

Targeting translation initiation in breast cancer

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List of abbreviations: 4E-BP, eukaryotic initiation factor 4E-binding protein; CI, confidence interval; eEF2, eukaryotic elongation factor 2; eEF2K, eukaryotic elongation factor 2 kinase; eIF, eukaryotic initiation factor; eIF2, eukaryotic initiation factor 2; eIF4A, eukaryotic initiation factor 4A; eIF4E, eukaryotic initiation factor 4E; eIF4G, eukaryotic initiation factor 4G; HR, hazard ratio; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; MAPK, mitogen-activated protein kinase; Mnk, MAPK-interacting kinase; mTOR, mammalian target of rapamycin; mTORC1, mTOR complex 1; MUC1, mucin 1; p-4E-BP1, phosphorylated eukaryotic initiation factor 4E-binding protein 1; PI3K, phosphatidylinositol 3-hydroxy kinase; pcdcd4, programmed cell death 4; PFS, progression-free survival; S6, ribosomal protein S6; S6K1, S6 kinase 1.

Over the past 20 years, a better understanding of cancer biology, screening for early detection, improved adjuvant treatment, and targeted therapies have decreased the rate of breast cancer deaths. However, resistance to treatment is common, and new approaches are needed. Deregulation of translation initiation is associated with the commencement and progression of cancer. Often, translation initiation factors are overexpressed and the related signaling pathways activated in human tumors. Recently, a significant number of inhibitors that target translation factors and pathways have become available. These inhibitors are being tested alone or in combination with chemotherapeutic agents in clinical trials. The results are varied, and it is not yet clear which drug treatments most effectively inhibit tumor growth. This review highlights the pathways and downstream effects of the activation of translation and discusses targeting the control of translation initiation as a therapeutic approach in cancer, focusing on breast cancer clinical trials.

Regulation of mRNA translation to protein is a major point of control for gene expression. Recently, deregulation of protein synthesis and its involvement in cancer development have become the subject of much discussion.²⁻⁶ Cancer cells are at a metabolically demanding state, which requires an increase in protein synthesis. Thus, sustained activation of protein expression may not only initiate but also maintain cancer growth. In addition, to increase overall protein synthesis, deregulation results in the activation of signaling pathways and synthesis of various proteins³ required for tumorigenesis. These proteins may facilitate cancer progression or help cancer cells develop resistance to treatment. Therefore, alterations in translation may activate major survival pathways. A significant amount of data suggests that translation initiation is an integral part of carcinogenesis, including breast cancer development. This review discusses the rapidly growing field of translation initiation inhibition in breast cancer.

A Summary of Translational Control

mRNA translation to protein can be divided into four stages: initiation, elongation, termination, and ribosome recycling.⁷ Translation initiation is the limiting step in this process.⁸ In higher eukaryotes, including humans, most mRNA translation is cap-dependent, relying on the complex of proteins that assemble at the 5' end of mRNA, which contains the 7-methylguanosine cap (5' cap) structure.^{7,9,10} This complex, called the eukaryotic initiation factor (eIF) 4F (eIF4F) complex, consists of the cap-binding protein eIF4E, the scaffold protein eIF4G, and the RNA helicase protein eIF4A. Polyadenylate-binding protein attaches to the 3' poly(A) tail and to eIF4G and brings the 3' and 5' ends of mRNA together.¹¹ This is followed by the binding of eIF4B, which interacts with eIF4F and eIF4A, further stabilizing the complex. Meanwhile, the 40S ribosomal subunit binds to additional initiation factors and a ternary complex (eIF2/GTP/met-tRNA) to form the 43S pre-initiation complex. Interacting with eIF3 and the scaffolding protein eIF4G, the 43S complex binds to the 5' cap. The cap-initiation complex scans the mRNA in a 5'-to-3' direction until it encounters a start codon. Recognition of a start codon results in hydrolysis of GTP bound to eIF2 and release of eIFs proteins. Once the 40S subunit is positioned and

Introduction

Breast cancer is the second-most frequently diagnosed cancer and is the second-most frequent cause of cancer-related death in women.¹ In the past decade, its incidence rates have not decreased. However, since 1989, early detection and better treatment have decreased mortality rates from breast cancer. Current treatment options include surgical removal of the tumor and radiation therapy (depending on surgery type and clinical variables), and with recurrence, chemotherapy in the adjuvant or neoadjuvant setting, endocrine therapy (e.g., estrogen response modifiers, aromatase inhibitors, and ovarian ablation), and recently, targeted therapy.

