mRNA Translation and Energy Metabolism in Cancer: The Role of the MAPK and mTORC1 Pathways

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mRNA translation is the most energy-consuming process in the cell and strongly correlates with cellular metabolic activity. Translation and energy metabolism play important roles in homeostatic cell growth and proliferation, and when dysregulated lead to cancer. eIF4E is a key regulator of translation, which promotes oncogenesis by selectively enhancing translation of a subset of tumor-promoting mRNAs (e.g., cyclins and c-myc). PI3K/AKT and mitogen-activated protein kinase (MAPK) pathways, which are strongly implicated in cancer etiology, exert a number of their biological effects by modulating translation. The PI3K/AKT pathway regulates eIF4E function by inactivating the inhibitory 4E-BPs via mTORC1, whereas MAPKs activate MAP kinase signal-integrating kinases 1 and 2, which phosphorylate eIF4E. In addition, AMP-activated protein kinase, which is a central sensor of the cellular energy balance, impairs translation by inhibiting mTORC1. Thus, eIF4E plays a major role in mediating the effects of PI3K/AKT, MAPK, and cellular energetics on mRNA translation.

A prominent feature of cancer cells is the use of aerobic glycolysis under conditions in which oxygen levels are sufficient to support energy production in the mitochondria (Jones and Thompson 2009; Cairns et al. 2010). This phenomenon, named the “Warburg effect,” after its discoverer Otto Warburg, is thought to fuel the biosynthetic requirements of the neoplastic growth (Warburg 1956; Koppenol et al. 2011) and has recently been acknowledged as one of the hallmarks of cancer (Hanahan and Weinberg 2011).

mRNA translation is the most energy-demanding process in the cell (Buttgereit and Brand 1995). In mammalian cells it consumes ~20% of cellular ATP, not considering the energy that is required for the biosynthesis of the components of the translational machinery (e.g., ribosome biogenesis; Buttgereit and Brand 1995). Control of mRNA translation plays a pivotal role in the regulation of gene expression (Sonenberg and Hinnebusch 2009). In fact, a recent study demonstrated that mammalian proteome is mostly governed at the mRNA translation level (Schwanhaussner et al. 2011).

Malfunction of mRNA translation critically contributes to human disease, including diabetes, heart disease, blood disorders, and, most notably, cancer (Fig. 1; Crozier et al. 2006; Narla and Ebert 2010; Silvera et al. 2010; Spriggs et al. 2010). The first account of changes in the translational apparatus in cancer dates back to 1896, showing enlarged and irregularly shaped nucleoli that are the site of ribosome biogenesis (Pianese 1896). Rapidly proliferating cancer cells have more ribosomes than normal cells (Delaunay and Schapira 1974; Johnson et al. 1976; Montanaro et al. 2008; Silvera et al. 2010).

In stark contrast to normal cells, in cancer cells ribosomal biogenesis is uncoupled from cell proliferation (Stanners et al. 1979). Accordingly, cancer cells exhibit abnormally high rates of protein synthesis (Silvera et al. 2010). That ribosomal dysfunction plays a central role in cancer is further corroborated by the findings that genetic alterations, which encompass the components of the ribosome machinery (i.e., “ribosomopathies”), are characterized by elevated cancer risk (Narla and Ebert 2010).

INITIATION, A KEY REGULATORY STEP OF TRANSLATION

mRNA translation proceeds in three steps: initiation, elongation, and termination (Mathews et al. 2007). Each of the steps consists of a series of highly orchestrated interactions between the mRNA and several factors, including ribosomes, aminoacyl-transfer RNAs (tRNAs), and auxiliary proteins collectively referred to as the translational factors (Mathews et al. 2007). Although all steps of mRNA translation are highly regulated, most of the translational control occurs at the rate-limiting initiation step (Sonenberg and Hinnebusch 2009; Jackson et al. 2010).

The vast majority of eukaryotic mRNAs are translated in a cap-dependent manner (Sonenberg and Hinnebusch 2009; Jackson et al. 2010). The eIF4F complex binds to the cap structure, which is present at the 5′-end of all nuclear-encoded eukaryotic mRNAs (Topisirovic et al. 2011). This complex consists of the cap-binding protein eukaryotic translation initiation factor (eIF) 4E (eIF4E),

Figure 1. Dysregulated mRNA translation plays a pivotal role in cancer. Malignant cells are characterized by enlarged nucleoli and a larger number of ribosomes than their normal counterparts. Mutations and/or altered expression of ribosomal proteins (e.g., RPS19, RPS 24), rRNA-modifying enzymes (e.g., dyskerin), translation initiation factors (e.g., eIF4E), or the initiator tRNA (tRNA^{Met}) result in malignant transformation. Signaling pathways whose dysfunction is frequent in cancer (e.g., MAPK, PI3K/AKT) affect mRNA translation. Perturbations in the translome result in aberrant cellular growth, proliferation, and survival characteristic of tumorigenesis.

