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The Akt of translational control

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The oncogene AKT (also called protein kinase B (PKB)) signals to the translational machinery, and activation of protein synthesis by Akt is associated with cancer formation. Akt directly stimulates the activity of translation initiation factors and upregulates ribosome biogenesis. Activation of protein synthesis by Akt is phylogenetically conserved from *Drosophila* to humans, and is important for regulating cell growth, proliferation and cell survival. Consequently, translation defects due to aberrant Akt activation may be a crucial mechanism leading to tumorigenesis. However, few *in vivo* studies have established a causative role for aberrant protein synthesis control in cancer. A major challenge in the future will be to identify the specific mRNAs regulated at the level of translation control directly relevant for cellular transformation. In this review, we highlight and discuss the emerging molecular and genetic evidence that support a model by which deregulation of specific or global protein synthesis contributes to cancer.
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PI3k/Akt/mTOR pathway talks to the translational machinery

Activation of the phosphatidylinositol 3-kinase (PI3K) pathway by growth factors, hormones and mitogen stimuli represents one of the major signal transduction cascades regulating global and specific mRNA translation (Gingras *et al*., 2001b; Ruggero and Pandolfi, 2003; Raught *et al*., 2004) (Figure 1). Biochemical and genetic approaches were used to decipher the mechanism by which the different players of the PI3K pathway are functionally connected and how their activities converge to turn on the downstream kinase, mammalian target of rapamycin (mTOR) (Cantley, 2002; Luo *et al*., 2003; Montagne and Thomas, 2004). mTOR activation has emerged as the major effector of the PI3K pathway to regulate protein synthesis, and its function is evolutionarily conserved from yeast to mammals (Chiu *et al*., 1994; Sabatini *et al*., 1994; Brown *et al*., 1995; Gingras *et al*., 2001b; Jacinto and Hall, 2003; Guertin and Sabatini, 2005). Extracellular signals activate PI3K at the membrane resulting in the phosphorylation of 4,5-phosphatidylinositol (PIP2) to yield 3,4,5-PIP3. This three phosphate-lipid product is responsible for the phosphorylation of the serine–threonine kinases Akt by the phosphoinositide-dependent kinase 1 (PDK1). This phosphorylation event stimulates the catalytic activity of Akt, resulting in the phosphorylation of target proteins including mTOR kinase that to date is the only example of an Akt target protein that is activated by the Akt-phosphorylation event (Cantley, 2002). The phosphatase PTEN dephosphorylates the 3′ position of 3,4,5-PIP3 to produce 4,5-PIP2, therefore negatively regulating Akt activity (Li *et al*., 1997; Maehama and Dixon, 1998; Stambolic *et al*., 1998). Studies using phospho-specific antibodies revealed that Akt phosphorylates mTOR directly on Ser-2448 and Thr-2446 *in vitro* and *in vivo*. However, the role of these phosphorylation sites remains unclear as they are not necessary for signaling downstream to mTOR (Scott *et al*., 1998; Nave *et al*., 1999; Sekulic *et al*., 2000; Reynolds *et al*., 2002). A major progress in understanding how Akt controls protein synthesis via mTOR derived from the recent discovery that Akt-phosphorylation inactivates the tuberous sclerosis complex (TSC) which negatively regulates the mTOR kinase activity (van Slegtenhorst *et al*., 1997; Gao and Pan, 2001; Potter *et al*., 2001, 2002; Inoki *et al*., 2002). The TSC complex is formed by two proteins known as TSC1 (or hamartin) and TSC2 (or tuberin). The heterodimeric complex negatively regulates mTOR by inhibiting a small G protein, Ras homolog enriched in brain (Rheb), considered the direct activator of mTOR through a mechanism not yet elucidated (Garami *et al*., 2003; Stocker *et al*., 2003; Tee *et al*., 2003; Zhang *et al*., 2003). Strikingly, the major targets of mTOR are components of the translation apparatus including the ribosomal protein S6 and initiation factors important for the recruitment of the ribosome to the mRNA (see below). This linear pathway from PI3K to mTOR activation and translational control is phylogenetically conserved from *Drosophila* to humans. The *Drosophila* genetic model system served to demonstrate how initiation of this signaling pathway and the activity of the translation components downstream control cell growth and cell proliferation (Gao

