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Review

Cancer Research

Translation Regulation as a Therapeutic Target in Cancer

Michal Grzmil and Brian A. Hemmings

Abstract

Protein synthesis is a vital cellular process that regulates growth and metabolism. It is controlled via signaling networks in response to environmental changes, including the presence of nutrients, mitogens, or starvation. The phosphorylation state of proteins involved in translation initiation is a limiting factor that regulates the formation or activity of translational complexes. In cancer cells, hyperactivated signaling pathways influence translation, allowing uncontrolled growth and survival. In addition, several components of translation initiation have been found to be mutated, posttranslationally modified, or differentially expressed, and some act as oncogenes in cancer cells. Translational alterations can increase the overall rate of protein synthesis as well as activate regulatory mechanisms leading to the translation of specific messenger RNAs for proteins that promote cancer progression and survival. Many recent studies investigating such mechanisms have produced ideas for therapeutic intervention. This review describes altered mechanisms of protein synthesis in human cancers and discusses therapeutic approaches based on the targeting of translation. *Cancer Res; 72(16); 3891–900. ©2012 AACR.*

Introduction

Protein synthesis is a major factor in determining cell phenotype and is tightly regulated during growth and development. A recent global analysis of mammalian gene expression showed that mRNA levels can explain ∼40% of variability in protein levels, and indicated that the translation rate has a dominant role in controlling cellular protein levels (1).

Improper protein synthesis can lead to cell apoptosis or disease. In human cancers, hyperactivation of signal transduction pathways induces cancer growth associated with an increase in overall protein synthesis. In addition, selective synthesis of many proteins that influence cancer progression or confer resistance to cancer treatment may be regulated posttranscriptionally via translation initiation. For example, an analysis of glioma cell response to radiation revealed that the number of genes whose expression was regulated via translation was 10-fold higher than those regulated via transcription (2). This indicates that cellular responses that occur via translation alterations may represent major survival pathways.

Cap-Dependent Protein Synthesis in Cancer

Translation proceeds by initiation, elongation, termination, and ribosome recycling, with most of the regulatory mechanisms occurring during the rate-limiting initiation step. As previously reviewed (3, 4), during the first steps of cap-dependent translation initiation, messenger RNA associates at its 5′UTR with the eukaryotic initiation factor eIF4F, comprising the cap-binding protein eIF4E, the scaffold protein eIF4G, and the 5′UTR unwinding RNA helicase eIF4A that operates in conjunction with eIF4B. At the 3′UTR end, associated poly-A binding proteins (PABP) bind eIF4G, leading to the circularization and activation of mRNAs (Fig. 1). The 43S preinitiation complex [composed of the 40S ribosomal subunit, the eIF2 ternary complex (eIF2, GTP, and Met-tRNA), eIF3, eIF1, eIF1A, and eIF5] joins the activated RNA structure (via eIF4G and eIF3 interaction) and scans 5′UTR until AUG start codon recognition occurs, followed by the hydrolysis of eIF2-bound GTP and the release of eIF2-bound GDP, eIF5, eIF3, and eIF1. The subsequent association of the 60S ribosomal subunit with eIF5B-bound GTP leads to eIF5B-mediated GTP hydrolysis and the release of eIF5B-GDP and eIF1, thus allowing the assembly of the 80S complex, which is then ready for translation elongation. Overexpression of eIF4E, a key player in cap-dependent translation, leads to oncogenic transformation (5), and increased eIF4E protein levels are found in the majority of human cancers, where its expression correlates with a poor prognosis (6). In addition to the regulation of general protein synthesis, studies have shown that eIF4E can also preferentially enhance the translation of carcinogenesis-associated mRNAs, including regulators of the cell cycle, apoptosis, angiogenesis, and invasion (7–10). This suggests that targeting cap-dependent translation or eIF4E may be a promising strategy for cancer treatment.

Translation Control in Response to Cancer Stress

During cancer progression, cells are constantly exposed to different types of stress. Rapid responses based on the accurate expression of particular proteins may allow their further growth and survival. Translation regulation is a rapid and

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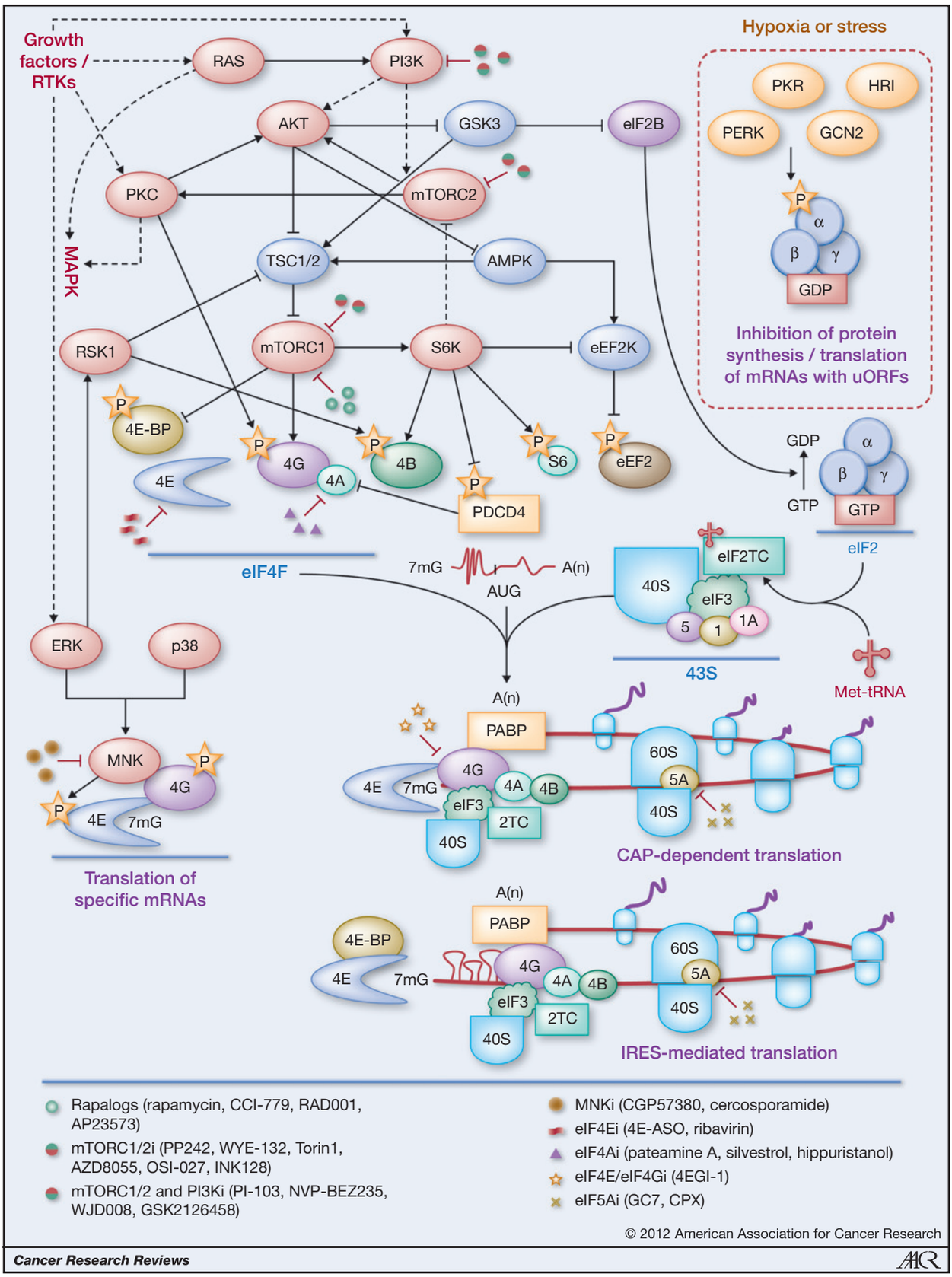

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elegant way of tuning gene expression by intensifying protein synthesis from existing mRNAs while silencing others, and also saves transcription-related energy. Thus, in the cancer situation, translational regulation may act to the advantage of tumor cells.