the RNA helicase eIF4A and the scaffolding protein eIF4G (Gingras et al. 1999b; Sonenberg and Hinnebusch 2009; Jackson et al. 2010). The role of eIF4E in translation initiation, as well as the mode of its binding to the 5' mRNA-cap structure, are conserved from yeast to human (Altmann et al. 1985; Marcotrigiano et al. 1997; Matsuo et al. 1997). eIF4G interacts directly with eIF4E, eIF3, the poly(A)-binding protein (PABP), and eIF4A (Sonenberg and Hinnebusch 2009; Jackson et al. 2010). eIF3 is a multicomponent factor that facilitates the recruitment of the 40S ribosomal subunit (Sonenberg and Hinnebusch 2009; Jackson et al. 2010). eIF4A unwinds the secondary structure present in the 5' untranslated region (UTR) of mRNA (Sonenberg and Hinnebusch 2009; Jackson et al. 2010), whereas the interaction of eIF4G and PABP leads to the circularization of the mRNA, which facilitates the recycling of the ribosomes on the mRNA, to stimulate translation (Kahvejian et al. 2005).

eIF4E: A PROTO-ONCOGENIC PROTEIN THAT SELECTIVELY STIMULATES THE TRANSLATION OF mRNAs ENCODING TUMOR-PROMOTING FACTORS

Alterations in the expression and/or function of a number of eIFs or tRNA^{Met} have been linked to tumorigenesis (Fig. 1; Marshall et al. 2008; Silvera et al. 2010). Amongst eIFs, the role of eIF4E in cancer is

perhaps the best established (De Benedetti and Graff 2004; Graff et al. 2008). Its overexpression results in neoplastic transformation of rodent and human immortalized cells (Lazaris-Karatzas et al. 1990; Avdulov et al. 2004) and is tumorigenic in vivo (Ruggero et al. 2004; Wendel et al. 2007). Expression of eIF4E is elevated in a large number of malignancies including cancers of breast, colon, prostate, head, and neck, lymphomas, and leukemias (De Benedetti and Graff 2004; Graff et al. 2008).

eIF4E is the most limiting among eIFs (Sonenberg and Hinnebusch 2009). Thus, its availability critically determines translation initiation rates (Sonenberg and Hinnebusch 2009). Notwithstanding that eIF4E acts as a general translation initiation factor, its overexpression does not strongly promote global protein synthesis but rather selectively stimulates translation of a subset of mRNAs referred to as “eIF4E-sensitive” (Koromilas et al. 1992; Graff et al. 2008). In general, these mRNAs contain long, highly structured 5'UTRs and are thus expected to be highly dependent on the unwinding activity of the eIF4A subunit of eIF4F for efficient translation (Sonenberg and Hinnebusch 2009; Parsyan et al. 2011). “eIF4E-sensitive” mRNAs encode proliferation and survival promoting factors and proto-oncogenic proteins, such as cyclins, c-myc, and Bcl_{xL} (De Benedetti and Graff 2004; Graff et al. 2008). Translation of mRNAs bearing short, unstructured 5'UTRs (e.g., tubulins, actins) is less dependent on the unwinding activity of eIF4A, and these mRNAs are only marginally sensitive to alterations in eIF4E levels (De Benedetti and Graff 2004; Graff et al.

2008). Thus, the proto-oncogenic activity of eIF4E stems from its ability to selectively stimulate translation of mRNAs, which encode tumor-promoting factors.

REGULATION OF eIF4E ACTIVITY AND CANCER

Hyperactivation of eIF4E in cancer is a consequence of up-regulation of its expression and/or alterations in the signaling pathways that activate it (De Benedetti and Graff 2004; Graff et al. 2008; Sonenberg and Hinnebusch 2009; Silvera et al. 2010). Expression of eIF4E is controlled by a variety of mechanisms including transcriptional regulation by c-myc (Jones et al. 1996) and modulation of mRNA stability by HuR and AUF1 (Fig. 2; Topisirovic et al. 2009b). eIF4E is a major downstream effector of the mitogen-activated protein kinase (MAPK) and the phosphoinositide-3-kinase (PI3K)/AKT/mechanistic/mammalian target of rapamycin (mTOR) pathways, which are frequently dysregulated in cancer (Fig. 2; Dhillon et al. 2007; Guertin and Sabatini 2007; Cargnello and Roux 2011; Zoncu et al. 2011).

MNKs AND eIF4E: DOWNSTREAM OF MAPKs

In mammals, eIF4E is phosphorylated at Ser209 by the MAPK signal-integrating kinases 1 and 2 (MNK1 and MNK2; Fukunaga and Hunter 1997; Waskiewicz et al. 1997). Whereas MNK2 is constitutively active, MNK1 is activated by stimuli such as phorbol-esters and growth factors or by cytokines and stress via an extracellular signal-regulated kinase (Erk) and p38 mitogen activated-protein kinase (MAPK), respectively (Wang et al. 1998; Scheper et al. 2001). Genetic studies in *Drosophila* revealed that the loss of eIF4E phosphorylation results in developmental defects and smaller flies (Lachance

et al. 2002). However, *Mnk1/2*^{-/-} mice develop normally and do not exhibit any gross phenotypic changes (Ueda et al. 2004).