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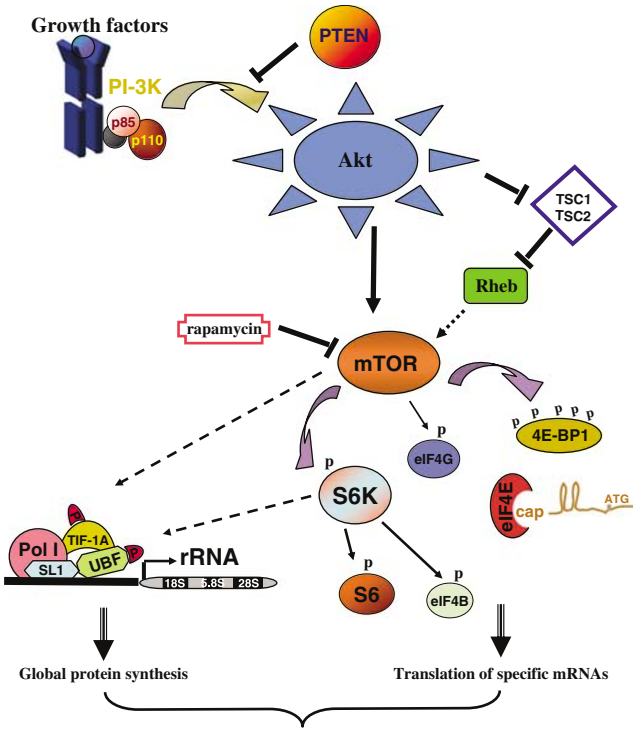

Figure 1 Activation of the PI3K/Akt/mTOR pathway by growth factors controls protein synthesis at the level of translation initiation and ribosome biogenesis. In this simplified cartoon Akt modulates the activity of transcription factors important for Pol I activity and rRNA synthesis, thereby regulating ribosome biogenesis and global proteins synthesis. The activation of Akt/mTOR pathway may also control translation of specific mRNAs, sensitive to rate limiting amounts of translational components, through phosphorylation of the ribosomal protein S6 and by activation of initiation factors such as eIF4E, eIF4G and eIF4B. These mRNAs encode for proteins, which are involved in cell growth, cell proliferation and cell survival. Alterations in translational control of the downstream Akt-signaling pathway represent an important step towards cellular transformation. The negative effect of rapamycin on mTOR activity represents a powerful therapeutic agent in Akt-induced tumorigenesis associated with deregulations in protein synthesis control

et al., 2000; Gingras *et al*., 2001b; Miron *et al*., 2001, 2003). Deregulation of the PI3K pathway occurs in many human cancers (see accompanying review by Altomare and Testa in this issue), and components of this pathway including PTEN and Akt, which act as key tumor suppressors and oncogenes, respectively, are mutated in a variety of tumors (Li *et al*., 1997; Liaw *et al*., 1997; Marsh *et al*., 1997; Di Cristofano *et al*., 1998; Hutchinson *et al*., 2001; Malstrom *et al*., 2001; Mende *et al*., 2001; Vivanco and Sawyers, 2002; Luo *et al*., 2003; Rathmell *et al*., 2003; Sansal and Sellers, 2004).

The importance of the mTOR pathway in cancer progression has been highlighted by the fact that the macrolide rapamycin, a potent inhibitor of mTOR, inhibits tumor growth of many cancers including those present in PTEN heterozygous mice as well as in teratocarcinomas derived from PTEN-null cells (Neshat *et al*., 2001; Podsypanina *et al*., 2001; Sawyers, 2003). Rapamycin and its derivatives (CCI-779 and RAD001) are currently in clinical trials. Importantly, these drugs do not have any effect on tumor cells that do not display hyperactivation of mTOR activity (Bjornsti and Houghton, 2004). This strongly supports the role of a deregulation of mTOR activity and the downstream targets in the initiation and/or progression of cancer. A causal relationship between aberrant translation initiation due to a constitutive activation of mTOR kinase and cellular transformation has also been suggested by the findings that some of the components of the translation machinery, that are direct or indirect targets of mTOR, are overexpressed in tumors (Mamane *et al*., 2004). Recent work has shed light on the mechanism by which initiation factors of translation can act as oncogenes to promote tumor formation *in vivo* (Ruggero *et al*., 2004). Despite the impressive advances in this field, there are many questions to be answered, including (1) To what extent is deregulation of translational control downstream of the Akt/mTOR pathway important for tumor formation? (2) What are the cellular mechanisms by which hyperactivation of translation components contribute to cancer? (3) Which are the translational target mRNAs downstream of the Akt/mTOR pathway that are important for tumor initiation and/or progression?