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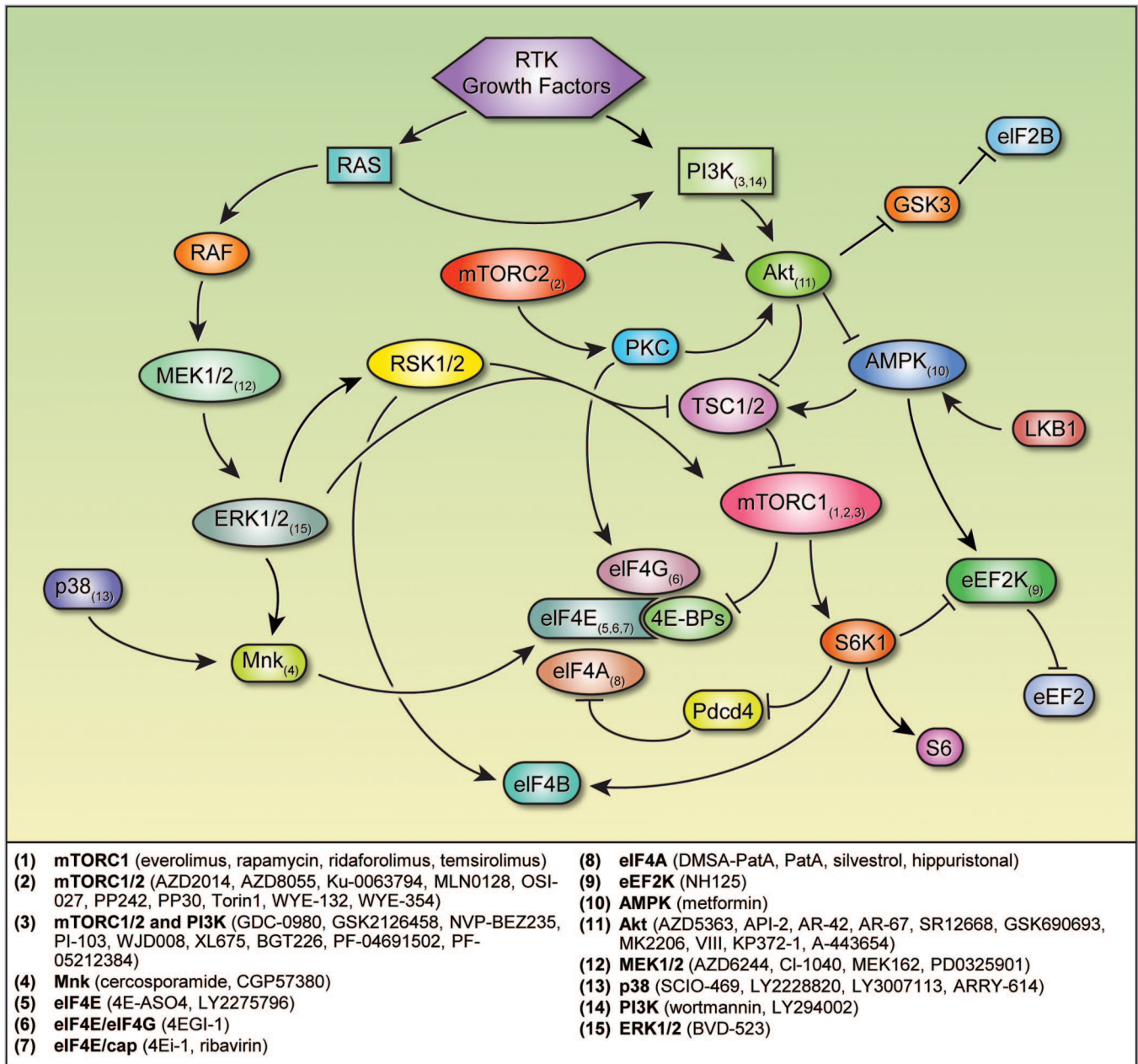


Figure 1. Regulatory networks involved in translation initiation and points of inhibition. Arrows represent activation, and bars represent inhibition. Small-molecule inhibitors of the signaling nodes are listed below. Abbreviations: 4E-BP, eukaryotic initiation factor 4E-binding protein; AMPK, adenosine monophosphate-activated protein kinase; eEF2, eukaryotic elongation factor 2; eEF2K, eukaryotic elongation factor 2 kinase; eIF2B, eukaryotic initiation factor 2B; eIF4A, eukaryotic initiation factor 4A; eIF4B, eukaryotic initiation factor 4B; eIF4E, eukaryotic initiation factor 4E; eIF4G, eukaryotic initiation factor 4G; GSK3, glycogen synthase kinase 3; Mnk, MAPK-interacting kinase; mTORC1/2, mTOR complex 1/2; RSK 1/2, p90 ribosomal S6 kinase 1/2; PI3K, phosphatidylinositol 3-hydroxy kinase; pdc4, programmed cell death 4; RTK, receptor tyrosine kinase; S6, ribosomal protein S6; S6K1, S6 kinase 1; TSC1/2, tuberous sclerosis 1/2.

the 60S subunit recruited, an elongation-competent 80S ribosome is formed, ready to begin protein synthesis.