eIF4G directly binds MNKs (Pyrnnet et al. 1999). Therefore, the phosphorylation of eIF4E by MNKs takes place after the assembly of the eIF4F complex, and is thus positioned to have a major effect on translation initiation (Pyrnnet et al. 1999). Nevertheless, how eIF4E phosphorylation influences cap-dependent translation is unclear. Depending on the experimental conditions, eIF4E phosphorylation has been reported to correlate with increased (Kaspar et al. 1990; Manzella et al. 1991; Walsh and Mohr 2004; Worch et al. 2004) or decreased global mRNA translation (Knauf et al. 2001; Morley and Naegele 2002; Naegele and Morley 2004). Phospho-eIF4E may also selectively stimulate translation of a subset of mRNAs, including Mcl-1 (Wendel et al. 2007).

Nonphosphorylatable mutant of eIF4E exhibits markedly impaired oncogenic potential as compared with wild-type eIF4E (Topisirovic et al. 2004; Wendel et al. 2007). To further establish the role of the phosphorylation of eIF4E in tumorigenesis, knockin mice expressing a nonphosphorylatable form of eIF4E were engineered (Furic et al. 2010). Similar to *Mnk1/2*^{-/-} animals, the eIF4E knockin mice do not exhibit any conspicuous phenotype (Furic et al. 2010). Nonetheless, embryonic fibroblasts isolated from these mice show lesser transformation capacity by oncogenes, such as Ras, in combination with c-myc (Furic et al. 2010). Crossing eIF4E knockin mice with animals in which the tumor suppressor phosphatase and tensin homolog (*Pten*) gene was selectively ablated in the prostate attenuated the early onset of high-grade prostate intraepithelial neoplasia and development of invasive carcinoma (Furic et al. 2010). Taken together, these results demonstrate that the phosphorylation of eIF4E is required for tumorigenesis caused by the loss of PTEN function. These observations are further corroborated by a study showing that the loss of MNK1/2 expression attenuates neoplastic growth in the loss-of-PTEN background (Ueda et al. 2010).

Phospho-eIF4E levels are highly elevated in human prostate cancers where they positively correlate with high Gleason scores, which are indicative of aggressive disease progression (Furic et al. 2010). A subset of mRNAs is differentially translated as a function of the phosphorylation status of eIF4E, including mRNAs encoding proteins important for tumor progression, such as inflammatory molecules Ccl2 and Ccl17 and the matrix metalloproteases, MMP3 and MMP9 (Furic et al. 2010). Thus, eIF4E phosphorylation appears to stimulate tumor inflammation and invasion by selectively affecting translation of mRNA that encodes proteins critical for these processes.

Figure 2. eIF4E is regulated by multiple mechanisms. The expression of eIF4E is regulated by several transcription factors (e.g., c-myc, hnRNP K, p53) and adenine-uracil-rich element binding proteins (i.e., HuR and AUF1). eIF4E is suppressed by 4E-BPs, which are regulated by mTORC1. MAP kinase signal-integrating kinases 1 and 2 (MNKs) phosphorylate eIF4E.

DOWNSTREAM FROM mTORC1: 4E-BPs GOVERN THE ACTIVITY OF eIF4E

The activity of eIF4E is also controlled by the 4E-binding proteins (4E-BPs; Pause et al. 1994; Sonenberg

and Hinnebusch 2009). In mammals, the 4E-BP family of proteins consists of 4E-BP1, 4E-BP2, and 4E-BP3 (Sonenberg and Hinnebusch 2009). 4E-BPs bind to the same site on eIF4E as eIF4G (Mader et al. 1995; Matsuo et al. 1997), thus preventing association of eIF4E with eIF4G and the eIF4F complex assembly. This reduces cap-dependent translation initiation (Pause et al. 1994).

mTOR phosphorylates 4E-BPs, causing their dissociation from eIF4E (Ma and Blenis 2009; Dowling et al. 2010b; Zoncu et al. 2011). mTOR is present in two distinct complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2; Martin and Hall 2005; Dowling et al. 2010b; Zoncu et al. 2011). mTORC1 phosphorylates substrates such as 4E-BPs, ribosomal protein S6 kinases 1 and 2 (S6Ks), proline-rich Akt substrate of 40 kDa (PRAS40) and serine/threonine kinase Ulk1 to regulate a variety of cellular processes including translation, proliferation, growth, metabolism and autophagy (Zoncu et al. 2011). mTORC2 phosphorylates members of the AGC kinase family (e.g., AKT, SGK1 and PKC) and controls cell survival and cytoskeletal organization (Sarbasov et al. 2004, 2005; Guertin and Sabatini 2007; Garcia-Martinez and Alessi 2008).