Lack of oxygen (hypoxia), starvation, or response to DNA-damage inducing therapy represses cap-dependent translation and leads to a reduction in overall protein synthesis, mostly by suppression of eIF4F and eIF2 ternary complex assembly by various mechanisms (11). On the other hand, inhibition of protein synthesis allows the enhancement or activation of the translation of mRNA subsets in a cap-independent manner using secondary RNA structures termed internal ribosomal entry sites (IRES), which are mostly located in the 5′UTR of mRNA (12). Highly structured IRES bypass the conventional scanning process by recruiting the 40S ribosome subunit and other eIFs directly to the start codons or the 5′UTR region independently of a cap. Of importance, these mRNAs encode proteins with oncogenic activity that promote the development, progression, and survival of cancer cells, such as c-MYC (13), lymphoid enhancer factor (LEF)-1 (14), VEGF (15), hypoxia-inducible factor (HIF)-1α (16), XIAP (17), and BCL2 (18). In addition, IRES mutations or deregulated IRES-*trans*-acting factors (ITAF) can further increase the translation of oncogenic proteins. In multiple myeloma, mutations in c-myc-IRES were shown to enhance its translation initiation (19), and a more recent study in the same cancer type (20) showed an increase in IRES-dependent c-myc translation via ITAFs such as Y-box binding protein 1 (YB-1) and polypyrimidine tract-binding protein 1 (PTB-1), which were previously reported to be involved in carcinogenesis and chemotherapy resistance (21–24). These findings both show the importance of IRES-driven carcinogenesis and have therapeutic implications.

Translation initiation factor eIF4G was first found to be overexpressed in squamous cell lung carcinoma (25). eIF4G recruits the 43S preinitiation complex to mRNA and is part of the eIF4F complexes. Therefore, its oncogenic activity was initially suggested to be very similar to that of eIF4E (26). However, eIF4G was shown to transform NIH3T3 cells without increasing the eIF4E level (27), and in a more recent study (28), overexpression of eIF4GI in inflammatory breast cancer promoted the formation of tumor emboli by enhanced translation of IRES-containing mRNAs, including catenin p120 mRNA. Thus, depending on the circumstances, eIF4G can contribute to oncogenic transformation either by forming active eIF4F (required for cap-dependent translation) or by increasing IRES-dependent translation. Furthermore, many components of the human eIF3 factor [comprising 13 subunits (a–m)] are deregulated in cancers. As reviewed recently (29), eIF3a, -c, and -h are upregulated in human cancers, and individual overexpression of eIF3a, -b, -c, -h, or -i promoted malignant transformation of NIH3T3 cells (30–32). In contrast, eIF3f is downregulated in melanoma and pancreatic cancer, and its overexpression inhibits proliferation and protein synthesis and induces apoptosis (33). The murine *Int-6* gene, encoding eIF3e, was first identified as a mouse mammary tumor virus integration site (34, 35) that results in the production of a truncated oncoprotein with transforming activity (36) capable of inducing cap-independent translation, as reported recently (37). Several subsequent studies of full-length eIF3e showed its tumor suppressor activity (38–40). However, further reports indicated its oncogenic activity (41, 42), and a recent screen identified eIF3e as a potential biomarker for the early detection of breast cancer (43). Therefore, as suggested by a recent study (44), eIF3e's involvement in carcinogenesis may depend on the tumor type or stage, such that its downregulation may transform normal mammary cells and its upregulation may favor the progression of malignant tumors. Nevertheless, in addition to eIF3's important action in recruiting the 40S ribosome subunit and the eIF2 ternary complex to mRNAs (in either a cap-dependent or –independent manner), deregulation of eIF3 components (e.g., eIF3a, -e, or -h) can alter the synthesis of specific cancer-related proteins and enhance resistance to cancer therapy (42, 45, 46). However, how the specific eIF3 components regulate selective translation of oncogenic transcripts is not clear. Mass spectrometry analysis identified phosphorylated subunits of eIF3 factor (a, b, c, f, g, h, and j) in serum-stimulated HeLa cells, implying that it may be possible to regulate them by phosphorylation (47). Furthermore, eIF3 subunits can interact with non-eIF proteins such as IFN-induced protein p56, which binds eIF3e and suppresses translation by inhibiting eIF3-mediated enhancement of ternary complex formation (48), or the tumor suppressor protein schwannomin, which inhibits cellular proliferation through direct interaction with eIF3c (49). Finally, eIF3 is a docking site

Figure 1. Targeting mRNA translation in cancer. During carcinogenesis, deregulated signaling pathways influence protein synthesis by modulating the translation triggering different types of mRNAs. Activation of RTK signaling pathways, together with hyperactivated downstream oncogenic pathways such as RAS, MAPK, PI3K/AKT, and PKC, activate the translational machinery via mTOR. Active mTORC1 enhances mRNA translation by the phosphorylation of 4EBPs, leading to release of eIF4E, the scaffold protein eIF4G, and the S6 kinases. Active S6K further phosphorylates S6 ribosomal protein and eIF4B, and also inactivates both eEF2K (negative regulator of eEF2) and PDCD4, an inhibitor of the helicase activity of eIF4A. Activated by PI3K pathways and by ribosome interaction, the mTORC2 complex phosphorylates and enhances AKT signaling and the PKC pathway. The TSC1/2 complex, which inhibits mTORC1, is negatively regulated by AKT and MAPK/RSK1, and is activated by AMPK and GSK3, which also regulate eEF2K and eIF2B, respectively. eIF2B facilitates the recycling of GDP to GTP on eIF2. eIF2-GTP and Met-tRNA form a ternary complex (eIF2TC), which together with the 40S ribosomal subunit and other initiation factors further assembles the 43S preinitiation complex. This is recruited to eIF4F-bound mRNA (via eIF4G-eIF3), facilitating cap-dependent translation. Under conditions of stress and/or inhibition of eIF4F, a cap-independent mechanism of translation can operate via recruitment of the 43S complex to the start codon by means of an IRES in the mRNA. Stimulation of MAPKs activates MNKs (via ERKs and p38), followed by PKC-dependent MNK/eIF4G association and eIF4E phosphorylation leading to translation of specific mRNAs. Hypoxia or stress induces eIF2α phosphorylation (via PERK, PKR, GCN2, or HRI), which suppresses GTP recycling on eIF2, causing inhibition of global protein synthesis and promoting the translation of specific mRNAs that contain uORFs. Inhibitors of translation factors (or the signaling events that control them) that are used in clinical and preclinical studies are summarized in the text.

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for cancer-associated kinases such as mTOR (via eIF3f interaction), and activation of mTORC1 by insulin was shown to increase the association of eIF3 and eIF4G factors (50). Active and eIF3-associated mTORC1 phosphorylates and activates S6K, followed by S6K dissociation from eIF3 factor and subsequent phosphorylation of S6K translational targets (51). Together, these results suggest that eIF3 is an important regulatory platform and a potential subject for the development of novel cancer treatments.

A further important mechanism that triggers selective translation during the response of cancer cells to stress, including hypoxia or chemotherapy, is part of the unfolded protein response (UPR) during endoplasmic reticulum (ER) stress (52). Phosphorylation of eIF2α by upstream kinases blocks recycling of GTP on eIF2 by the guanine exchange factor eIF2B and reduces global protein synthesis. This promotes the translation of mRNAs containing 5′UTR upstream open reading frames (uORF) that are normally silenced for translation. In human cancers, induced eIF2α phosphorylation leads to the synthesis of basic leucine-zipper transcription factors such as ATF4 (53) and ATF5 (54), which further support cancer cell survival.

Translation can also be regulated via sequence-specific noncoding microRNAs (miRNA), the expression of which is very often deregulated in human cancers or is induced by stress. Processed and mature miRNAs together with argonaute protein and the glycine-tryptophan protein of 182 kDa (GW182) make up the miRNA-induced silencing complex. This complex base-pairs with a complementary sequence mostly in the 3′UTR of mRNAs, leading to deadenylation or repression of translation initiation or elongation and mRNA decay (55). Although they are beyond the scope of this review, miRNAs can undoubtedly control crucial steps in carcinogenesis, and miRNA-based therapies have already shown promise for cancer treatment (56). However, the mechanisms of miRNA-mediated inhibition of cancer-related mRNA translation require further investigation.

