

Review

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-depend-

ent 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

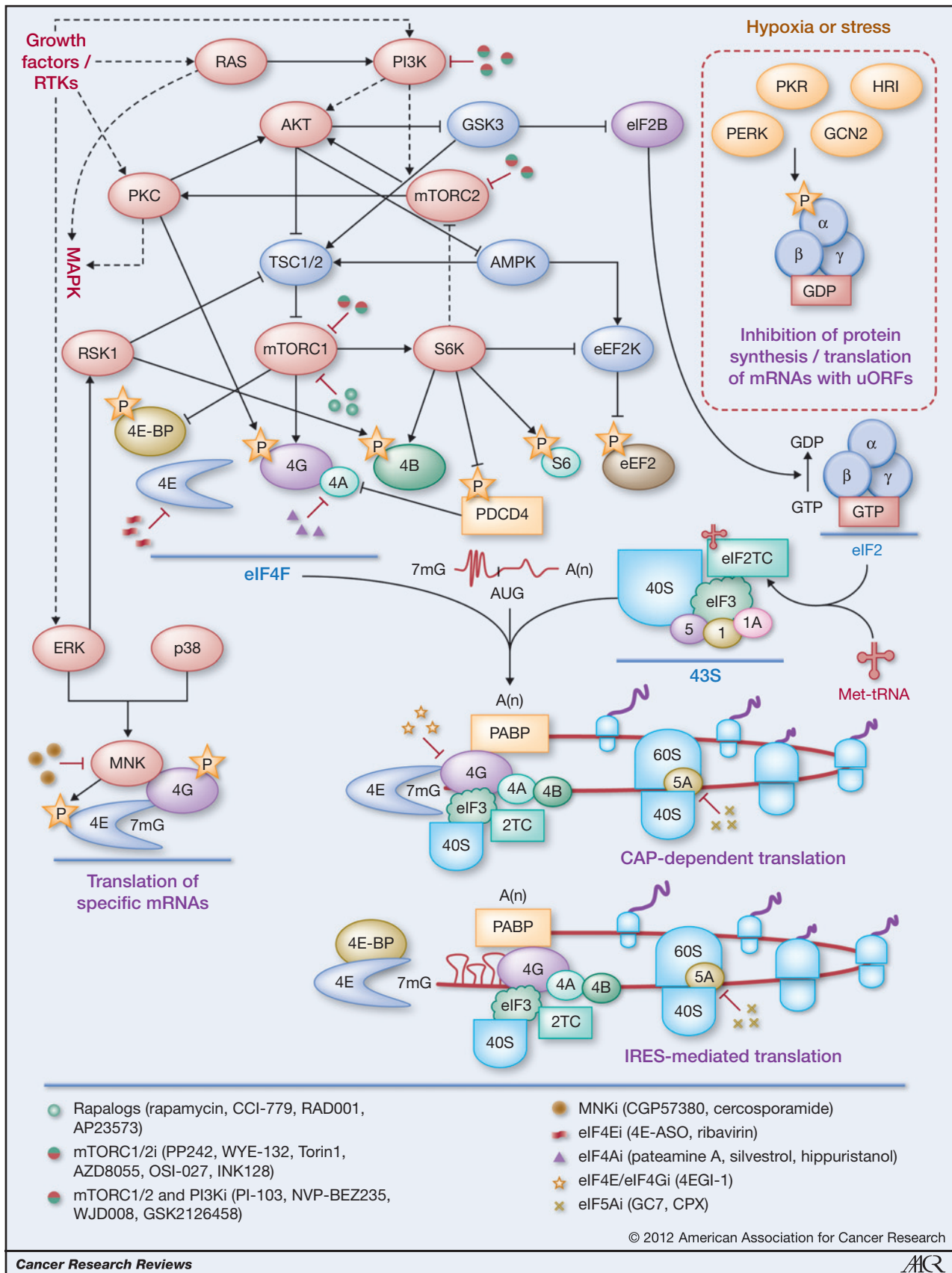
During cancer progression, cells are constantly exposed to different types of stress. Rapid responses based on the accurate expression of particular proteins may allow their further growth and survival. Translation regulation is a rapid and

Authors' Affiliation: Friedrich Miescher Institute for Biomedical Research, Basel, Switzerland

Corresponding Author: Michal Grzmil, Friedrich Miescher Institute for Biomedical Research, Maulbeerstrasse 66, CH-4058 Basel, Switzerland. Phone: 41-61-6978565; Fax: 41-61-6973976; E-mail: michal.grzmil@fmi.ch

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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)-1 α (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 eIF2 α 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.

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 eIF2 α 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 eIF2 α 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). Nev-

ertheless, 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 eIF4B (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 AMPK α 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

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 PKC α 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 eIF2 α 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 eIF2 α phosphorylation and maintained eIF2 α in an unphosphorylated state in proliferating cancer cells (104). Phosphorylated eIF2 α 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-1 α (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-BE235, 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-

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, hippur-

istol, 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. Grznil, B.A. Hemmings

Writing, review, and/or revision of the manuscript: M. Grznil, B.A. Hemmings

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Michal Grzmil and Brian A. Hemmings

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