Major signaling pathways, such as the phosphatidylinositol 3-hydroxy kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway, also participate in translation initiation. These steps indicate that deregulation of translation initiation can have a key role in cancer development and maintenance. Therefore, targeting the factors and pathways involved in this process with

inhibitors may offer novel treatment options for overcoming resistance to chemotherapeutics.

Activation of mitogen-activated protein kinases (MAPKs), PI3K/Akt/mTOR signaling, RAS signaling, and receptor tyrosine kinases, such as human epidermal growth factor receptor 2 (HER2), EGFR, and IGF1R, may contribute to tumor growth and aggressiveness (Fig. 1). These pathways regulate both global translation and the translation of specific mRNAs that take part

in cell proliferation and survival. The PI3K/Akt/mTOR pathway is deregulated through several mechanisms, including overexpression or activation of growth factor receptors (including HER2), mutation or amplification of PI3K or of Akt, amplification or overexpression of PDK1, and decreased expression of tumor suppressor phosphatase and tensin homolog.^{12,13} Akt controls translation initiation mainly through activation of mTOR complex 1 (mTORC1).¹³ mTORC1 phosphorylates eIF4E-binding proteins (4E-BPs). The 4E-BPs compete with eIF4G for binding to eIF4E, thus preventing eIF4G recruitment. Once hypophosphorylated, 4E-BPs release and activate eIF4E. Increased availability of eIF4E is associated with progression and poor survival in several types of cancer, including breast cancer.^{14,15} In addition, mTORC1 regulates cell growth through ribosomal proteins S6 kinase 1 (S6K1) and S6 kinase 2. Phosphatase and tensin homolog, tuberous sclerosis 1, and tuberous sclerosis 2 mutations also activate S6K1 and S6 kinase 2. S6K1 phosphorylates eIF4B, which in turn stimulates eIF4A helicase activity.

Translation elongation also is regulated by Akt/mTOR signaling.¹³ In this process, a charged tRNA docks onto the ribosome/mRNA complex and adds amino acids into the growing polypeptide, and the process is repeated.¹⁶ Further down, S6K1 phosphorylates and inhibits eukaryotic elongation factor 2 (eEF2) kinase (eEF2K), which is a negative regulator of eEF2, which catalyzes the translocation of the tRNA from the A-site to the P-site of the ribosome. S6 proposed to phosphorylate and regulate both the activity and the protein stability of programmed cell death 4 (pdc4).¹⁷⁻¹⁹ In addition, S6K1 regulates estrogen receptor α activation.²⁰ Overall, S6K1 promotes tumor progression suggesting additional involvement of Akt/mTOR signaling in poor outcomes in cancer.

Akt/mTOR signaling also regulates ribosome biosynthesis,¹³ which involves transcription and folding of pre-rRNAs, the folding and assembly of these RNAs with ribosomal proteins, and transport of these complexes to the cytoplasm for maturation. Akt signaling regulates ribosomal biogenesis by controlling the synthesis of rRNAs and ribosomal proteins. However, it is not clear whether activated Akt signaling increases ribosomal biogenesis and in turn increases protein synthesis.¹³

Lastly, another mechanism of translation initiation, internal ribosome entry site-mediated translation, may also be regulated by Akt. This mechanism uses secondary RNA structures called internal ribosome entry sites (which are located mostly in the 5' untranslated region of mRNA) to initiate translation in an eIF4E- and cap-independent manner and is thought to take part in translation of key mRNAs under conditions such as hypoxia, starvation, and DNA damage-inducing therapy.²¹ These mRNAs encode proteins such as BCL-2, c-MYC, hypoxia-inducible factor-1 α , vascular endothelial growth factor, and XIAP.²²⁻²⁶