Cancer Signaling Networks That Regulate Protein Synthesis

The major hyperactivated signaling pathways that promote carcinogenesis include growth factor signaling via activation of receptor tyrosine kinases (RTK), mitogen-activated protein kinases (MAPK), RAS signaling, phosphatidylinositol-3-OH kinase (PI3K), and AKT signaling. In addition to transcription activation, these pathways control protein synthesis by phosphorylation and the regulation of translation factors or ribosomal proteins. AKT signaling inactivates the tuberous sclerosis tumor-suppressor TSC1/2 complex, which negatively regulates the mammalian target of rapamycin complex 1 (mTORC1), a major regulator of protein synthesis that comprises mTOR, Raptor, and mLst8. In its active form, mTORC1 phosphorylates eIF4E-binding proteins (4E-BP), leading to the release and activation of the cap-binding protein eIF4E (57–59). Inactivation of 4E-BPs by downregulation or hyperphosphorylation correlates with higher tumor grades and reduced patient survival in prostate (60) and breast (61) cancer, and leads to an increase in cap-dependent translation (62). Nevertheless, hypophosphorylation of 4E-BPs and the sequestering of eIF4E can shift translation initiation toward cap-independent mechanisms that support the synthesis of proteins that may be influential at certain stages of carcinogenesis. Thus, 4E-BPs and their phosphorylation status are crucial factors that regulate the assembly of eIF4F and the type of translation during carcinogenesis.

Active mTORC1 also supports global protein translation by phosphorylating the scaffold protein eIF4G and the S6 kinase (S6K) that regulates ribosomal protein S6 and eIF4B factor (63). S6K also phosphorylates and inactivates eEF2 kinase (eEF2K), which inhibits elongation factor eEF2, as well as translation inhibitor programmed cell death 4 (PDCD4), leading to its proteasomal degradation (64). PDCD4 blocks RNA helicase eIF4A activity, which allows the unwinding of highly structured 5′UTRs of cancer-promoting mRNAs, thus suppressing tumorigenesis and cancer progression (65, 66). In addition to regulating overall protein synthesis, mTORC1 can also increase the translation of mRNAs with terminal oligopyrimidine tracts in their 5′UTR that encode ribosomal proteins and translation factors, thus supporting the translation of key components required for protein synthesis (67, 68). mTOR pathways also support ribosome biogenesis by regulating RNA polymerases (Pol I and III) that generate ribosomal RNAs, and by influencing rRNA processing (69, 70). Similarly, a recent study showed that hyperactivated AKT cooperates with c-MYC and synergistically activates rRNA synthesis and ribosome biogenesis, highlighting AKT/mTORC1 and c-MYC as an important growth-regulating network (71). In cancer, the activation of mTORC1 can also be supported by MAPKs that act downstream of hyperactivated RTKs and RAS pathways. Extracellular signal-regulated kinases (ERK) can phosphorylate and inhibit tuberin (TSC2) directly (72) or via activation of RSK kinase ($p90^{RSK}$), which further phosphorylates and impairs TSC2 function (73) and additionally stimulates mTORC1 activity via direct raptor phosphorylation (74). RSKs can also support protein synthesis in a manner very similar to that observed for S6K by phosphorylating and regulating IF4B (75) and eEF2K (76).

On the other hand, the activation of mTORC1 can be inhibited by AMP-activated protein kinase (AMPK), a major sensor of the energy status that induces the activity of the mTORC1 negative regulator TSC1/2 complex (77). AMPK-mediated phosphorylation and activation of TSC2 are strongly supported by active GSK3 (78), which is negatively regulated by AKT (79) and other oncogenic pathways, including MAPK, PKC, and Wnt signaling (80). In addition to mTORC1 inhibition, activated GSK3 inhibits the initiation factor eIF2B (81), whereas active AMPK can suppress elongation factor eEF2 via eEF2K, leading to a decrease in global protein synthesis and cell-cycle arrest (82, 83). In human cancers, suppression of AMPK activity is maintained by hyperactivated AKT, which phosphorylates the AMPKα subunit and inhibits its activation via AMPK-upstream kinase LKB1 (84). Heterozygous loss of LKB1 function increases the risk of malignant cancers, and loss of the *STK11* (LKB1) gene is very frequent in lung and cervical cancers (85). Furthermore, in a recent study, AMPK activators (metformin, phenformin, and A-769662) were found to

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suppress tumorigenesis in PTEN-deficient mice (86), suggesting AMPK pathway reactivation as a potential strategy for cancer treatment. Metformin and phenformin impair mitochondrial respiration, leading to an increase in the cellular AMP:ATP ratio that activates AMPK (87), whereas A-769662 can directly bind and activate AMPK by mimicking AMP and inhibiting AMPK dephosphorylation (88).

The activated mTORC2 complex composed of mTOR, Rictor, Protor, mLst8, and Sin1 (59) can further enhance AGC kinase activity by phosphorylating AKT and PKC hydrophobic and turn motifs in a Sin1-dependent manner (89). A recent study in yeast, followed by validation experiments in cancer cells, showed that mTORC2 activation via the PI3K pathway after insulin stimulation requires association with ribosomes, thus leading to mTORC2 activity only in growing cells with a high level of ribosome biogenesis (90). Taken together, these findings indicate that the hyperactivated PI3K/AKT/mTOR signaling network influences tumor growth by its effects on crucial steps of protein synthesis in highly proliferating cancer cells.

Although carcinogenesis is promoted by the activation of growth pathways, at certain stages of cancer development, further tumor progression or the survival of cancer cells depends on the synthesis of a subset of proteins whose expression is very often controlled by translation. MAPK interacting kinases (MNK1/2), regulated by upstream ERKs and p38 kinases, bind to eIF4G and phosphorylate eIF4E (91). A recent report showed that phosphorylation of eIF4G1 by PKCα is required for MNK1 binding to eIF4G1, indicating a link between PKC activity and EIF4E phosphorylation (92). The PKC kinase family can also support protein synthesis via phosphorylation of AKT and MAPK, and by inactivation of GSK3 (93). Of importance, eIF4E phosphorylation at serine-209 by MNKs was shown to be required for eIF4E oncogenic activity *in vivo* (94), and an increase in phospho-eIF4E has been reported in various cancers (95). The role of eIF4E phosphorylation in regulating translation is not clear. One study suggested a model in which eIF4E phosphorylation can occur as a transient event during translation initiation (96). After assembly of the eIF4F complex, phosphorylation of eIF4E weakens its affinity for capped RNA, allowing for the release of eIF4F from the 5′UTR-end of the mRNA and enhancing RNA unwinding and ribosome migration. In addition to translation initiation, other studies indicate a role for eIF4E in the nucleus, where phosphorylated eIF4E promotes the transport of growth-supporting mRNAs such as cyclin D or HDM2 and thus contributes to oncogenic transformation (97, 98). Nevertheless, mice lacking both MNK1 and MNK2 develop normally without detectable eIF4E phosphorylation, indicating that the MNK/eIF4E pathway is not required for global protein synthesis (99) but may be important in conditions such as stress or cancer. Indeed, MNK1 activation can be induced by different types of stress, including radiation, whereas MNK2 shows much higher basic activity in comparison with MNK1 (91). A previous study (100) suggested a MNK-induced, cap-independent translation in which the MNK/eIF4E pathway negatively regulates cap-dependent protein synthesis, thereby enhancing the availability of initiation complexes for cap-independent mechanisms of translation. In addition, recent studies showed that downstream MNK pathways enhance the translation of specific mRNAs involved in carcinogenesis, including MCL1 (94), CCL2/7, MMP3/7 (10), and SMAD2 (101). Thus, the activation of MNKs may represent a survival pathway that is hyperactivated in cancers.

Malignant progression leads to various cancer stresses (e.g., hypoxia) that induce the activation of eIF2α kinases such as dsRNA–dependent protein kinase (PKR), PKR-like endoplasmic reticulum kinase (PERK), general control nonderepressible 2 (GCN2), and heme-regulated inhibitor [HRI (102, 103)]. In a recent study, hyperactivated AKT inhibited PERK-mediated eIF2α phosphorylation and maintained eIF2α in an unphosphorylated state in proliferating cancer cells (104). Phosphorylated eIF2α inhibits global protein synthesis and reduces cancer cell proliferation, but it also activates a survival mechanism via regulation of translation. Therefore, eIF2 phosphorylation appears to play a role in the acquisition of a malignant phenotype by enhancing the translation of specific proteins that promote the survival and adaptation of cancer cells to stress conditions at the expense of global protein synthesis and proliferation.