mTORC1 is activated by a multitude of extracellular stimuli and intracellular cues such as hormones, growth factors, and nutrients via various signaling pathways including the PI3K/AKT pathway and Ras-related small GTP-binding proteins (Rag-GTPases; Fig. 3; Sengupta et al. 2010; Zoncu et al. 2011). mTORC1 is a major regulator of translation (Ma and Blenis 2009). Activation of mTORC1 leads to initial phosphorylation of 4E-BPs on amino acids corresponding to Thr 37 and 46 in human 4E-BP1 (Brunn et al. 1997; Hara et al. 1997; Gingras et al. 1999a, 2001), which act as priming sites for the phosphorylation of residues corresponding to Thr 70 and Ser 65, leading to its dissociation from eIF4E (Gingras et al. 1999a, 2001). Importantly, the loss of 4E-BP1 and 2, or the expression of a nonphosphorylatable mutant of 4E-BP1, which constitutively binds to eIF4E, only marginally affects global translation levels (Lynch et al. 2004; Colina et al. 2008). This is consistent with the findings that eIF4E affects translation of only a subset of "eIF4E-sensitive" mRNAs (Graff and Zimmer 2003; De Benedetti and Graff 2004; Graff et al. 2008; Sonenberg and Hinnebusch 2009). Indeed, selected mRNAs (e.g., IRF-7, Gas2, cyclin D3, ODC, and VEGF) are translated more efficiently in the absence of 4E-BPs (Colina et al. 2008; Petroulakis et al. 2009; Dowling et al. 2010a).

In addition to 4E-BPs, mTORC1 modulates translation by activating S6K1 and 2 (Hay and Sonenberg 2004; Ma and Blenis 2009; Dowling et al. 2010b; Zoncu et al. 2011). Notwithstanding the expanding catalog of the targets of S6Ks, which are implicated in translational control such as ribosomal protein S6 (rpS6; Banerjee et al. 1990; Kozma et al. 1990), eukaryotic initiation factor 4B (eIF4B; Shahbazian et al. 2006), and programmed cell death 4 protein (PDCD4; Dorrello et al. 2006), it is not precisely known how S6Ks impact translation. Global translation is only marginally affected by the loss of S6K

expression and modestly increased in mouse embryonic fibroblasts expressing the nonphosphorylatable mutant of rpS6 as compared to wild-type cells (Pende et al. 2004; Ruvinsky et al. 2005). It was suggested that S6Ks control translation of the 5' terminal oligopyrimidine tract (5'TOP) containing mRNAs, which encode components of the translational machinery (Kawasome et al. 1998; Shima et al. 1998; Loreni et al. 2000). However, neither S6K expression nor the phosphorylation status of ribosomal protein S6 influences translation of 5'TOP mRNAs (Tang et al. 2001; Pende et al. 2004; Ruvinsky et al. 2005). Thus, the role of S6Ks in the regulation of mRNA translation is still moot.

mTORC1 was also suggested to promote translational initiation via the phosphorylation of eIF4G (Raught et al. 2000) and elongation by indirectly inhibiting the eukaryotic translation elongation factor 2 kinase (eEF2-kinase; Redpath et al. 1996). It also stimulates rRNA and tRNA synthesis by activating TIF-IA and inhibiting the repressor of RNA polymerase III transcription MAF1 homolog, respectively (Mayer et al. 2004; Kantiakakis et al. 2010; Shor et al. 2010).

mTORC1, 4E-BPs, AND REGULATION OF CELL GROWTH AND PROLIFERATION

The control of cell proliferation (increase in cell number) and growth (increase in cell volume) is intimately linked inasmuch as cell cycle progression is tightly coordinated with the increase in cell size (Hartwell et al. 1974; Nurse et al. 1976; Zetterberg et al. 1995; Jorgensen and Tyers 2004). In yeast, the G₁ cell cycle checkpoint START restricts the cell from entering the S phase if the availability of growth factors and nutrients is insufficient (Hartwell et al. 1974; Nurse et al. 1976). The START checkpoint prevents cells proceeding through the cell cycle if they do not reach a certain size (Hartwell et al. 1974; Nurse et al. 1976). Thus, in yeast, cell size acts as a sensor for nutrient availability to ensure that cells enter the mitotic cycle only when nutrient availability is optimal (Hartwell et al. 1974; Nurse et al. 1976). In higher eukaryotes, cells must overcome similar, but multiple, growth-factor- and nutrient-dependent cell size restriction points to progress from the G₁ phase into the S phase of the cell cycle (Zetterberg et al. 1995). Importantly, progression through the G₁ restriction point requires increased protein synthesis, as even moderate inhibition of mRNA translation causes exit from the G₁ phase of the cell cycle into a state of quiescence (G₀; Zetterberg et al. 1995).