Translational Control in Breast Cancer and Other Cancers

A significant amount of data suggests a relationship between translational control and breast cancer. A recent study showed that alterations in several translational regulators were associated

with clinical-pathologic factors and with survival outcomes in hormone receptor-positive breast cancer.²⁷ High eEF2, S6, phosphorylated S6, and phosphorylated 4E-BP1 (p-4E-BP1) levels were associated with lymph node metastasis. High 4E-BP1 and p-4E-BP1 levels were associated with poor relapse-free survival. High p-4E-BP1, high phosphorylated S6, and low pdc4 levels were associated with poor overall survival. In multivariate analysis, lymph node metastasis and high p-4E-BP1 level were predictors of shorter relapse-free survival, and high phosphorylated S6, high eEF2K, and low pdc4 were associated with poor overall survival. Thus, this study confirmed an association between deregulation of translation and worse breast cancer outcomes. These results are consistent with those of another study, where PI3K pathway activation predicted poor outcomes after endocrine therapy in 64 patients with hormone receptor-positive breast cancer.²⁸

eIF3 subunits

In mammals, eIF3 is the largest scaffolding initiation factor, made up of 13 proteins.³ It is involved in bridging the interaction between the 43S pre-initiation complex and eIF4F-bound mRNA. Several of its subunits take part in global protein expression, whereas others are involved in regulation of the eIF3 complex or interaction with specific mRNAs.

Alterations in expression of the eIF3 subunits -a, -b, -c, -h, and -i have been associated with oncogenic properties, such as increased cell growth, in vitro.²⁹ Of these, expression subunits -a, -c, and -h are increased in human cancers. For instance, eIF3a is overexpressed in breast, lung, cervix, stomach and esophagus cancers.^{30,31} eIF3a regulates mRNAs that inhibit the cell cycle and is required to maintain the malignant phenotype.^{32,33} eIF3c is overexpressed in seminomas and meningiomas.^{34,35} The oncogenic properties associated with eIF3c overexpression, such as high proliferation, are thought to result from the activation of translation and protein synthesis and the inactivation of the tumor suppressor merlin.^{29,35} In addition, in 18% of untreated primary breast tumors, *EIF3H* was amplified.³⁶ The chromosomal location of *EIF3H* is adjacent to that of the proto-oncogene *MYC*, and they are frequently amplified together.

Conversely, eIF3f expression is suppressed in several cancers, including breast cancer.³⁷ Overexpression of eIF3f inhibits cell proliferation, induces apoptosis, and inhibits translation and protein expression.³⁷ eIF3e binds both to eIF4G and to 40S, thus generating an interaction between the eIF4F complex and the ribosome.³⁸ Several studies support a tumor suppressor role for eIF3e. Increased expression of truncated eIF3e induces malignant transformation of normal mammary cells in vitro.³⁹ The *EIF3E* gene was found to have reduced expression in 37% and loss of heterozygosity in 21% of human breast cancers, implicating a loss of EIF3 activity in the development and progression of breast cancer.⁴⁰ In tamoxifen-treated breast cancer patients, high levels of EIF3E were significantly associated with prolonged progression-free survival and with therapy resistance.⁴¹ A recent study reported that decreased expression of eIF3e induced epithelial-mesenchymal transition, invasive and migratory properties in breast epithelial cells, and an increase in the expression of key epithelial-mesenchymal transition regulators.⁴² However, the loss of

eIF3e expression reportedly did not significantly decrease global protein synthesis, although it did increase translation of mRNAs involved in cell proliferation, invasion, and apoptosis.^{43,44} Also, in primary breast cancer patients, eIF3e expression correlated positively with tumor grade.⁴⁴ These findings imply that eIF3e upregulates translation of oncoproteins, which conflicts with its tumor suppressor role. The exact function of eIF3e in breast cancer is not clear yet.

eIF4A

mTORC1 can activate cap-dependent translation by phosphorylating S6K. Activated S6K results in degradation of pdc4, which is an eIF4A inhibitor, thus enhancing eIF4A activity.¹⁷ The eIF4A helicase in turn initiates translation by unwinding highly structured 5' untranslated regions in mRNAs.⁴⁵ eIF4A is overexpressed in primary hepatocellular carcinomas⁴⁶ and melanoma cell lines⁴⁷; beyond this, the role of eIF4A in cancer has not been well documented.

The overexpression of Mucin 1 (MUC1) in transgenic mice is associated with the formation of breast tumors.⁴⁸ MUC1 C-terminal (MUC1-C) subunit interacts with epidermal growth factor receptor (EGFR) and other receptor tyrosine kinases.⁴⁹ Translation MUC1-C is regulated by mTOR/S6K/programmed cell death protein 4 (pdc4), which is an inhibitor of eIF4A.⁵⁰ Growth factor stimulation of MUC1 expression in vitro is inhibited by the eIF4A inhibitors silvestrol and CR-1-31-B, which points to eIF4A as a potential target in the treatment of breast cancer in patients with high MUC1 expression.⁵⁰ Furthermore, silvestrol has shown antitumor activity in mouse lymphoma and leukemia models, supporting the use of eIF4A inhibition for cancer treatment.⁵¹⁻⁵³