Targeting Deregulated Translation in Cancer

In the past decade, the blocking of deregulated signaling pathways by kinase inhibitors has shown great promise for cancer treatment. In this review, we concentrate on targeting kinases that directly and extensively regulate translation factors and protein synthesis.

mTORC1 can be inhibited by rapalogs (rapamycin and its derivatives) that bind to FKBP-12 and inhibit mTOR in complex 1. Although mTORC2 was thought to be insensitive, decreased mTORC2 activity after extended rapalog treatment has been reported (105, 106). In many preclinical and clinical studies, rapalogs were shown to inhibit tumor growth, vascularization, invasion, and metastasis by reducing global protein synthesis, as well as by inhibiting mTORC1-specific mRNA translation, including cyclin D, c-MYC, and HIF-1α (107). Although rapalogs have shown promising antitumor effects, many cancers become resistant to treatment because of mutations in FKBP-12 (108) or an increase in the activity of compensatory or survival pathways. Rapalog-mediated inhibition of mTORC1 induces the activation of AKT via suppression of an inhibitory effect of S6K on IRS1, which normally activates the PI3K/AKT pathway (109). In addition, the rapalog-insensitive mTORC2 complex phosphorylates the AKT hydrophobic motif and further enhances AKT activity. In an attempt to overcome resistance pathways, investigators have developed mTORC1/2 inhibitors (e.g., PP242, WYE-132, Torin1, AZD8055, OSI-027, and INK128) and inhibitors targeting mTORC1/2 and PI3K (e.g., PI-103, NVP-BEZ235, WJD008, and GSK2126458), and these agents have shown antitumor activity superior to that of rapalogs in various *in vivo* and *in vitro* cancer models, including lymphoma, leukemia, glioma, breast, lung, and renal carcinoma (110–119). mTORC1/2 inhibitors (e.g., PP242) were more efficient in the inhibition of global protein synthesis and in eIF4F complex formation than rapamycin, illustrating the more-effective approach of targeting cap-

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dependent translation in cancer (120). It is worth mentioning that inhibition of PI3K/AKT/mTOR by PI-103 and rapamycin was more effective against malignant melanoma compared with a single-agent treatment, indicating that "vertical inhibition" is a promising strategy to improve therapeutic approaches (121). Rapalogs can also enhance MNK-regulated eIF4E phosphorylation in a PI3K-dependent manner (122). Genetic or pharmacologic inhibition of MNK pathways by CGP57380 sensitized cancer cells to rapalogs and showed significantly stronger effects than a single drug treatment (101, 123, 124). More recently, in xenograft tumor models, MNK1-depleted glioma cells showed a decrease in tumor formation (125), and the MNK inhibitor cercosporamide (126) suppressed the outgrowth of melanoma pulmonary metastases and colon carcinoma growth. Thus, targeting MNK-controlled translational pathways may have potential as an effective cancer therapy.

As an alternative to the inhibition of signaling pathways, therapeutic approaches that interfere with the deregulated translation typical of some cancers have been studied. Treatment with eIF4E-specific antisense oligonucleotides reduced eIF4E expression as well as eIF4E-regulated proteins, and suppressed tumor growth in nude mice bearing human breast and prostate tumor xenografts (127). Although eIF4E is a general initiation factor required for cap-dependent translation, the reduction of eIF4E expression appeared to have no effect on normal tissues, suggesting that cancer tissues are more susceptible to eIF4E inhibition than normal tissues. Sequestering of eIF4E by a physical mimic of the m7G cap structure ribavirin (128) induced the reduction and relocalization of nuclear eIF4E to the cytoplasm, and this was associated with a clinical response in patients with myeloid leukemia (129). Furthermore, a synthetic peptide (eIF4GI-1) that disrupts eIF4E/eIF4G association inhibited cap-dependent translation, enhanced eIF4E association with 4E-BP1, and reduced protein levels of c-MYC and Bcl-xL, showing a preferential effect on transformed cells, including lymphoma and lung cancer cells (130). Another compound that inhibits the cap complex is the antiproliferative and proapoptotic marine natural product pateamine A, which targets eIF4A and stimulates its RNA binding. This results in sequestration of eIF4A onto RNA and a reduction in eIF4A's availability to recycle through the eIF4F complex (131). More recently, des-methyl, des-amino pateamine A (DMDA-PatA) showed potent anticancer activity in a melanoma mouse model and low cytotoxicity against nonproliferating human fibroblasts (132). Similarly, silvestrol inhibited translation initiation and ribosome recruitment by targeting eIF4A and interfering with eIF4F complex formation (133). Silvestrol has exhibited anticancer activity in mouse cancer models, including breast and prostate cancer (133) and B-cell leukemias (134). Furthermore, hippuristanol, a selective and potent inhibitor of eIF4A RNA-binding activity (135), showed anticancer activity in an adult T-cell leukemia mouse model (136).

The translation factor eIF5A requires specific posttranslational modification (hypusination) for full functionality. N1-guanyl-1,7-diaminoheptane (GC7) and ciclopirox olamine (CPX) are potent inhibitors of deoxyhypusine synthase, which catalyzes eIF5A hypusination. GC7 and CPX have shown antiproliferative effects in various cell lines (137, 138) and antitumor activity *in vivo* in breast cancer, melanoma, leukemia, and myeloma models (139–141).

Conclusions

Deregulated translation not only allows an increase in protein synthesis in cancer cells and thus further growth, it also enhances the synthesis of proteins that are advantageous for the survival of tumor tissues and their adaptation to environmental changes during disease progression and response to therapy. Further study of translation regulation in cancer will undoubtedly uncover novel potential therapeutic targets. Mechanisms that drive selective translation of specific mRNAs also warrant further investigation, especially in defined types and stages of cancer. Clearly, deregulated signaling networks in cancer regulate translation, and many novel phosphosites that have been identified in proteomics-based screens await further characterization (47, 142). Additionally, the analysis of other posttranslational modifications in the translational machinery may reveal novel regulatory mechanisms that are suitable as targets for therapeutic intervention. Furthermore, because rapid regulation of translation can enhance resistance to many cancer treatments, targeting translation-based survival mechanisms in combination with already approved compounds or with standard-of-care therapy may substantially improve the success of cancer treatments.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: M. Grzmil, B.A. Hemmings
Writing, review, and/or revision of the manuscript: M. Grzmil, B.A. Hemmings
Administrative, technical, or material support: B.A. Hemmings

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References

1. Schwanhäusser B, Busse D, Li N, Dittmar G, Schuchhardt J, Wolf J, et al. Global quantification of mammalian gene expression control. Nature 2011;473:337–42.
2. Lü X, de la Peña L, Barker C, Camphausen K, Tofilon PJ. Radiation-induced changes in gene expression involve recruitment of existing messenger RNAs to and away from polysomes. Cancer Res 2006;66:1052–61.
3. Sonenberg N, Hinnebusch AG. Regulation of translation initiation in eukaryotes: mechanisms and biological targets. Cell 2009;136:731–45.