Ribosome as a target of Akt

rRNA synthesis

It is well established that the negative effect of rapamycin on tumor cell growth is accompanied by a downregulation in the synthesis of ribosomal RNA (rRNA) (Mahajan, 1994; Hannan *et al*., 2003; James and Zomerdijk, 2004). Recent data added an important aspect to the mechanism in elucidating how the Akt/mTOR pathway controls the activity of RNA polymerase I (Pol I) (Mayer *et al*., 2004). Importantly, it was demonstrated that TIF-1A, a Pol I transcription factor essential for rRNA synthesis, is a target of mTOR signaling. Interestingly, inhibition of the mTOR pathway results in phosphorylation of TIF-1A at Ser199 and a decrease in Ser44 phosphorylation. While phosphorylation of Ser44 activates TIF-IA and Pol I transcription, phosphorylation at Ser199 causes the reverse effect (Mayer *et al*., 2004). These results suggest the existence of an mTOR-dependent kinase and a phosphatase that modify the activity of TIF-IA in response to a cellular cue aimed to stimulate cell growth and proliferation. The kinase that directly modifies the activity of TIF-IA upon mTOR activation is unknown. However, this phosphorylation homeostasis highlights the importance of TIF-1A as a master regulator of Pol I activity and introduces a new role for the Akt/mTOR pathway in the regulation of rRNA synthesis in cell growth and proliferation. Importantly, TIF-IA−/− cells show a severe proliferation defect as the cells are arrested in the

G0/G1 phase of the cell cycle (Yuan *et al*., 2005). This phenotype is associated with a drastic impairment in ribosome biogenesis and a 60% reduction in translation activity. Genetic ablation of TIF-IA also results in disruption of the nucleolar structure with a concomitant accumulation of p53 in induction of apoptosis. Therefore cell proliferation defects may represent the end point in this process due to a direct role of p53 in cell cycle arrest. It is clear from these results that a network consisting of ribosome biogenesis/protein synthesis and cell cycle control is coordinated by TIF-IA, but a central unanswered question is the effect of increased rRNA synthesis on cell cycle entry. Addressing this important question would shed light on the mechanism by which Pol I activity could have a causative effect in cancer initiation. The exciting result that the mTOR pathway regulates growth and proliferation possibly through control of rRNA synthesis suggests that Akt might, in part, elicit its oncogenic activity through activation of Pol I.

Other studies have also linked Akt activation to rDNA transcription as a mechanism to control cell growth and proliferation. mTOR stimulates rDNA transcription through the phosphorylation of another transcription factor required for Pol I activity and rRNA synthesis, UBF (Hannan *et al*., 2003). Although the exact mechanism by which this is achieved remains elusive, S6K1 kinase, a well-known target of mTOR (see below), activates UBF. In addition, and more importantly, mTOR-S6K1 signaling positively affects rDNA transcription in primary cultures of proliferation-arrested postmitotic cardiomyocytes, resulting in hypertrophic growth (Hannan *et al*., 2003). This work is in agreement with other studies that showed that components of the PI3K signal transduction pathway such as PTEN and Akt are important negative and positive regulators, respectively, of cardiac hypertrophy (Crackower *et al*., 2002; Matsui *et al*., 2002; Shioi *et al*., 2002). Thus, activation of rDNA transcription could provide a mechanism by which activation of the PI3K/Akt/mTOR pathway controls cell growth independent from its control of cell proliferation (Figure 1).

The significance of Pol I transcription as a downstream target of the PI3K/Akt/mTOR pathway is further underscored by insulin-like growth factor 1 (IGF-1) stimulation of rapamycin-sensitive rRNA synthesis (James and Zomerdijk, 2004). The IGF signal transduction pathway plays a major role in controlling cell and body size by coordinating growth and cell proliferation in flies and mammals (Baserga, 2004). The main IGF pathway signals through the insulin receptor substrate 1 (IRS-1) which activates PI3K/Akt signaling and, downstream of this signal axis, UBF and other rDNA transcription factors such as the essential TBP–TAF complex SL1 which coordinates rRNA synthesis and ribosome biogenesis (Baserga, 2004; James and Zomerdijk, 2004). A reasonable but unanswered question is whether the IGF/IRS-1/Akt pathway contributes to cellular transformation through rRNA synthesis. The answer to this question is not yet clear because of the lack of *in vivo* models. However, two lines of evidence suggest that at least in part this may be the case. First, elevated levels of IRS-1 contribute to malignant transformation when overexpressed in NIH3T3 cells (Ito *et al*., 1996; Valentinis and Baserga, 2001). Secondly, overexpression of UBF and PES-1, another protein involved in ribosome biogenesis, causes transformation of fibroblasts that express substantial levels of IRS-1 (Prisco *et al*., 2004).