eIF4E, eIF4G, and 4E-BPs

The most well-known oncogenic alteration in translation is overexpression of eIF4E. The availability of eIF4E is controlled by its binding with 4E-BPs and its phosphorylation by MAPK-interacting kinases (Mnks) 1 and 2.^{54,55} However, eIF4E expression and phosphorylation levels in nontransformed mammary epithelial cells and in breast cancer cells do not significantly differ; instead, eIF4G1 protein expression and 4E-BP1 phosphorylation were greater in the transformed cells than in the nontransformed cells.⁵⁶ Thus, breast cancer cells can use not only eIF4E but also eIF4G and phosphorylation of 4E-BP1 to activate the eIF4F complex.

Increased activity of eIF4E regulates the selective expression of proteins such as cyclin D1, Bcl-2, Bcl-xL, and vascular endothelial growth factor by boosting nucleocytoplasmic transport for selected mRNAs, such as cyclin D1, and upregulating Nijmegen breakage syndrome protein 1 to activate Akt.⁵⁷⁻⁶³ These proteins are involved in cellular growth, angiogenesis, survival, and tumorigenesis. Until recently, this selective translation of mRNAs was not explained thoroughly. In addition to cap binding, eIF4E has been shown to stimulate eIF4A helicase by binding to eIF4G⁶⁴; the eIF4E/eIF4G binding interaction throughout scanning likely explains the selective translation of highly structured mRNAs.⁶⁴

The association between eIF4E and cancer has been demonstrated preclinically and clinically observed. eIF4E overexpression has contributed to the transformation of fibroblasts and

mammary epithelial cells, enabling uncontrolled cell proliferation.⁶⁵ In transgenic mice, eIF4E overexpression initiates the formation of tumors with various histologies, including B-cell lymphomas, angiosarcomas, lung adenocarcinomas, and hepatocellular adenomas.⁶⁶ Also, ectopic expression of eIF4E in vitro repairs the defect in eIF4F formation due to drugs targeting HER2 and EGFR, whereas high eIF4E expression has been associated with incomplete response in patients receiving anti-HER therapies, and thus is a potential marker of resistance.⁶⁷ eIF4E overexpression has been shown in breast, bladder, cervix, colorectal, head and neck, lung, prostate, and skin cancers, as well as lymphomas.^{3,57} In breast cancer, high eIF4E has been suggested as an indicator of increased cancer recurrence and risk of death, and several clinical studies show that high eIF4E indicates a poor prognosis independently of nodal or HER2 status.^{15,68-72}

Another mediator of translation initiation is the binding and unbinding of eIF4E by 4E-BPs, which compete with eIF4G for a eIF4E binding site. Hyperphosphorylation of 4E-BPs decreases this binding and inactivates the 4E-BPs, increasing eIF4E availability to engage in the cap-complex and to activate eIF4F. Conversely, phosphorylated 4E-BPs bind to eIF4E and remove eIF4G, thereby inhibiting translation initiation.

Low total 4E-BP1 levels in prostate cancer patients were associated with shorter survival than normal 4E-BP1 expression was.⁷³ Similarly, higher p-4E-BP1 levels in advanced prostate cancer were associated with shorter survival.⁷³ In breast cancer, increased eIF4E and p-4E-BP1 levels correlate with higher tumor grade and shorter survival, whereas increased expression of total 4E-BP1 and 4E-BP2 is associated with lower tumor grade.⁷⁴ In these studies, both the loss of 4E-BP1 expression, and increased p-4E-BP1 and eIF4E levels indicate poor prognosis.

However, contradicting data show that total 4E-BP1 and eIF4G are overexpressed in large advanced breast cancers.⁷⁵ Under hypoxia, elevated levels of these two proteins inhibit cap-dependent translation and facilitate selective translation of mRNAs that contain internal ribosome entry sites, promoting tumor angiogenesis and growth.⁷⁵

In a recent study, protein phosphatase PPM1G dephosphorylated 4E-BP1 and negatively regulated protein translation in vitro.⁷⁶ A time course experiment showed that 4E-BP1 dephosphorylation by amino acid starvation or by mTOR inhibition was significantly delayed in PPM1G knockdown cells.⁷⁶ It is not yet known whether PPM1G expression affects the prognosis of cancer patients.