Published OnlineFirst July 31, 2012; DOI: 10.1158/0008-5472.CAN-12-0026

4. Jackson RJ, Hellen CU, Pestova TV. The mechanism of eukaryotic translation initiation and principles of its regulation. Nat Rev Mol Cell Biol 2010;11:113–27.
5. Smith MR, Jaramillo M, Liu YL, Dever TE, Merrick WC, Kung HF, et al. Translation initiation factors induce DNA synthesis and transform NIH 3T3 cells. New Biol 1990;2:648–54.
6. De Benedetti A, Graff JR. eIF-4E expression and its role in malignancies and metastases. Oncogene 2004;23:3189–99.
7. Mamane Y, Petroulakis E, Martineau Y, Sato TA, Larsson O, Rajasekhar VK, et al. Epigenetic activation of a subset of mRNAs by eIF4E explains its effects on cell proliferation. PLoS ONE 2007;2:e242.
8. Larsson O, Li S, Issaenko OA, Avdulov S, Peterson M, Smith K, et al. Eukaryotic translation initiation factor 4E induced progression of primary human mammary epithelial cells along the cancer pathway is associated with targeted translational deregulation of oncogenic drivers and inhibitors. Cancer Res 2007;67:6814–24.
9. Chung J, Bachelder RE, Lipscomb EA, Shaw LM, Mercurio AM. Integrin (alpha 6 beta 4) regulation of eIF-4E activity and VEGF translation: a survival mechanism for carcinoma cells. J Cell Biol 2002;158:165–74.
10. Furic L, Rong L, Larsson O, Koumakpayi IH, Yoshida K, Brueschke A, et al. eIF4E phosphorylation promotes tumorigenesis and is associated with prostate cancer progression. Proc Natl Acad Sci U S A 2010;107:14134–9.
11. Spriggs KA, Bushell M, Willis AE. Translational regulation of gene expression during conditions of cell stress. Mol Cell 2010;40:228–37.
12. Holcik M, Sonenberg N, Korneluk RG. Internal ribosome initiation of translation and the control of cell death. Trends Genet 2000;16:469–73.
13. Notari M, Neviani P, Santhanam R, Blaser BW, Chang JS, Galietta A, et al. A MAPK/HNRPK pathway controls BCR/ABL oncogenic potential by regulating MYC mRNA translation. Blood 2006;107:2507–16.
14. Jimenez J, Jang GM, Semler BL, Waterman ML. An internal ribosome entry site mediates translation of lymphoid enhancer factor-1. RNA 2005;11:1385–99.
15. Miller DL, Dibbens JA, Damert A, Risau W, Vadas MA, Goodall GJ. The vascular endothelial growth factor mRNA contains an internal ribosome entry site. FEBS Lett 1998;434:417–20.
16. Lang KJ, Kappel A, Goodall GJ. Hypoxia-inducible factor-1alpha mRNA contains an internal ribosome entry site that allows efficient translation during normoxia and hypoxia. Mol Biol Cell 2002;13:1792–801.
17. Holcik M, Yeh C, Korneluk RG, Chow T. Translational upregulation of X-linked inhibitor of apoptosis (XIAP) increases resistance to radiation induced cell death. Oncogene 2000;19:4174–7.
18. Sherrill KW, Byrd MP, Van Eden ME, Lloyd RE. BCL-2 translation is mediated via internal ribosome entry during cell stress. J Biol Chem 2004;279:29066–74.
19. Chappell SA, LeQuesne JP, Paulin FE, deSchoolmeester ML, Stoneley M, Soutar RL, et al. A mutation in the c-myc-IRES leads to enhanced internal ribosome entry in multiple myeloma: a novel mechanism of oncogene de-regulation. Oncogene 2000;19:4437–40.
20. Cobbold LC, Wilson LA, Sawicka K, King HA, Kondrashov AV, Spriggs KA, et al. Upregulated c-myc expression in multiple myeloma by internal ribosome entry results from increased interactions with and expression of PTB-1 and YB-1. Oncogene 2010;29:2884–91.
21. Evdokimova V, Tognon C, Ng T, Ruzanov P, Melnyk N, Fink D, et al. Translational activation of snail1 and other developmentally regulated transcription factors by YB-1 promotes an epithelial-mesenchymal transition. Cancer Cell 2009;15:402–15.
22. Chatterjee M, Rancso C, Stühmer T, Eckstein N, Andrulis M, Gerecke C, et al. The Y-box binding protein YB-1 is associated with progressive disease and mediates survival and drug resistance in multiple myeloma. Blood 2008;111:3714–22.
23. He X, Pool M, Darcy KM, Lim SB, Auersperg N, Coon JS, et al. Knockdown of polypyrimidine tract-binding protein suppresses ovarian tumor cell growth and invasiveness in vitro. Oncogene 2007;26:4961–8.
24. Wang C, Norton JT, Ghosh S, Kim J, Fushimi K, Wu JY, et al. Polypyrimidine tract-binding protein (PTB) differentially affects malignancy in a cell line-dependent manner. J Biol Chem 2008;283:20277–87.
25. Bauer C, Diesinger I, Brass N, Steinhart H, Iro H, Meese EU. Translation initiation factor eIF-4G is immunogenic, overexpressed, and amplified in patients with squamous cell lung carcinoma. Cancer 2001;92:822–9.
26. Bauer C, Brass N, Diesinger I, Kayser K, Grässer FA, Meese E. Overexpression of the eukaryotic translation initiation factor 4G (eIF4G-1) in squamous cell lung carcinoma. Int J Cancer 2002;98:181–5.
27. Fukuchi-Shimogori T, Ishii I, Kashiwagi K, Mashiba H, Ekimoto H, Igarashi K. Malignant transformation by overproduction of translation initiation factor eIF4G. Cancer Res 1997;57:5041–4.
28. Silvera D, Arju R, Darvishian F, Levine PH, Zolfaghari L, Goldberg J, et al. Essential role for eIF4GI overexpression in the pathogenesis of inflammatory breast cancer. Nat Cell Biol 2009;11:903–8.
29. Silvera D, Formenti SC, Schneider RJ. Translational control in cancer. Nat Rev Cancer 2010;10:254–66.
30. Ahlemann M, Zeidler R, Lang S, Mack B, Münz M, Gires O. Carcinoma-associated eIF3i overexpression facilitates mTOR-dependent growth transformation. Mol Carcinog 2006;45:957–67.
31. Savinainen KJ, Helenius MA, Lehtonen HJ, Visakorpi T. Overexpression of EIF3S3 promotes cancer cell growth. Prostate 2006;66:1144–50.
32. Zhang L, Pan X, Hershey JW. Individual overexpression of five subunits of human translation initiation factor eIF3 promotes malignant transformation of immortal fibroblast cells. J Biol Chem 2007;282:5790–800.
33. Shi J, Kahle A, Hershey JW, Honchak BM, Warneke JA, Leong SP, et al. Decreased expression of eukaryotic initiation factor 3f deregulates translation and apoptosis in tumor cells. Oncogene 2006;25:4923–36.
34. Marchetti A, Buttitta F, Miyazaki S, Gallahan D, Smith GH, Callahan R. Int-6, a highly conserved, widely expressed gene, is mutated by mouse mammary tumor virus in mammary preneoplasia. J Virol 1995;69:1932–8.
35. Asano K, Merrick WC, Hershey JW. The translation initiation factor eIF3-p48 subunit is encoded by int-6, a site of frequent integration by the mouse mammary tumor virus genome. J Biol Chem 1997;272:23477–80.
36. Rasmussen SB, Kordon E, Callahan R, Smith GH. Evidence for the transforming activity of a truncated Int6 gene, in vitro. Oncogene 2001;20:5291–301.
37. Chiluiza D, Bargo S, Callahan R, Rhoads RE. Expression of truncated eukaryotic initiation factor 3e (eIF3e) resulting from integration of mouse mammary tumor virus (MMTV) causes a shift from cap-dependent to cap-independent translation. J Biol Chem 2011;286:31288–96.
38. Marchetti A, Buttitta F, Pellegrini S, Bertacca G, Callahan R. Reduced expression of INT-6/eIF3-p48 in human tumors. Int J Oncol 2001;18:175–9.
39. Buttitta F, Martella C, Barassi F, Felicioni L, Salvatore S, Rosini S, et al. Int6 expression can predict survival in early-stage non-small cell lung cancer patients. Clin Cancer Res 2005;11:3198–204.
40. Chen L, Uchida K, Endler A, Shibasaki F. Mammalian tumor suppressor Int6 specifically targets hypoxia inducible factor 2 alpha for degradation by hypoxia- and pVHL-independent regulation. J Biol Chem 2007;282:12707–16.
41. Traicoff JL, Chung JY, Braunschweig T, Mazo I, Shu Y, Ramesh A, et al. Expression of EIF3-p48/INT6, TID1 and Patched in cancer, a profiling of multiple tumor types and correlation of expression. J Biomed Sci 2007;14:395–405.
42. Grzmil M, Rzymski T, Milani M, Harris AL, Capper RG, Saunders NJ, et al. An oncogenic role of eIF3e/INT6 in human breast cancer. Oncogene 2010;29:4080–9.
43. Anderson KS, Sibani S, Wallstrom G, Qiu J, Mendoza EA, Raphael J, et al. Protein microarray signature of autoantibody biomarkers for the early detection of breast cancer. J Proteome Res 2011;10:85–96.