Ribosomal proteins

The S6 ribosomal protein is phosphorylated upon Akt activation and has been used as one of the most reliable readouts for PI3K activation. Phosphorylation of S6 was originally observed *in vivo* during liver regeneration when protein synthesis is augmented to sustain hepatocyte proliferation (Gressner and Wool, 1974). Subsequent studies have demonstrated that S6 phosphorylation is a common response to growth-factor stimulation (Nielsen *et al*., 1981; Kozma *et al*., 1989). Therefore, phosphorylation of this ribosomal protein was suggested to be a general mechanism to signal and induce cell growth and proliferation. The kinases which are responsible for S6 phosphorylation; S6K1 and S6K2 belong to the AGC family of serine/threonine protein kinases (Shima *et al*., 1998). S6 kinases are direct targets of mTOR which activates these kinases through phosphorylation at specific serine (Ser) and threonine (Thr) residues (Brown *et al*., 1995; Burnett *et al*., 1998). Therefore, Akt positively signals to S6 kinases in a rapamycin-sensitive manner. Biochemical and genetic studies have highlighted the importance of S6 kinases in cell growth and proliferation. In the fly, loss of function of dS6k affects cell size but not cell number (Montagne *et al*., 1999). In mammalian cells, however, these kinases control growth and proliferation in a tissue-dependent manner (Shima *et al*., 1998; Pende *et al*., 2000, 2004; Ohanna *et al*., 2005). Deletion of both kinases is sufficient to abolish rapamycin-sensitive S6 phosphorylation (Pende *et al*., 2004). Originally, the functional role of S6 phosphorylation has been attributed to translational control of specific set of mRNAs that contain a 5′TOP (terminal oligopyrimidine tract); a short polypyrimidine stretch (4–14 nucleotides) immediately next to the cap structure of the mRNA (Hornstein *et al*., 2001). This class of mRNAs includes translation elongation factors, several proteins involved either in translational control or ribosome biogenesis and ribosomal proteins. TOP mRNAs are regulated at the translational level as they are shifted from polysomes in growing cells into mRNPs (inactive translational particles) in quiescent cells. Therefore, a conventional model was that activated S6K promotes translation of 5′TOP mRNAs via S6 phosphorylation, and this mechanism might serve to control cell growth and proliferation (Jefferies *et al*., 1997; Schwab *et al*., 1999; Loreni *et al*., 2000). Supporting data for this model derived from the demonstration that a rapamycin-resistant S6K1 mutant confers rapamycin resistance to the translation of 5′TOP mRNAs (Jefferies *et al*., 1997; Schwab *et al*., 1999). In addition, S6

phosphorylation is impaired in S6K1−/− embryonic stem cells, and upon serum stimulation 5′TOP mRNAs are not recruited to the polysome as compared with WT cells (Kawasome *et al*., 1998). To date there are no direct data to indicate that the effect on cell growth and proliferation by S6Ks is due to translation of 5′TOP mRNAs. Furthermore, recent studies have argued that S6K activation or S6 phosphorylation are not important for 5′TOP mRNA translation (Pende *et al*., 2004). Moreover, mitogenic stimuli selectively activate the translation of 5′TOP mRNAs in a PI3K/Akt-dependent, but S6K/S6-independent manner (Stolovich *et al*., 2002). Therefore, further experiments need to be performed to identify the components responsible for control of 5′TOP mRNA translation downstream of the PI3K pathway. Importantly, the activity of S6K1 and 2 is upregulated in tumors from different histological origins (Filonenko *et al*., 2004; Sahin *et al*., 2004; Savinska *et al*., 2004; Sawhney *et al*., 2004; Surace *et al*., 2004) and, remarkably, cancer cells harboring mutations that aberrantly upregulate the PI3K/Akt pathway display a hyperactivation of S6K activity (Ruggero and Pandolfi, 2003; Stephens *et al*., 2005).