Like eIF4E overexpression, overexpression of eIF4G1 in vitro leads to malignant transformation.⁷⁷ eIF4G may contribute to this transformation by promoting cap-dependent translation by forming active eIF4F or by increasing translation of internal ribosome entry site-dependent mRNAs.⁴ In contrast, decreased eIF4G1 expression impairs cell proliferation and bioenergetics and promotes autophagy by inhibiting translation of mRNAs.⁷⁸ The significant overexpression of eIF4G and 4E-BP1 in locally advanced breast cancers was shown to result in a hypoxia-activated shift from cap-dependent translation to cap-independent translation.⁷⁵ This shift results in cap-independent translation of mRNAs such as vascular endothelial growth factor

(pro-angiogenic), hypoxia-inducible factor-1 α (hypoxia stress-induced), and Bcl2 (survival-promoting), increasing tumor angiogenesis and local tumor growth. Indeed, in inflammatory breast cancer, most tumors show overexpression of eIF4G1 without any change in levels of eIF4E and 4E-BP1.⁷⁹ eIF4G1 also promotes cap-independent translation of mRNAs that are responsible for tumor cell emboli and invasion.

The eIF4F complex and its components eIF4E, eIF4G, and eIF4A are widely studied and are a major focus of therapeutic interventions.^{5,63} New inhibitors that target various mechanisms within this complex are emerging. These developments should provide new insights into translational control in cancer and should open new therapeutic possibilities.

Translation Elongation via eEF2K and eEF2

Many signaling pathways control eEF2K activity, and these signals are relayed through eEF2. For example, MAPK and mTOR pathways inhibit eEF2K in response to nutrient and growth factor signals, whereas adenosine monophosphate-activated protein kinase, PKA, and calmodulin activate eEF2K in response to energy- and Ca²⁺-dependent signaling.⁸⁰ eEF2K downregulates eEF2 to inhibit protein synthesis when conservation of resources is necessary. eEF2K/eEF2 signaling may promote cancer cell survival under stress conditions, such as starvation, hypoxia, or autophagy.⁸¹ The activity of eEF2 is increased in several cancer cell lines and tumor types including ovarian, gastric, and colon cancer.⁸²⁻⁸⁴ In gastric cancer cell lines, eEF2 overexpression promotes progression in the cell cycle, inactivates eEF2K, and activates Akt and cdc2.⁸⁴ eEF2K upregulates autophagy, and its inhibition activates apoptosis.^{81,85} eEF2K is upregulated in malignant rat glial cells and in human melanoma and breast cancer.⁸⁶⁻⁸⁹ In a mouse model of triple-negative breast cancer, systemic administration of eEF2K siRNA downregulated eEF2K expression and eEF2 phosphorylation, leading to inhibition of tumor growth.⁹⁰ Overexpression of these proteins in cancer makes them targets for treatment.

Additional Translation Mechanisms

Pcd4

Pcd4 is a tumor suppressor protein that inhibits cancer cell invasion, and its expression is often decreased in breast cancer.⁹¹ It inhibits translation of specific mRNAs, with downstream effects on cell signaling and oncogenic mRNA transcription.⁹² Pcd4 also binds eIF4A and thus inhibits the formation and function of the eIF4F complex.⁹³ It is downregulated by tumor promoters and undergoes degradation by β -TrCP after phosphorylation by S6K1.^{17,94}

Unfolded protein response

Endoplasmic reticulum stress induces selective translation in cancer cells. Unfolded protein response heals the damage from this stress and restores endoplasmic reticulum homeostasis. To reduce the influx of nascent peptides into overloaded endoplasmic reticulum, a protein kinase, PERK, phosphorylates eIF2.⁹⁵ This phosphorylation also aids translation of stress-related

mRNAs.⁹⁵ Glucose-related protein 78 has a central role in the unfolded protein response; it is overexpressed in many cancers and usually associated with poor response.⁹⁶

MicroRNAs

MicroRNAs are non-coding RNAs that play important roles in all biologic pathways. They also regulate several cancer-related processes such as proliferation and apoptosis.⁹⁷ Several studies address the relationships between microRNAs and cancer and between microRNAs and translation initiation.^{97,98}

The roles of the unfolded protein response and microRNAs in cancer are beyond the scope of this review, but considering the important steps that they control, they are potential platforms for development of novel cancer treatments.