Published OnlineFirst July 31, 2012; DOI: 10.1158/0008-5472.CAN-12-0026

44. Suo J, Snider SJ, Mills GB, Creighton CJ, Chen AC, Schiff R, et al. Int6 regulates both proteasomal degradation and translation initiation and is critical for proper formation of acini by human mammary epithelium. Oncogene 2011;30:724–36.
45. Saletta F, Suryo Rahmanto Y, Richardson DR. The translational regulator eIF3a: the tricky eIF3 subunit! Biochim Biophys Acta 2010;1806:275–86.
46. Cappuzzo F, Varella-Garcia M, Rossi E, Gajapathy S, Valente M, Drabkin H, et al. MYC and EIF3H Coamplification significantly improve response and survival of non-small cell lung cancer patients (NSCLC) treated with gefitinib. J Thorac Oncol 2009;4:472–8.
47. Damoc E, Fraser CS, Zhou M, Videler H, Mayeur GL, Hershey JW, et al. Structural characterization of the human eukaryotic initiation factor 3 protein complex by mass spectrometry. Mol Cell Proteomics 2007;6:1135–46.
48. Hui DJ, Bhasker CR, Merrick WC, Sen GC. Viral stress-inducible protein p56 inhibits translation by blocking the interaction of eIF3 with the ternary complex eIF2.GTP.Met-tRNAi. J Biol Chem 2003;278: 39477–82.
49. Scoles DR, Yong WH, Qin Y, Wawrowsky K, Pulst SM. Schwannomin inhibits tumorigenesis through direct interaction with the eukaryotic initiation factor subunit c (eIF3c). Hum Mol Genet 2006;15:1059–70.
50. Harris TE, Chi A, Shabanowitz J, Hunt DF, Rhoads RE, Lawrence JC Jr. mTOR-dependent stimulation of the association of eIF4G and eIF3 by insulin. EMBO J 2006;25:1659–68.
51. Holz MK, Ballif BA, Gygi SP, Blenis J. mTOR and S6K1 mediate assembly of the translation preinitiation complex through dynamic protein interchange and ordered phosphorylation events. Cell 2005;123:569–80.
52. Rzymski T, Milani M, Singleton DC, Harris AL. Role of ATF4 in regulation of autophagy and resistance to drugs and hypoxia. Cell Cycle 2009;8:3838–47.
53. Vattem KM, Wek RC. Reinitiation involving upstream ORFs regulates ATF4 mRNA translation in mammalian cells. Proc Natl Acad Sci U S A 2004;101:11269–74.
54. Zhou D, Palam LR, Jiang L, Narasimhan J, Staschke KA, Wek RC. Phosphorylation of eIF2 directs ATF5 translational control in response to diverse stress conditions. J Biol Chem 2008;283: 7064–73.
55. Fabian MR, Sonenberg N, Filipowicz W. Regulation of mRNA translation and stability by microRNAs. Annu Rev Biochem 2010;79: 351–79.
56. Bernards R, Filipowicz W, Livingston DM, Mihich E. Twenty-second annual Pezcoller Symposium: RNA biology and cancer. Cancer Res 2010;70:10034–7.
57. Fayard E, Tintignac LA, Baudry A, Hemmings BA. Protein kinase B/Akt at a glance. J Cell Sci 2005;118:5675–8.
58. Averous J, Proud CG. When translation meets transformation: the mTOR story. Oncogene 2006;25:6423–35.
59. Proud CG. mTOR signalling in health and disease. Biochem Soc Trans 2011;39:431–6.
60. Graff JR, Konicek BW, Lynch RL, Dumstorf CA, Dowless MS, McNulty AM, et al. eIF4E activation is commonly elevated in advanced human prostate cancers and significantly related to reduced patient survival. Cancer Res 2009;69:3866–73.
61. Coleman LJ, Peter MB, Teall TJ, Brannan RA, Hanby AM, Honarpisheh H, et al. Combined analysis of eIF4E and 4E-binding protein expression predicts breast cancer survival and estimates eIF4E activity. Br J Cancer 2009;100:1393–9.
62. Avdulov S, Li S, Michalek V, Burrichter D, Peterson M, Perlman DM, et al. Activation of translation complex eIF4F is essential for the genesis and maintenance of the malignant phenotype in human mammary epithelial cells. Cancer Cell 2004;5:553–63.
63. Proud CG. Signalling to translation: how signal transduction pathways control the protein synthetic machinery. Biochem J 2007;403: 217–34.
64. Dorrello NV, Peschiaroli A, Guardavaccaro D, Colburn NH, Sherman NE, Pagano M. S6K1- and betaTRCP-mediated degradation of PDCD4 promotes protein translation and cell growth. Science 2006;314:467–71.
65. Yang HS, Jansen AP, Komar AA, Zheng X, Merrick WC, Costes S, et al. The transformation suppressor Pdcd4 is a novel eukaryotic translation initiation factor 4A binding protein that inhibits translation. Mol Cell Biol 2003;23:26–37.
66. Jansen AP, Camalier CE, Colburn NH. Epidermal expression of the translation inhibitor programmed cell death 4 suppresses tumorigenesis. Cancer Res 2005;65:6034–41.
67. Levy S, Avni D, Hariharan N, Perry RP, Meyuhas O. Oligopyrimidine tract at the 5¢ end of mammalian ribosomal protein mRNAs is required for their translational control. Proc Natl Acad Sci U S A 1991;88:3319–23.
68. Loreni F, Thomas G, Amaldi F. Transcription inhibitors stimulate translation of 5¢ TOP mRNAs through activation of S6 kinase and the mTOR/FRAP signalling pathway. Eur J Biochem 2000;267: 6594–601.
69. Mayer C, Grummt I. Ribosome biogenesis and cell growth: mTOR coordinates transcription by all three classes of nuclear RNA polymerases. Oncogene 2006;25:6384–91.
70. Michels AA. MAF1: a new target of mTORC1. Biochem Soc Trans 2011;39:487–91.
71. Chan JC, Hannan KM, Riddell K, Ng PY, Peck A, Lee RS, et al. AKT promotes rRNA synthesis and cooperates with c-MYC to stimulate ribosome biogenesis in cancer. Sci Signal 2011;4:ra56.
72. Ma L, Chen Z, Erdjument-Bromage H, Tempst P, Pandolfi PP. Phosphorylation and functional inactivation of TSC2 by Erk implications for tuberous sclerosis and cancer pathogenesis. Cell 2005; 121:179–93.
73. Roux PP, Ballif BA, Anjum R, Gygi SP, Blenis J. Tumor-promoting phorbol esters and activated Ras inactivate the tuberous sclerosis tumor suppressor complex via p90 ribosomal S6 kinase. Proc Natl Acad Sci U S A 2004;101:13489–94.
74. Carrière A, Cargnello M, Julien LA, Gao H, Bonneil E, Thibault P, et al. Oncogenic MAPK signaling stimulates mTORC1 activity by promoting RSK-mediated raptor phosphorylation. Curr Biol 2008;18: 1269–77.
75. Shahbazian D, Roux PP, Mieulet V, Cohen MS, Raught B, Taunton J, et al. The mTOR/PI3K and MAPK pathways converge on eIF4B to control its phosphorylation and activity. EMBO J 2006;25:2781–91.
76. Wang X, Li W, Williams M, Terada N, Alessi DR, Proud CG. Regulation of elongation factor 2 kinase by p90(RSK1) and p70 S6 kinase. EMBO J 2001;20:4370–9.
77. Corradetti MN, Inoki K, Bardeesy N, DePinho RA, Guan KL. Regulation of the TSC pathway by LKB1: evidence of a molecular link between tuberous sclerosis complex and Peutz-Jeghers syndrome. Genes Dev 2004;18:1533–8.
78. Inoki K, Ouyang H, Zhu T, Lindvall C, Wang Y, Zhang X, et al. TSC2 integrates Wnt and energy signals via a coordinated phosphorylation by AMPK and GSK3 to regulate cell growth. Cell 2006;126: 955–68.
79. Cross DA, Alessi DR, Cohen P, Andjelkovich M, Hemmings BA. Inhibition of glycogen synthase kinase-3 by insulin mediated by protein kinase B. Nature 1995;378:785–9.
80. Mishra R. Glycogen synthase kinase 3 beta: can it be a target for oral cancer. Mol Cancer 2010;9:144.
81. Welsh GI, Miller CM, Loughlin AJ, Price NT, Proud CG. Regulation of eukaryotic initiation factor eIF2B: glycogen synthase kinase-3 phosphorylates a conserved serine which undergoes dephosphorylation in response to insulin. FEBS Lett 1998;421:125–30.
82. Horman S, Browne G, Krause U, Patel J, Vertommen D, Bertrand L, et al. Activation of AMP-activated protein kinase leads to the phosphorylation of elongation factor 2 and an inhibition of protein synthesis. Curr Biol 2002;12:1419–23.
83. Gwinn DM, Shackelford DB, Egan DF, Mihaylova MM, Mery A, Vasquez DS, et al. AMPK phosphorylation of raptor mediates a metabolic checkpoint. Mol Cell 2008;30:214–26.
84. Horman S, Vertommen D, Heath R, Neumann D, Mouton V, Woods A, et al. Insulin antagonizes ischemia-induced Thr172 phosphorylation of AMP-activated protein kinase alpha-subunits in heart via hierarchical phosphorylation of Ser485/491. J Biol Chem 2006;281: 5335–40.