Translation initiation factors are regulated by Akt

Translation rates can be controlled during three distinct steps of translation: initiation, elongation and termination. Experimental data have highlighted the role of the initiation step as a key modulator of either general protein synthesis or for specific mRNAs (Sonenberg *et al*., 2000). This control of gene expression is in general achieved by the activity of eukaryotic initiation factors (eIFs), which function as discriminating components in controlling mRNAs translation (Gingras *et al*., 1999b). eIFs play important roles in the control of cell growth, proliferation and apoptosis (Miron *et al*., 2001; Pyronnet *et al*., 2001; Gingras *et al*., 2001b; Fingar *et al*., 2002; Avdulov *et al*., 2004; Ruggero *et al*., 2004; Richter and Sonenberg, 2005). Consistent with these findings, aberrant activity of some eIFs may contribute to the initiation and/or progression of tumorigenesis. Initiation of translation is considered to be the rate-limiting step of translation, and translation initiation rates of different mRNAs may vary dramatically (Gingras *et al*., 1999b). These differences can be explained in many instances by differential requirement for the eIF4F initiation factor complex (see below) in recruiting ribosomes to the mRNA. Remarkably, all the components of the eIF4F complex have been directly implicated in tumorigenesis (Mamane *et al*., 2004). In the most general mechanism of translation initiation, the assembly of the eIF4F complex on the mRNA 5′cap structure (m7GTP) is essential for the recruitment of the 40S small ribosomal subunit to the mRNA. eIF4F is comprised of three polypeptides; eIF4E, the protein that binds the 5′cap structure of the mRNA; eIF4A, an ATP-dependent RNA helicase thought to be required to unwind regions of secondary structure in the mRNA 5′UTR; and eIF4G, a large modular protein that interacts with eIF4E, eIF4A and other initiation factors and functions as a scaffold to form a functional bridge between the ribosome and mRNA. It is a commonly thought that specificity of translation initiation is derived mainly by modulating the activity of the eIF4F complex, and importantly all components of this complex have been found to be targets of Akt activity.

The cap-binding protein eIF4E is present in limiting amounts relative to other initiation factors (Duncan *et al*., 1987). The activity of eIF4E is regulated by phosphorylation and interaction with inhibitory proteins. These features render eIF4E a key player in regulation of translation and cell growth/proliferation. The PI3K/Akt/mTOR pathway has been the focus of many recent studies aimed at establishing the molecular mechanism by which it regulates the activity of eIF4E. eIF4E-binding proteins (4E-BPs) are a family of repressor proteins that negatively control eIF4E activity and represent one of the major direct targets of the PI3K/Akt/mTOR pathway (Gingras *et al*., 2001b). Three members of this protein family have been characterized in mammals, 4E-BP1, 4E-BP2 and 4E-BP3 (Lin *et al*., 1994; Pause *et al*., 1994; Poulin *et al*., 1998). They share approximately 60% identity, and all inhibit cap-dependent translation both *in vitro* and *in vivo*. Binding of the 4E-BPs to eIF4E prevents the interaction between eIF4E and eIF4G, because they compete with eIF4G for a shared binding site on eIF4E. Thus, 4E-BP proteins suppress cap-dependent translation by inhibiting the formation of a functional eIF4F complex (Haghighat *et al*., 1995; Mader *et al*., 1995; Marcotrigiano *et al*., 1997).

The 4E-BPs proteins are phosphorylated on several Ser and Thr residues in response to different stimuli such as hormones, cytokines and growth factors. These modifications decrease the affinity of the 4E-BPs for eIF4E: when hypophosphorylated, they bind avidly to eIF4E while hyperphosphorylation causes a decrease in binding. The best studied member of the 4E-BP family is 4E-BP1 (Gingras *et al*., 1998). Seven Ser/Thr phosphorylation sites have been identified in 4E-BP1 (Raught *et al*., 2000). Different studies have pointed to the fact that multiple phosphorylation events, in a hierarchical manner, are required for the release of 4E-BP1 from eIF4E. An mTOR kinase immunoprecipitate phosphorylates 4E-BP1 on two priming sites, Thr 37 and Thr 46, and these modifications trigger the phosphorylation of Thr 70 followed by Ser 65, which then results in the release of 4E-BP1 from eIF4E (Brunn *et al*., 1997; Burnett *et al*., 1998; Gingras *et al*., 1999a, 2001a; Mothe-Satney *et al*., 2000). Therefore, the phosphorylation status of 4E-BPs may be an important event in cell cycle progression and its deregulation may contribute to cancer (Figure 1).