Targeting of Proteins Involved in Protein Synthesis

Several approaches to altering the rate of translation are in development, pursuing translation initiation as a therapeutic target. Of the factors that are involved in translational control and summarized above, eIF4E and 4E-BPs are prominent potential targets. eIF4E is required for cap-dependent translation; however, decreased eIF4E levels appear to have no effect on normal tissues, rendering cancer tissue more susceptible to targeting of this factor.⁹⁹ siRNA knockdown of eIF4E inhibits cancer cell growth in a variety of breast cancer cell lines.¹⁰⁰ In addition, treatment with second-generation antisense oligonucleotides targeting eIF4E (4E-ASO4) reduces tumor growth in nude mice bearing human prostate and breast cancer xenografts.¹⁰¹ A phase I trial of the eIF4E-targeting antisense oligonucleotide LY2275796 was recently completed¹⁰²; the treatment was well tolerated and tumor eIF4E expression suppressed, but no objective tumor responses were observed. The efficacy of eIF4E antisense oligonucleotides in combination with chemotherapy is still being evaluated in clinical trials.^{103,104}

eIF4E inhibitor 1, a cap analog competing with the cap structure for binding to eIF4E, inhibited cap-dependent translation in zebrafish embryos and prevented eIF4E-initiated epithelial-mesenchymal transition in zebrafish ectoderms.¹⁰⁵ Another physical mimic of the 7-methylguanosine cap structure, ribavirin, competes with eIF4E binding and disrupts transport and translation of mRNAs regulated by eIF4E.⁹⁹ Of 11 acute myeloid leukemia cases treated with ribavirin, there was one complete remission and two partial remissions, and reduced eIF4E levels after the treatment were associated with clinical response.¹⁰⁶ Unfortunately, these responses were transient, and all patients developed resistance in months.¹⁰⁷ Most of the following trials of ribavirin in acute myeloid leukemia combined ribavirin with cytotoxic chemotherapy, such as cytosine arabinoside.¹⁰⁷⁻¹⁰⁹ Ribavirin also was given to metastatic breast cancer patients as a single agent in a recently terminated phase I/II study.¹¹⁰ Despite the presented evidence on the use of ribavirin in treating human cancer, some studies question its role as a functional mimic of the mRNA cap in vitro.^{111,112}

Peptides based on the eIF4E-binding motifs of 4E-BPs and eIF4G interfere with eIF4E-eIF4G binding, translation initiation, the cell cycle, and survival in vitro.^{113,114} A 4E-BP-based

peptide fused to an analog of gonadotropin-releasing hormone is taken up by ovarian tumor cells expressing the gonadotropin-releasing hormone receptor and inhibits growth in vitro and in vivo.¹¹⁵ A synthetic peptide, 4EGI-1, binds eIF4E and inhibits eIF4E/eIF4G interaction,¹¹⁶ thus inhibiting cap-dependent translation, increasing eIF4E–4E-BP1 association, and decreasing expression of oncogenic proteins. The use of another synthetic peptide, 4E1RCat, to interfere with the eIF4E–eIF4G interaction was reported to reverse tumor resistance in a lymphoma mouse model.¹¹⁷

Pdcd4 inhibits protein translation by binding to eIF4A.⁹³ Pdcd4 also inhibits Jun kinase activation, AP-1–dependent transcription, transformation, tumorigenesis, and invasion.⁹⁴ In at least some cancer cell lines, PI3K/mTOR inhibitors can be used to increase pdcd4 expression. However, an alternative strategy is to target eIF4A directly. The natural product pateamine A is a small-molecule modulator of eIF4A activity and an inhibitor of translation.¹¹⁸ Pateamine A causes eIF4A to be sequestered on RNA and limits eIF4A availability for incorporation into the eIF4F complex.¹¹⁹ Des-methyl, des-amino pateamine A is a structurally simplified analog of pateamine A and shows potent antiproliferative activity in a variety of human cancer cell lines and xenograft models.¹²⁰ Silvestrol is a compound with a similar mechanism, promoting interaction between eIF4A and capped RNA, interfering with the assembly of eIF4F complex, and thus inhibiting translation initiation.^{51,121} This drug was shown to inhibit translation and anticancer activity in breast and prostate cancer xenograft models and in B-cell leukemias in vitro and in vivo.^{52,121} Hippuristanol, a natural eIF4A RNA-binding activity inhibitor, induced cell cycle arrest and apoptosis in vitro and reduced tumor growth in vivo.^{122,123}