Published OnlineFirst July 31, 2012; DOI: 10.1158/0008-5472.CAN-12-0026

85. Hardie DG. AMP-activated protein kinase: an energy sensor that regulates all aspects of cell function. Genes Dev 2011;25:1895–908.
86. Huang X, Wullschleger S, Shpiro N, McGuire VA, Sakamoto K, Woods YL, et al. Important role of the LKB1-AMPK pathway in suppressing tumorigenesis in PTEN-deficient mice. Biochem J 2008;412:211–21.
87. Hawley SA, Ross FA, Chevtzoff C, Green KA, Evans A, Fogarty S, et al. Use of cells expressing gamma subunit variants to identify diverse mechanisms of AMPK activation. Cell Metab 2010;11: 554–65.
88. Göransson O, McBride A, Hawley SA, Ross FA, Shpiro N, Foretz M, et al. Mechanism of action of A-769662, a valuable tool for activation of AMP-activated protein kinase. J Biol Chem 2007;282:32549–60.
89. Cameron AJ, Linch MD, Saurin AT, Escribano C, Parker PJ. mTORC2 targets AGC kinases through Sin1-dependent recruitment. Biochem J 2011;439:287–97.
90. Zinzalla V, Stracka D, Oppliger W, Hall MN. Activation of mTORC2 by association with the ribosome. Cell 2011;144:757–68.
91. Buxade M, Parra-Palau JL, Proud CG. The Mnks: MAP kinase-interacting kinases (MAP kinase signal-integrating kinases). Front Biosci 2008;13:5359–73.
92. Dobrikov M, Dobrikova E, Shveygert M, Gromeier M. Phosphorylation of eukaryotic translation initiation factor 4G1 (eIF4G1) by protein kinase Calpha regulates eIF4G1 binding to Mnk1. Mol Cell Biol 2011;31:2947–59.
93. Mackay HJ, Twelves CJ. Targeting the protein kinase C family: are we there yet? Nat Rev Cancer 2007;7:554–62.
94. Wendel HG, Silva RL, Malina A, Mills JR, Zhu H, Ueda T, et al. Dissecting eIF4E action in tumorigenesis. Genes Dev 2007;21: 3232–7.
95. Fan S, Ramalingam SS, Kauh J, Xu Z, Khuri FR, Sun SY. Phosphorylated eukaryotic translation initiation factor 4 (eIF4E) is elevated in human cancer tissues. Cancer Biol Ther 2009;8:1463–9.
96. Scheper GC, van Kollenburg B, Hu J, Luo Y, Goss DJ, Proud CG. Phosphorylation of eukaryotic initiation factor 4E markedly reduces its affinity for capped mRNA. J Biol Chem 2002;277:3303–9.
97. Topisirovic I, Ruiz-Gutierrez M, Borden KL. Phosphorylation of the eukaryotic translation initiation factor eIF4E contributes to its transformation and mRNA transport activities. Cancer Res 2004;64: 8639–42.
98. Phillips A, Blaydes JP. MNK1 and EIF4E are downstream effectors of MEKs in the regulation of the nuclear export of HDM2 mRNA. Oncogene 2008;27:1645–9.
99. Ueda T, Watanabe-Fukunaga R, Fukuyama H, Nagata S, Fukunaga R. Mnk2 and Mnk1 are essential for constitutive and inducible phosphorylation of eukaryotic initiation factor 4E but not for cell growth or development. Mol Cell Biol 2004;24:6539–49.
100. Knauf U, Tschopp C, Gram H. Negative regulation of protein translation by mitogen-activated protein kinase-interacting kinases 1 and 2. Mol Cell Biol 2001;21:5500–11.
101. Grzmil M, Morin P Jr, Lino MM, Merlo A, Frank S, Wang Y, et al. MAP kinase-interacting kinase 1 regulates SMAD2-dependent TGF-b signaling pathway in human glioblastoma. Cancer Res 2011;71: 2392–402.
102. Wek RC, Jiang HY, Anthony TG. Coping with stress: eIF2 kinases and translational control. Biochem Soc Trans 2006;34:7–11.
103. Bi M, Naczki C, Koritzinsky M, Fels D, Blais J, Hu N, et al. ER stress-regulated translation increases tolerance to extreme hypoxia and promotes tumor growth. EMBO J 2005;24:3470–81.
104. Mounir Z, Krishnamoorthy JL, Wang S, Papadopoulou B, Campbell S, Muller WJ, et al. Akt determines cell fate through inhibition of the PERK-eIF2a phosphorylation pathway. Sci Signal 2011;4:ra62.
105. Jacinto E, Loewith R, Schmidt A, Lin S, Rüegg MA, Hall A, et al. Mammalian TOR complex 2 controls the actin cytoskeleton and is rapamycin insensitive. Nat Cell Biol 2004;6:1122–8.
106. Sarbassov DD, Ali SM, Sengupta S, Sheen JH, Hsu PP, Bagley AF, et al. Prolonged rapamycin treatment inhibits mTORC2 assembly and Akt/PKB. Mol Cell 2006;22:159–68.
107. Faivre S, Kroemer G, Raymond E. Current development of mTOR inhibitors as anticancer agents. Nat Rev Drug Discov 2006;5: 671–88.
108. Dumont FJ, Staruch MJ, Grammer T, Blenis J, Kastner CA, Rupprecht KM. Dominant mutations confer resistance to the immunosuppressant, rapamycin, in variants of a T cell lymphoma. Cell Immunol 1995;163:70–9.
109. Shi Y, Yan H, Frost P, Gera J, Lichtenstein A. Mammalian target of rapamycin inhibitors activate the AKT kinase in multiple myeloma cells by up-regulating the insulin-like growth factor receptor/insulin receptor substrate-1/phosphatidylinositol 3-kinase cascade. Mol Cancer Ther 2005;4:1533–40.
110. Hsieh AC, Costa M, Zollo O, Davis C, Feldman ME, Testa JR, et al. Genetic dissection of the oncogenic mTOR pathway reveals druggable addiction to translational control via 4EBP-eIF4E. Cancer Cell 2010;17:249–61.
111. Yu K, Shi C, Toral-Barza L, Lucas J, Shor B, Kim JE, et al. Beyond rapalog therapy: preclinical pharmacology and antitumor activity of WYE-125132, an ATP-competitive and specific inhibitor of mTORC1 and mTORC2. Cancer Res 2010;70:621–31.
112. Liu Q, Chang JW, Wang J, Kang SA, Thoreen CC, Markhard A, et al. Discovery of 1-(4-(4-propionylpiperazin-1-yl)-3-(trifluoromethyl)phenyl)-9-(quinolin-3-yl)benzo[h][1,6]naphthyridin-2(^{1}H)-one as a highly potent, selective mammalian target of rapamycin (mTOR) inhibitor for the treatment of cancer. J Med Chem 2010;53:7146–55.
113. Chresta CM, Davies BR, Hickson I, Harding T, Cosulich S, Critchlow SE, et al. AZD8055 is a potent, selective, and orally bioavailable ATP-competitive mammalian target of rapamycin kinase inhibitor with in vitro and in vivo antitumor activity. Cancer Res 2010;70:288–98.
114. Carayol N, Vakana E, Sassano A, Kaur S, Goussetis DJ, Glaser H, et al. Critical roles for mTORC2- and rapamycin-insensitive mTORC1-complexes in growth and survival of BCR-ABL-expressing leukemic cells. Proc Natl Acad Sci U S A 2010;107:12469–74.
115. Fan QW, Knight ZA, Goldenberg DD, Yu W, Mostov KE, Stokoe D, et al. A dual PI3 kinase/mTOR inhibitor reveals emergent efficacy in glioma. Cancer Cell 2006;9:341–9.
116. Kharas MG, Janes MR, Scarfone VM, Lilly MB, Knight ZA, Shokat KM, et al. Ablation of PI3K blocks BCR-ABL leukemogenesis in mice, and a dual PI3K/mTOR inhibitor prevents expansion of human BCR-ABL+ leukemia cells. J Clin Invest 2008;118:3038–50.
117. Maiso P, Liu Y, Morgan B, Azab AK, Ren P, Martin MB, et al. Defining the role of TORC1/2 in multiple myeloma. Blood 2011;118:6860–70.
118. Li T, Wang J, Wang X, Yang N, Chen SM, Tong LJ, et al. WJD008, a dual phosphatidylinositol 3-kinase (PI3K)/mammalian target of rapamycin inhibitor, prevents PI3K signaling and inhibits the proliferation of transformed cells with oncogenic PI3K mutant. J Pharmacol Exp Ther 2010;334:830–8.
119. Leung E, Kim JE, Rewcastle GW, Finlay GJ, Baguley BC. Comparison of the effects of the PI3K/mTOR inhibitors NVP-BEZ235 and GSK2126458 on tamoxifen-resistant breast cancer cells. Cancer Biol Ther 2011;11:938–46.
120. Huo Y, Iadevaia V, Proud CG. Differing effects of rapamycin and mTOR kinase inhibitors on protein synthesis. Biochem Soc Trans 2011;39:446–50.
121. Werzowa J, Koehrer S, Strommer S, Cejka D, Fuereder T, Zebedin E, et al. Vertical inhibition of the mTORC1/mTORC2/PI3K pathway shows synergistic effects against melanoma in vitro and in vivo. J Invest Dermatol 2011;131:495–503.
122. Wang X, Yue P, Chan CB, Ye K, Ueda T, Watanabe-Fukunaga R, et al. Inhibition of mammalian target of rapamycin induces phosphatidylinositol 3-kinase-dependent and Mnk-mediated eukaryotic translation initiation factor 4E phosphorylation. Mol Cell Biol 2007;27: 7405–13.
123. Bianchini A, Loiarro M, Bielli P, Busà R, Paronetto MP, Loreni F, et al. Phosphorylation of eIF4E by MNKs supports protein synthesis, cell cycle progression and proliferation in prostate cancer cells. Carcinogenesis 2008;29:2279–88.
124. Marzec M, Liu X, Wysocka M, Rook AH, Odum N, Wasik MA. Simultaneous inhibition of mTOR-containing complex 1 (mTORC1) and MNK induces apoptosis of cutaneous T-cell lymphoma (CTCL) cells. PLoS ONE 2011;6:e24849.
125. Ueda T, Sasaki M, Elia AJ, Chio II, Hamada K, Fukunaga R, et al. Combined deficiency for MAP kinase-interacting kinase 1 and 2