As discussed in the Introduction section, the importance of mTOR kinase activity in tumorigenesis is highlighted by the fact that Akt activates mTOR, and this process is negatively regulated by the phosphatase PTEN (Stambolic *et al*., 1998). Importantly, in PTEN−/− cells, 4E-BP1 is hyperphosphorylated at the

steady-state level and this can be reverted by the mTOR inhibitor rapamycin (Neshat *et al*., 2001). The deregulation in 4E-BP1 phosphorylation may be responsible for increased cell cycle progression in tumors lacking PTEN function. In agreement with this possibility, 4E-BP1 phosphorylation controls cell growth and proliferation in human and rat cell lines (Rousseau *et al*., 1996; Fingar *et al*., 2002, 2004). Interestingly, *Drosophila* d4E-BP regulates cell growth in the wing imaginal disc (Miron *et al*., 2001). Thus, these findings highlight the relevance of eIF4E activity in cancer development. In this regard, the regulation of 4E-BP1 and eIF4E activity downstream of the Akt signal transduction pathway is perhaps the best characterized link between translational control and neoplasia.

In the early 1990s Sonenberg and colleagues implicated eIF4E in oncogenesis as its overexpression in NIH 3T3 and Rat 2 fibroblasts induced malignant transformation of these immortal cells (Lazaris-Karatzas *et al*., 1990). Moreover, eIF4E is also able to transform primary rat fibroblasts in cooperation with the immortalizing oncogenes v-Myc and E1A (Lazaris-Karatzas and Sonenberg, 1992). In addition, the same authors established an important link between the signal transduction activity of Ras and eIF4E (Lazaris-Karatzas *et al*., 1992). Overexpression of eIF4E was shown to lead to an increase in Ras activity, whereas overexpression of GAP, a negative regulator of Ras, reverts the eIF4E-induced transformed cellular phenotype (Lazaris-Karatzas *et al*., 1992). These studies opened new avenues in searching for genomic aberrations in eIF4E resulting in hyperactivity of this initiation factor in tumors. eIF4E is overexpressed in a variety of tumors and malignant cell lines including carcinomas of head and neck, lung, breast, colon, as well as in non-Hodgkin's lymphoma (Sorrells *et al*., 1998; De Benedetti and Harris, 1999; Rosenwald *et al*., 1999; Sorrells *et al*., 1999a, b, c; Wang *et al*., 1999; Rosenwald *et al*., 2001). In addition, the function of eIF4E as a *bona fide* oncogene was established through *in vivo* studies utilizing transgenic mice (Ruggero *et al*., 2004). eIF4E transgenic mice ($eIF4E^T$) develop tumors of distinct histological origins which include B-cell lymphomas, angiosarcomas, lung adenocarcinomas and hepatocellular adenomas. Notably, many of the tumor types observed in these mice are among the human cancers characterized by eIF4E overexpression (Ruggero *et al*., 2004). These mice represent the first *in vivo* evidence that delineate a role for deregulation of cap-dependent translation as a critical event in the genesis of tumors downstream of the Akt/mTOR pathway.

What is the cellular mechanism by which eIF4E exerts oncogenic activity? Data from $eIF4E^T$ mice and other studies indicate that eIF4E oncogenic activity is attributed to its ability to suppress programmed cell death (Li *et al*., 2003; Ruggero *et al*., 2004; Wendel *et al*., 2004). The importance of the antiapoptotic activity of eIF4E is emphasized by the finding that eIF4E overexpression cooperates with c-Myc in lymphomagenesis to abrogate c-Myc-induced apoptosis, resulting in an acceleration of tumor formation (Ruggero *et al*., 2004). In addition, eIF4E overexpression in primary cells induces cellular senescence. This is in agreement with the notion that eIF4E is an oncogene, and eIF4E-driven senescence is abrogated in $eIF4E^T/Myc^T$ double transgenic mice (Ruggero *et al*., 2004; Dimri, 2005). Thus, studies of $eIF4E^T/Myc^T$ double transgenic mice unraveled a new mechanism by which eIF4E and c-Myc might cooperate in tumorigenesis; eIF4E suppresses c-Myc-induced apoptosis and c-Myc antagonizes eIF4E-induced cellular senescence. Recently, another study demonstrated that control of cap-dependent translation by the Akt/mTOR pathway serves as an essential mechanism in suppressing apoptosis and maintaining the tumorigenic phenotype in human breast carcinoma cell lines (Avdulov *et al*., 2004). Overexpression of eIF4E in immortalized human mammary epithelial cells caused their transformation as judged by their ability to form foci on a monolayer of cells and grow in soft agar (Avdulov *et al*., 2004). The eIF4E oncogenic activity in these cells was inhibited by the ectopic expression of 4E-BP1 resulting in induction of apoptosis. The antiapoptotic role of eIF4E has also been proposed to be a critical component for tumor chemosensitivity (Wendel *et al*., 2004). Tumors generated by constitutive activation of Akt in c-Myc transgenic mice are resistant to apoptosis by anticancer drugs such as doxorubicin and cyclophosphamide as compared to c-Myc-derived tumors (Wendel *et al*., 2004). In contrast, rapamycin in combination with one of these cytoxic compounds reverted this phenotype, suggesting that mTOR activation contributes to the Akt antiapoptotic pathway. Importantly, when eIF4E is overexpressed together with Myc, the tumors derived from these cells are resistant to rapamycin (Wendel *et al*., 2004). Thus, eIF4E functions as a downstream target of mTOR in transducing the Akt antiapoptotic signal.