The TOR pathway plays an evolutionarily conserved role in coordinating cell growth and cell proliferation (Wullschleger et al. 2006). In yeast, TOR1 promotes cell growth and thus impinges on cell cycle progression through the START checkpoint (Heitman et al. 1991; Martin and Hall 2005; De Virgilio and Loewith 2006). In *Drosophila*, dTOR regulates cell growth and proliferation by modulating the activity of dS6K and d4E-BPs, whereby each protein regulates both growth and

Figure 3. Ras/MAPK and PI3K/AKT/mTORC1 regulate the activity of eIF4E. Various stimuli activate phosphoinositide-3-kinase (PI3K) through the receptor tyrosine kinases (RTKs). Upon activation, PI3K converts phosphatidylinositol 4,5-bisphosphate (PIP2) into phosphatidylinositol-3,4,5-triphosphate (PIP3). This reaction is reversed by PTEN. Phosphoinositide-dependent protein kinase 1 (PDK1) and AKT bind to PIP3 via their pleckstrin homology domains, which allows for the phosphorylation and activation of AKT by PDK1. In addition, the mammalian target of rapamycin complex 2 (mTORC2) modulates the activity of AKT by phosphorylating its hydrophobic motif. AKT phosphorylates tuberous sclerosis complex 2 (TSC2) at multiple sites, which results in its inhibition and consequent activation of Ras homolog enriched in brain (Rheb), which is a small GTPase that activates mTORC1. mTORC1 phosphorylates 4E-BPs leading to their dissociation from eIF4E. In addition to the PI3K/AKT pathway, the activity of mTORC1 is regulated by the serine/threonine kinase 11/LKB1/AMP-kinase (LKB1/AMPK) pathway, regulated in development and DNA damage response 1 (REDD1) and Rag GTPases in response to the changes in cellular energy balance, oxygen and amino acid availability, respectively. Ras and the MAPK pathways are activated by various stimuli through receptor tyrosine kinases (RTKs). In addition the MAPK pathway is activated through the G protein–coupled receptors (GPCRs) and by protein kinase C (PKC; not shown). The MAPK pathways encompass an initial GTPase-regulated kinase (MAPKKK), which activates an effector kinase (MAPK) via an intermediate kinase (MAPKK). In response to stimuli such as growth factors, hormones, and phorbol-esters, Ras GTPase stimulates Raf kinase (MAPKKK), which activates extracellular signal-regulated kinases 1 and 2 (ERK 1 and 2) via extracellular signal-regulated kinase activator kinases MEK1 and 2 (MAPKK). Cellular stresses, including osmotic shock, inflammatory cytokines, and UV light, activate p38 MAPKs via multiple mechanisms including Rac kinase (MAPKKK) and MKK3 and 6 (MAPKK). p38 MAPK and ERK activate the MAPK signal–integrating kinases 1 and 2 (MNK1/2), which phosphorylate eIF4E. Additional abbreviations are provided in the text.

proliferation (Montagne et al. 1999; Miron et al. 2001). In contrast to insects, the loss of 4E-BP expression in mammalian cells has little impact on the reduction in cell size caused by mTOR inhibition (Dowling et al. 2010a). Conversely, mouse embryonic fibroblasts that do not express 4E-BPs proliferate faster than wild-type cells under conditions in which mTOR signaling is inhibited (Dowling et al. 2010a). Thus, the loss of 4E-BPs appears to alleviate the mTORC1-dependent cell size restriction point in G₁ phase, inasmuch as mouse embryonic fibroblasts lacking 4E-BPs can efficiently enter the S phase of the cell cycle even under conditions when the cell growth is attenuated owing to the inhibition of mTORC1 signaling (Dowling et al. 2010a). In stark contrast to wild-type

cells, suppression of mTORC1 in cells lacking 4E-BPs does not lead to translational down-regulation of cell-cycle-promoting factors (e.g., cyclin D3 and ODC; Dowling et al. 2010a). Thus, 4E-BPs execute the effects of mTORC1 on cell proliferation by selectively regulating translation of mRNAs that are necessary for cell cycle progression (Fig. 4).

Factors that control the cell-size dependent G₁ restriction point and accelerate entry into the S phase of cell cycle, such as c-myc and D-type cyclins, are encoded by eIF4E-sensitive mRNAs (De Benedetti et al. 1994; Rosenwald et al. 1995; Rousseau et al. 1996; Graff and Zimmer 2003; Dowling et al. 2010a). Overexpression of c-myc results in the uncoupling of cell division from

Figure 4. In mammals, 4E-BPs regulate cell cycle progression and proliferation, but not cell growth downstream of mTORC1. (Upper panels) Under optimal nutrient conditions, mTORC1 phosphorylates and inactivates 4E-BPs, which leads to the increase in translation of “eIF4E-sensitive” mRNAs encoding proteins required for the S phase entry and cell cycle progression. Under these conditions cells lacking 4E-BPs ($4e-bp^{-/-}$; t_1) and wild-type cells (WT; t_2) progress from the G₁ to S phase of the cell cycle at the same rate ($t_1 = t_2$). (Lower panels) Inhibition of mTORC1 signaling decreases the phosphorylation of 4E-BPs and translational activity of “eIF4E-sensitive” mRNAs. This results in the prolonged G₁ phase (t_3). Although the effect of mTORC1 inhibition on the reduction of cell size in $4e-bp^{-/-}$ and wild-type cells is comparable, under these conditions $4e-bp^{-/-}$ cells maintain efficient translation of eIF4E-sensitive mRNAs which enables them to enter into the S phase of the cell cycle (t_4).

cell size, which is a consequence of the accelerated entry into the S phase of cell cycle (Kuystermans and Al-Rubeai 2009). Similarly, loss of N-myc expression in the mouse developing eye decreases proliferation, but not retinal cell size (Martins et al. 2008). Forced expression of D-type cyclins accelerates progression through the G₁ phase in mouse and rat fibroblasts and renders their proliferation resistant to serum deprivation (Quelle et al. 1993). Collectively, these data suggest that the uncoupling of cell size and cell proliferation is a consequence of dysregulated translation of “eIF4E-sensitive” mRNAs (Fig. 4).