Published OnlineFirst July 31, 2012; DOI: 10.1158/0008-5472.CAN-12-0026

(Mnk1 and Mnk2) delays tumor development. Proc Natl Acad Sci U S A 2010;107:13984–90.
126. Konicek BW, Stephens JR, McNulty AM, Robichaud N, Peery RB, Dumstorf CA, et al. Therapeutic inhibition of MAP kinase interacting kinase blocks eukaryotic initiation factor 4E phosphorylation and suppresses outgrowth of experimental lung metastases. Cancer Res 2011;71:1849–57.
127. Graff JR, Konicek BW, Vincent TM, Lynch RL, Monteith D, Weir SN, et al. Therapeutic suppression of translation initiation factor eIF4E expression reduces tumor growth without toxicity. J Clin Invest 2007;117:2638–48.
128. Kentsis A, Topisirovic I, Culjkovic B, Shao L, Borden KL. Ribavirin suppresses eIF4E-mediated oncogenic transformation by physical mimicry of the 7-methyl guanosine mRNA cap. Proc Natl Acad Sci U S A 2004;101:18105–10.
129. Assouline S, Culjkovic B, Cocolakis E, Rousseau C, Beslu N, Amri A, et al. Molecular targeting of the oncogene eIF4E in acute myeloid leukemia (AML): a proof-of-principle clinical trial with ribavirin. Blood 2009;114:257–60.
130. Moerke NJ, Aktas H, Chen H, Cantel S, Reibarkh MY, Fahmy A, et al. Small-molecule inhibition of the interaction between the translation initiation factors eIF4E and eIF4G. Cell 2007;128:257–67.
131. Bordeleau ME, Cencic R, Lindqvist L, Oberer M, Northcote P, Wagner G, et al. RNA-mediated sequestration of the RNA helicase eIF4A by Pateamine A inhibits translation initiation. Chem Biol 2006;13: 1287–95.
132. Kuznetsov G, Xu Q, Rudolph-Owen L, Tendyke K, Liu J, Towle M, et al. Potent in vitro and in vivo anticancer activities of des-methyl, des-amino pateamine A, a synthetic analogue of marine natural product pateamine A. Mol Cancer Ther 2009;8:1250–60.
133. Cencic R, Carrier M, Galicia-Vázquez G, Bordeleau ME, Sukarieh R, Bourdeau A, et al. Antitumor activity and mechanism of action of the cyclopenta[b]benzofuran, silvestrol. PLoS ONE 2009;4:e5223.
134. Lucas DM, Edwards RB, Lozanski G, West DA, Shin JD, Vargo MA, et al. The novel plant-derived agent silvestrol has B-cell selective activity in chronic lymphocytic leukemia and acute lymphoblastic leukemia in vitro and in vivo. Blood 2009;113:4656–66.
135. Bordeleau ME, Mori A, Oberer M, Lindqvist L, Chard LS, Higa T, et al. Functional characterization of IRESes by an inhibitor of the RNA helicase eIF4A. Nat Chem Biol 2006;2:213–20.
136. Tsumuraya T, Ishikawa C, Machijima Y, Nakachi S, Senba M, Tanaka J, et al. Effects of hippuristanol, an inhibitor of eIF4A, on adult T-cell leukemia. Biochem Pharmacol 2011;81:713–22.
137. Shi XP, Yin KC, Ahern J, Davis LJ, Stern AM, Waxman L. Effects of N1-guanyl-1,7-diaminoheptane, an inhibitor of deoxyhypusine synthase, on the growth of tumorigenic cell lines in culture. Biochim Biophys Acta 1996;1310:119–26.
138. Clement PM, Hanauske-Abel HM, Wolff EC, Kleinman HK, Park MH. The antifungal drug ciclopirox inhibits deoxyhypusine and proline hydroxylation, endothelial cell growth and angiogenesis in vitro. Int J Cancer 2002;100:491–8.
139. Zhou H, Shen T, Luo Y, Liu L, Chen W, Xu B, et al. The antitumor activity of the fungicide ciclopirox. Int J Cancer 2010;127:2467–77.
140. Jasiulionis MG, Luchessi AD, Moreira AG, Souza PP, Suenaga AP, Correa M, et al. Inhibition of eukaryotic translation initiation factor 5A (eIF5A) hypusination impairs melanoma growth. Cell Biochem Funct 2007;25:109–14.
141. Eberhard Y, McDermott SP, Wang X, Gronda M, Venugopal A, Wood TE, et al. Chelation of intracellular iron with the antifungal agent ciclopirox olamine induces cell death in leukemia and myeloma cells. Blood 2009;114:3064–73.
142. Jastrzebski K, Hannan KM, House CM, Hung SS, Pearson RB, Hannan RD. A phospho-proteomic screen identifies novel S6K1 and mTORC1 substrates revealing additional complexity in the signaling network regulating cell growth. Cell Signal 2011;23: 1338–47.

Published OnlineFirst July 31, 2012; DOI: 10.1158/0008-5472.CAN-12-0026

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