Whether eIF4E exerts its oncogenic activity solely through inhibition of apoptosis is still under investigation. Yet, a remaining gap in our knowledge concerns the identity of the cap-dependent translational targets, which are important for tumor initiation and/or progression. Several studies proposed that overexpression of eIF4E results in an increase in eIF4F complex formation concomitant with enhanced expression of proteins encoded by poorly translated mRNAs. These mRNAs contain long and highly structured G-C-rich 5′UTR, and it has been hypothesized that these mRNAs are inefficiently translated because the helicase activity of eIF4F is rate limiting due to the low amount of eIF4E in the cell (Koromilas *et al*., 1992; Sonenberg, 1993). In fact, many of these mRNAs encode for regulators of the cell cycle, growth factors and their receptors (Clemens and Bommer, 1999). Experiments designed to search for eIF4E target mRNAs identified poorly translated mRNAs whose translation is upregulated in eIF4E-overexpressing cell lines and have been associated with tumor formation. These mRNAs include ornithine decarboxylase (ODC), fibroblast growth factor (FGF-2) and vascular endothelial growth factor (VEGF) (Manzella and Blackshear, 1990; Kevil *et al*., 1995, 1996). These targets of eIF4E may explain how

overexpression of eIF4E contributes to cellular transformation. However, it remains to be determined whether these proposed targets of eIF4E are deregulated in expression during eIF4E-mediated cellular transformation, such as in the context of $eIF4E^T$ mice.

In agreement with the idea that deregulation in translational control may lead to tumorigenesis, other members of the eIF4F initiation complex are regulated by the Akt-signaling pathway. Overexpression of the scaffold protein eIF4G in rodent fibroblast cell lines leads to transformation (Fukuchi-Shimogori *et al*., 1997), and amplification of the *eIF4G* gene has been detected in squamous cell lung carcinoma (Brass *et al*., 1997; Bauer *et al*., 2002). Importantly, eIF4G is a phosphoprotein, and its phosphorylation is stimulated by insulin and other extracellular stimuli that promote cell growth and proliferation (Tuazon *et al*., 1989; Raught *et al*., 2000). Serines 1148, 1188 and 1232 are phosphorylation sites, which are dependent on the PI3K/Akt/mTOR pathway (Raught *et al*., 2000). However, the functional role of eIF4G phosphorylation has not been reported yet. Elevated levels of the eIF4A helicase are detected in human melanoma and hepatoma cells (Eberle *et al*., 1997, 2002; Shuda *et al*., 2000). Furthermore, a novel putative tumor suppressor, Pdcd4, has been characterized as an inhibitor of eIF4A activity and cap-dependent translation (Yang *et al*., 2003). Interestingly, eIF4B, an RNA-binding protein that stimulates eIF4A activity to promote the recruitment of the ribosome to the mRNA, has been shown to be phosphorylated by S6Ks, and this phosphorylation is abrogated by rapamycin (Rogers *et al*., 2002; Raught *et al*., 2004). *In vitro* data suggest that native eIF4B (which is possibly phosphorylation) is more efficient than recombinant eIF4B in promoting binding of the 40S ribosomal subunit to mRNAs containing secondary structures (Dmitriev *et al*., 2003).