Whereas S6Ks may play a role in regulation of cell proliferation in hepatocytes (Espeillac et al. 2011), in other cell types, including myoblasts and fibroblasts, S6Ks

mediate the effects of mTORC1 on cell size, but not proliferation (Pende et al. 2004; Ohanna et al. 2005; Dowling et al. 2010a). The observed “division of labor” between 4E-BPs and S6Ks suggests that cell size and cell cycle control in most mammalian cell types can be uncoupled downstream of mTORC1, which is in sharp contrast to insects, in which 4E-BPs and S6Ks impact both cell proliferation and growth equally. Consistently, it has been reported that cell proliferation is largely independent of cell growth in mammalian Schwann cells, but not yeast (Conlon et al. 2001; Conlon and Raff 2003). In addition, proliferation and cell cycle progression in human lymphoblasts are independently modulated by cell size and age (i.e., time after division), whereby the probability of division for cells of the same size increases with age (Tzur et al. 2009). These results strongly suggest that mammals coordinate cell growth with cell proliferation via mechanisms that are distinct from those of evolutionarily lower organisms.

mTORC1, 4E-BPs, ABERRANT CELL PROLIFERATION, AND TUMORIGENESIS

Aberrant proliferation is a hallmark of cancer (Hanahan and Weinberg 2000; Hanahan and Weinberg 2011). Thus, it is not surprising that mTOR signaling is frequently deregulated in malignancies (Mamane et al. 2006; Guertin and Sabatini 2007). This can typically result from the inactivation of tumor suppressors such as LKB1 and PTEN, which antagonize PI3K-dependent activation of mTOR, or activating mutations in PI3K subunits (Inoki et al. 2003; Shaw et al. 2004a; Feng et al. 2005; Sabatini 2006). 4E-BPs are major downstream effectors of mTORC1 on cell proliferation (Dowling et al. 2010a). Studies using mTOR inhibitors provide evidence that 4E-BPs act as crucial mediators of oncogenic mTORC1 signaling. Rapamycin, a naturally occurring macrolide antibiotic and its analogs (rapalogs) function as allosteric inhibitors of mTORC1, but they do not inhibit mTORC2 in most cell types (Guertin and Sabatini 2009). Whereas rapalogs are used for the treatment of malignancies, such as advanced renal cell carcinoma, their overall success as cancer monotherapies has so far been disappointing (Guertin and Sabatini 2009). This has been attributed in part to the compensatory up-regulation of PI3K/AKT signaling owing to the inhibition of the activity of S6Ks by rapamycin (Manning 2004; Easton et al. 2006). ATP-competitive mTOR inhibitors [asTORi; e.g., PP242 (Feldman et al. 2009), Torin 1 (Thoreen et al. 2009) and Ku-0063794 (Garcia-Martinez et al. 2009)], which target its catalytic site, were recently developed to overcome this problem. Unlike rapamycin, asTORi inhibit AKT signaling via down-regulation of mTORC2 signaling. These compounds also exhibit stronger antiproliferative effects than rapamycin (Feldman et al. 2009; Thoreen et al. 2009). Unexpectedly, the effects of asTORi on proliferation do not appear to be a consequence of the inhibition of AKT signaling, as they are mTORC2 independent

(Feldman et al. 2009; Thoreen et al. 2009). Instead, asTORi decrease the phosphorylation of 4E-BPs much more potently than rapamycin, whereas their effects on S6Ks and their substrates are comparable (Feldman et al. 2009; Garcia-Martinez et al. 2009; Thoreen et al. 2009; Dowling et al. 2010a). These findings suggest that the superb antiproliferative effects of asTORi are caused by inhibition of rapamycin-resistant mTORC1 outputs toward 4E-BPs (Feldman et al. 2009; Thoreen et al. 2009). Accordingly, cells lacking 4E-BPs are resistant to the antiproliferative and antineoplastic effects of asTORi (Dowling et al. 2010a).

