoptosis (reviewed in Clemens 2001; Dua *et al*. , 2001). Firstly, eIF4E overexpression compensates for serum/growth factor deprivation by promoting the survival of NIH 3T3 cells (Polunovsky *et al*., 1996). Secondly, high levels of eIF4E rescue rat embryo fibroblasts ectopically expressing c-Myc from genotoxic and non-genotoxic cytostatic drugs (Tan *et al*., 2000). Increased levels of cyclin D1 due to eIF4E overexpression seems in part to be the downstream effector in this antiapoptotic mechanism (Tan *et al*., 2000). eIF4E also rescues cells from Myc-dependent apoptosis by inhibiting mitochondrial cytochrome *c* release through an increase in Bcl-$X_L$ mRNA translation (Li *et al*., 2003). Ectopic expression of 4E-BP1 is pro-apoptotic in both normal as well as ras-transformed fibroblasts (Polunovsky *et al*., 2000; Li *et al*., 2002b). Finally, a constitutively active 4E-BP1 mutant in which the critical phosphorylation sites (Thr36, Thr45, Ser64 and Thr 69) are mutated to Ala, slows G1 progression and blocks c-myc induced transformation (Lynch *et al*., 2004).

## eIF4E in cancer

Is eIF4E is a *bonafide* proto-oncogene? Since eIF4E overexpression leads to cellular transformation (De Benedetti and Rhoads, 1990; Lazaris-Karatzas *et al*., 1990; De Benedetti *et al*., 1991; Lazaris-Karatzas and Sonenberg, 1992; Rinker-Schaeffer *et al*., 1993; Graff *et al*., 1995), several groups have investigated the levels of eIF4E expression in human cancers (reviewed in Clemens and Bommer, 1999; De Benedetti and Harris, 1999; Nathan *et al*., 1999; Dua *et al*., 2001; Graff and Zimmer, 2003). eIF4E is indeed overexpressed in many solid tumors and tumor cell lines. The list includes cancers of the colon, breast, bladder, lung, prostate, gastrointestinal tract, head and neck, Hodgkin's lymphomas and neuroblastomas (Kerekatte *et al*., 1995; Anthony *et al*., 1996; De Benedetti and Harris, 1999; Nathan *et al*., 1999; Rosenwald *et al*., 1999, 2001; Wang *et al*., 1999, 2001; Li *et al*., 2002a). A role for eIF4E as a prognosis marker has also been suggested in certain cancers (reviewed in Thornton *et al*., 2003). The potential involvement of eIF4E in metastasis is also being considered (reviewed in Clemens and Bommer, 1999; De Benedetti and Harris, 1999; Graff and Zimmer, 2003; Thornton *et al*., 2003).

Other translation initiation factors which are subunits of the eIF4F complex are also implicated in malignant transformation (reviewed in Watkins and Norbury, 2002). Overexpression of eIF4GI, the scaffolding protein, in NIH3T3 cells leads to anchorage-independent growth of cells, growth in soft agar and tumor formation in nude mice (Fukuchi-Shimogori *et al*., 1997). eIF4GI is overexpressed in squamous cell lung carcinomas (Brass *et al*., 1997; Keiper *et al*., 1999; Bauer *et al*., 2001, 2002; Prevot *et al*., 2003). eIF4A, the ATP-dependent RNA helicase, is overexpressed in human melanoma cells and in primary hepatocellular carcinomas (Eberle *et al*., 1997; Shuda *et al*., 2000). Furthermore, a novel tumor suppressor, Pdcd4, binds and inhibits the helicase activity of eIF4A and consequently abrogates translation (Yang *et al*., 2003). Thus, a potential therapeutic approach for cancer emerges: the suppression of eIF4E expression or inhibition of its function as part of the eIF4F complex in cancer cells may prove to be an effective tool. The use of antisense RNA to suppress eIF4E has had some success in reducing the tumorigenic and angiogenic properties of head and neck cancer cells (DeFatta *et al*., 2000). Furthermore, rapamycin analogues, inhibitors of the mTOR signaling pathway (Figure 1), are currently being tested in cancer clinical trials (reviewed in Jacinto and Hall, 2003; Mita *et al*., 2003; Houghton and Huang, 2004). An interesting therapeutic approach would be to use a combination of anticancer agents such as inhibitors of polyamine synthesis, G1-S blockers such as flavopiridol (Dai and Grant, 2003; Dobashi *et al*., 2003; Vermeulen *et al*., 2003), antiangiogenesis compounds (Shepherd, 2001; Zogakis and Libutti, 2001; Ribatti *et al*., 2002, 2003; Bisacchi *et al*., 2003) and rapamycin (reviewed in Mita *et al*., 2003; Houghton and Huang, 2004). Interestingly, Maeshima *et al*. demonstrated that tumstatin is a potent antiangiogenesis agent because it specifically inhibits protein synthesis in vascular endothelial cells through the inhibition of the PI3K/mTOR pathway, thus increasing the association of eIF4E with 4E-BP1 (Maeshima *et al*., 2002). These results further highlight the growing importance of targeting cap-dependent translation in future cancer treatments.

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