Thus, Akt positively signals to the eIF4F complex and, in principle, activation of any of the eIF4F components could result in enhanced translation of a unique subset of mRNAs. Although the mRNAs that are translationally upregulated by eIF4E activity encode for proteins that are associated with tumor formation, the precise role of these attractive candidate genes in eIF4E-induced tumorigenesis remains to be corroborated *in vivo* by genetic evidence.

How does translational control translate into cancer?

Research into the signal transduction pathway downstream of Akt demonstrated that several pathways converge to regulate protein synthesis (Figure 1). This is accomplished either by regulation of translation initiation factors or direct control of rDNA transcription via Akt signaling. How this impacts on cancer initiation and progression needs to be further studied. Relatively few mouse models exist to delineate the role of translational control in normal cell physiology and when deregulated in cancer. One of the outstanding questions is the nature of the mRNAs which are affected. Such target mRNAs, which encode for factors directly implicated in cancer, are limited in number, and evidence of their translational control in primary cells or *in vivo* mouse models is lacking. Recently, it has been shown that upon activation of the Ras and Akt-signaling pathways, a sizable number ($\sim$200) of cellular mRNAs become associated with polysomes and therefore are regulated at the level of translation (Rajasekhar *et al*., 2003). Thus, the differential recruitment of groups of mRNAs to polysomes may be an immediate effect of an oncogenic insult. It remains unclear from these studies, which specific components of the translation apparatus are regulated by Akt and are directly responsible for this mechanism of gene expression.

The finding that rDNA transcription is also directly regulated by Akt signaling may argue in favor of the idea that global protein synthesis rates may be affected during cellular transformation. The idea that upregulation in translation rates may contribute to cancer formation has also been invoked in connection with other oncogenic stimuli. For example, overexpression of the c-Myc proto-oncogene results in the upregulation of numerous components of the protein synthesis apparatus, and primary cells derived from Myc transgenic mice display a twofold increase in global protein synthesis associated with an increase in cell size, and tumor formation (Ruggero and Pandolfi, 2003). The effects of Akt hyperactivation on total protein synthesis and cell size in mammalian cells remain poorly understood. Notably, it has been shown that PTEN inactivation results in increased cell size, presumably through Akt hyperactivation, in certain cell types such as the granule-cell soma of the cerebellum and cardiomyocytes (Backman *et al*., 2001; Crackower *et al*., 2002). However, it remains to be determined whether this effect is due to an increase in general protein synthesis. Drawing from the similarities in the capacity of c-Myc and Akt signaling to upregulate multiple components of the protein synthesis apparatus, it can be proposed that an increase in general protein synthesis accompanied by an increase in cell size, may represent an early event in the cellular transformation process.

To date, the most compelling evidence for a direct role of aberrant control of translation in the oncogenic process has been derived from eIF4E transgenic animals (Ruggero *et al*., 2004). These results have validated early studies (Lazaris-Karatzas *et al*., 1990) in an *in vivo* context that eIF4E can act as a *bona fide* proto-oncogene. The ability of eIF4E to exert its oncogenic activity is tightly linked to its ability to inhibit programmed cell death (Ruggero *et al*., 2004). This is also evidenced by the genetic cooperation of eIF4E and c-Myc towards lymphomagenesis. This cooperation is achieved through a cellular mechanism by which eIF4E specifically antagonizes Myc-dependent apoptosis *in vivo*, while eIF4E did not affect Myc-mediated B-cell growth and proliferation (Ruggero *et al*., 2004; Wendel *et al*., 2004). These findings are supported by the observation that constitutive activation of eIF4F complex in breast cancer is associated with resistance to

apoptosis (Avdulov *et al*., 2004). The molecular mechanism by which cap-dependent translation inhibits programmed cell death is unknown (Li *et al*., 2003, 2004). Specifically, the identification of antiapoptotic target mRNAs whose translation efficiency is sensitive to increased eIF4F formation within the context of these animal models remains to be determined. The identification of such target mRNAs should prove important for the use of chemosensitizing agents in tumors, which arise because of genetic abnormalities in the eIF4E gene locus.

The identification of multiple translational components as direct targets of Akt signaling underscore the potential importance of changes in translation as a critical role in cancer initiation or progression. In the future, a major challenge will be the identification of specific mRNAs regulated at the level of translation control directly relevant for cellular transformation. In addition it will be important to discriminate between the growing list of translational components downstream of Akt signaling in terms of their specific effects towards cancer initiation and progression. Finally, the causal link between aberrant translation control and cancer will ultimately be validated by the availability of animal models that will directly address these questions *in vivo*.

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