4E-BPs are down-regulated and/or hyperphosphorylated (i.e., inactivated due to the constitutively activated mTORC1 signaling) in breast, ovarian, and several other cancers (Castellvi et al. 2006; Petricoin et al. 2007; Rojo et al. 2007). Ectopic expression of a nonphosphorylatable, constitutively active mutant of 4E-BP1 suppresses the tumorigenicity of human breast carcinoma cells and c-myc-transformed rodent fibroblasts (Avdulov et al. 2004; Lynch et al. 2004). Recent data further corroborate the tenet that 4E-BPs act as tumor suppressors. Loss of 4E-BP expression in fibroblasts leads to premature senescence (Petroulakis et al. 2009), which mirrors the phenotype observed in cells lacking tumor suppressors such as PTEN (Chen et al. 2005). Similarly to cells lacking functional PTEN, the underlying mechanism of premature senescence in the *4e-bp*^{-/-} background appears to be p53 dependent (Chen et al. 2005; Petroulakis et al. 2009). p53 protein levels are elevated in *4e-bp1/2*^{-/-} cells, which is a consequence of increased translation of growth-arrest-specific 2 (Gas2) mRNA and subsequent increase in Gas2 protein (Petroulakis et al. 2009). Gas2 suppresses the degradation of p53 protein by inhibiting calpain protease activity (Benetti et al. 2001). In turn, the loss of 4E-BPs accelerates tumorigenesis in *p53*^{-/-} mice (Petroulakis et al. 2009). These results are further corroborated by the findings in which an AKT-driven lymphoma mouse model was deployed. In these experiments, expression of a constitutively active, nonphosphorylatable mutant of 4E-BP1 in *AktT* transgenic mice led to a dramatic decrease in lymphoma development (Hsieh et al. 2010). Notably, expression of a nonphosphorylatable mutant of rpS6, which is a major downstream target of S6Ks, in *AktT* transgenic animals failed to attenuate lymphomagenesis (Hsieh et al. 2010). These results suggest that, by suppressing eIF4E function, 4E-BPs act as major inhibitors of oncogenic Akt signaling (Hsieh et al. 2010). Indeed, the ability of a constitutively active, nonphosphorylatable 4E-BP1 mutant to suppress lymphomagenesis downstream of AKT appears to be a result of the inhibition of translation of “eIF4E-sensitive” Mcl-1 mRNA (Hsieh et al. 2010). These findings are compatible with previous studies, revealing that oncogenic AKT signaling induces perturbations in mRNA translation and that elevated activity of eIF4E plays a major role in AKT-driven tumorigenesis (Rajasekhar et al. 2003; Wendel et al. 2004). Collectively, these studies strongly suggest that 4E-BPs act as bona fide tumor suppressors.

eIF4E IS A CENTRAL NODE THAT LINKS MAPK AND PI3K/AKT SIGNALING

The MAPK and PI3K/AKT pathways stimulate the activity of eIF4E via its phosphorylation and inactivation of 4E-BPs, respectively (Fig. 3). The phosphorylation of eIF4E requires the association of MNKs with eIF4G bound to eIF4E (Pyrone et al. 1999). Down-regulation of PI3K/AKT signaling leads to increased binding of 4E-BPs to eIF4E and its dissociation from eIF4G (Pause et al. 1994). This raises the possibility that the PI3K/AKT pathway may modulate MAPK-dependent phosphorylation of eIF4E indirectly by impairing the recruitment of MNKs to eIF4E via eIF4G. Surprisingly, it has been shown that rapamycin induces phosphorylation of eIF4E (Wang et al. 2007). This apparent discrepancy can be explained by the inability of rapamycin to completely and sustainably inhibit the phosphorylation of 4E-BPs (Choo et al. 2008), which is further exacerbated by the stimulatory effect of rapamycin on MAPK signaling (Carracedo et al. 2008). Consistently, asTORi diminish the phosphorylation of 4E-BPs and dramatically reduce the levels of phosphorylated eIF4E (Furic et al. 2010).

In cancer cells in which both MAPK and PI3K/AKT pathways are activated, inhibitors of each pathway alone fail as antiproliferative and proapoptotic agents, whereas a combination thereof strongly suppresses proliferation and induces apoptosis (Shaw and Cantley 2006). Oncogenic MAPK and AKT signals converge on 4E-BP1 (She et al. 2010). Accordingly, combined inhibition of MAPK and PI3K/AKT completely and sustainably inhibits the phosphorylation of 4E-BPs, which is paralleled by tumor growth reduction (She et al. 2010). These data indicate that the MAPK and PI3K/AKT pathways converge on eIF4E via multiple mechanisms and raise the intriguing possibility that both pathways exert their oncogenic effects at least in part by modulating translation of “eIF4E-sensitive” mRNAs.

ENERGY METABOLISM AND mRNA TRANSLATION IN CANCER

Increased cell growth and proliferation correlate with the elevated mRNA translation (Johnson et al. 1976). Thus, rapidly growing and proliferating cells need to accommodate the high-energy demand of mRNA translation (Buttgereit and Brand 1995). The AMP-activated protein kinase (AMPK) acts as an evolutionarily conserved sensor of the energy status of the cell (Kahn et al. 2005; Shaw 2009). AMPK is activated via upstream kinases such as serine/threonine kinase 11 (STK11/LKB1; Hawley et al. 2003; Woods et al. 2003; Lizcano et al. 2004; Shaw et al. 2004b; Suter et al. 2006) when nutrient or oxygen resources are limited, leading to increase in cellular AMP levels (Kahn et al. 2005; Shaw 2009). AMPK inhibits anabolic processes and impairs cell growth and proliferation (Kahn et al. 2005; Shaw 2009). In this way, AMPK acts as a central node to coordinate intracellular energy status with growth and proliferation (Kahn et al. 2005;

Shaw 2009). This is in part achieved via mTORC1, which is one of the major downstream targets of the LKB1/AMPK pathway (Shaw et al. 2004a). Importantly, down-regulation of mTORC1 signaling is required for efficient cell cycle arrest and inhibition of proliferation following AMPK activation (Gwinn et al. 2008), which is paralleled by a decrease in mRNA translation (Dowling et al. 2007). Thus, the AMPK/mTOR pathway links energy metabolism with translational control and cell growth and proliferation.

In cancer cells, AMPK activity is frequently compromised, resulting in aberrant growth and proliferation (Wang and Guan 2009). This is in most circumstances a consequence of inactivating mutations in the *LKB1* gene (Wang and Guan 2009). The *LKB1* gene is mutated in Peutz–Jeghers syndrome (PJS) patients (Hemminki et al. 1998). This disorder is characterized by benign polyps in the gastrointestinal tract and increased predisposition to development of malignant tumors in a variety of tissues (Hearle et al. 2006). PJS, Cowden disease, and tuberous sclerosis patients share a large number of clinical features. Cowden disease and tuberous sclerosis are characterized by the hyperactivation of mTORC1 owing to the mutations in PTEN or tuberous sclerosis complex 1/2, respectively (Short et al. 1995; Liaw et al. 1997; Stambolic et al. 1998). Somatic *LKB1* mutations are frequently detected in non-small-cell lung cancer patients (Sanchez-Cespedes et al. 2002; Ji et al. 2007). mTORC1 signaling is hyperactivated in lung cancer cell lines in which the function of LKB1 is abrogated (Carretero et al. 2007). These data suggest that hyperactivation of mTORC1 contributes to LKB1-dependent tumorigenesis.

CONCLUDING REMARKS

The large body of data summarized here demonstrates that dysregulation of mRNA translational plays a paramount role in tumorigenesis and tumor progression. However, several important issues remain to be addressed. For instance, it is important to discern whether the mutations in ribosomal proteins characteristic of ribosomopathies affect their ribosomal or “extraribosomal” functions (i.e., cellular activities of ribosomal proteins that are not associated with their role in the ribosome; Wool 1996; Warner and McIntosh 2009). In response to DNA damage, ribosomal protein L26 (RPL26) promotes translation of p53 mRNA by directly binding to its 5'UTR (Takagi et al. 2005). As RPL26 associates with the p53 mRNA in the nucleus, its role in regulating the expression of p53 is illustrative of its extraribosomal function (Chen and Kastan 2010). In addition to ribosomal proteins, eukaryotic translation factors have been suggested to have a role outside of mRNA translation. For instance, eIF4E appears to regulate the nucleocytoplasmic export of a subset of mRNAs (e.g., cyclin D1), which harbor a specific 4E-sensitivity element in their 3'UTR (Rousseau et al. 1996; Culjkovic et al. 2005; Topisirovic et al. 2009a).

Figure 5. Potential link between malignant translomes and metabolomes. Activation of oncogenes (e.g., c-myc) and/or aberrant activity of the signaling pathways (e.g., mTORC1, AMPK) lead to alterations in mRNA translation and metabolic activity in the cell. Given that mRNA translation is the most energy-consuming process in the cell, it is plausible that the translome of malignant cells is affected by perturbations in energy metabolism, inasmuch as the malignant cells need to accommodate the elevated activity of the translational apparatus to the alterations in the energy balance. In turn, changes in translational activity of mRNAs encoding proteins implicated in the regulation of cellular metabolism may critically contribute to the Warburg effect observed in cancer cells. Future research is necessary to establish whether changes in cell metabolism influence mRNA translation and, vice versa, whether aberrant mRNA translation impacts the metabolome of malignant cells.

It is thought that cancers are frequently “addicted” to a high-energy supply (Cairns et al. 2010) and elevated protein synthesis (Silvera et al. 2010). Nonetheless, it is still not clear whether changes in cellular energetics in cancer cells affect mRNA translation and, vice versa, whether the perturbations in mRNA translation in cancer contribute to the changes in gene expression necessary for the Warburg effect (Fig. 5). A better understanding of the link between the dysregulation of mRNA translation and energy metabolism in cancer is necessary to devise better and more personalized therapeutic regimens in the future. Consistent with this hypothesis, metformin, a biguanide antidiabetic drug that has been shown to be associated with decreased incidence of cancer in diabetic patients (Larsson et al. 2005, 2007), affects energy metabolism and mRNA translation by modulating the activity of AMPK and mTORC1 via multiple mechanisms (Zakikhani et al. 2006; Dowling et al. 2007; Kalender et al. 2010; Ben Sahra et al. 2011).

Pianese (1896) observed irregularly shaped and enlarged nucleoli in malignant cells. Following this finding, a bevy of studies established a role for aberrant mRNA translation in neoplastic transformation and tumor progression. Thus, dysregulated mRNA translation represents a longstanding “hallmark of cancer” that remains to be recognized.

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