N1-guanyl-1,7-diaminoheptane and ciclopirox olamine are inhibitors of deoxyhypusine synthase and deoxyhypusine hydroxylase, respectively.^{124,125} These agents inhibit hypusination of eIF5A and reduce proliferation in various cancer cell lines and inhibit tumor growth in xenograft models of human breast cancer, melanoma, and leukemia.^{126–128}

eEF2K integrates a variety of signals and thus may be a target for different strategies. For example, insulin and serum stimulation activates eEF2K and inhibits eEF2; these effects are blocked by rapamycin.¹²⁹ Another study showed that high doses of the rapamycin analog temsirolimus reduced S6K1 and eEF2K phosphorylation but, unexpectedly, increased eEF2 phosphorylation on Thr56, the eEF2K phosphorylation site.¹³⁰ This increase involved an S6K1-independent mechanism, as it did not correlate with decreased S6K1 activity or with decreased eEF2K phosphorylation. Additional studies are needed to determine the effect of clinically achievable doses of PI3K/mTOR inhibitors in vivo and their effect on hormone receptor–positive breast cancers that express low or high eEF2K. NH125, a 2-methyl-imidazolium derivative, is a potent and relatively specific eEF2K inhibitor⁸²; a panel of cell lines, including a breast cancer cell line, that were treated with NH125 showed inhibited cell growth.

Protein elongation is also targeted by omacetaxine mepesuccinate (formerly homoharringtonine). This agent prevents aminoacyl-tRNA binding to the ribosomal acceptor site and peptide

bond formation.^{131,132} It competes with amino acid side chains of incoming aminoacyl-tRNAs for binding at the A-site cleft in the peptidyl transferase center.¹³³ Omacetaxine induces loss of proliferation and survival proteins, such as Mcl-1, cyclin D1, c-Myc, in a cell lines of chronic myeloid leukemia, acute myeloid leukemia, chronic lymphocytic leukemia and multiple myeloma. Only cells that rely on expression of these proteins are likely to be affected by omacetaxine, in other cancer types it is not sufficient to induce apoptosis.¹³⁴

Targeting of Signaling Networks Involved in Protein Synthesis in Clinical Trials

The PI3K/Akt/mTOR pathway has essential roles in normal cellular function. Akt and its downstream effectors control cell growth and survival, and mTOR participates in biologic processes and regulates protein synthesis. The activation of mTOR is driven by mitogens through PI3K/Akt. Alternatively, mTOR can be activated through the Ras/MEK/ERK pathway.¹³⁵ The prototypical allosteric mTOR inhibitor is rapamycin. Its analogs (also called rapalogs) are everolimus, ridaforolimus, and temsirolimus. These agents primarily inhibit mTORC1. In addition to translation inhibition, they induce cell cycle arrest and sensitize cancer cells to chemotherapeutic agents.¹³⁶ Since the PI3K/Akt/mTOR pathway is frequently activated in cancer, several clinical trials are testing the therapeutic effect of combining rapamycin analogs with other inhibitors.

In a phase III trial, 626 patients with previously untreated, poor-prognosis metastatic renal carcinoma were randomized into temsirolimus, interferon α or combination therapy groups.¹³⁷ The temsirolimus group had longer overall survival (hazard ratio [HR], 0.73; 95% confidence interval [95% CI], 0.58–0.92; $P = 0.008$) and progression-free survival (PFS) ($P < 0.001$) than the interferon group. The median overall survival times for the interferon, temsirolimus, and combination groups were 7.3, 10.9, and 8.4 mo, respectively. Another phase III trial compared everolimus and placebo treatment in patients with previously treated progressive metastatic renal cell carcinoma.¹³⁸ The trial was stopped early because of the significant efficacy of everolimus (HR, 0.30; 95% CI, 0.22–0.40; $P < 0.0001$). The median PFS times were 4.0 mo in the everolimus group and 1.9 mo in the placebo group. The RADIANT-3 trial randomized 410 patients with advanced pancreatic neuroendocrine tumors to receive everolimus or placebo, and both with best supportive care.¹³⁹ The median PFS times were 11.0 mo with everolimus and 4.6 mo with the placebo (HR, 0.35; 95% CI, 0.27–0.45; $P < 0.001$). Everolimus decreased the estimated risk of progression or death by 65%, thus significantly prolonging PFS. In the EXIST-1 trial, 117 patients with subependymal giant cell astrocytomas associated with tuberous sclerosis received either everolimus or a placebo.¹⁴⁰ At least a 50% reduction in tumor volume was observed in 35% of the patients in the everolimus group and 0% of the patients on the placebo ($P < 0.0001$). In the EXIST-2 study, 118 patients with angiomyolipoma and tuberous sclerosis or lymphangioleiomyomatosis were assigned into everolimus or placebo groups.¹⁴¹ At least a 50% reduction in tumor volume was observed in 42% of the patients

in the everolimus group and 0% of patients in the placebo group ($P < 0.0001$).

Several clinical trials have been conducted using mTOR inhibitors in breast cancer. Of 33 patients with metastatic breast cancer who received daily everolimus as a single agent, 12% showed a response (95% CI, 3.4–28.2%).¹⁴² Most estrogen receptor–positive patients benefit from aromatase inhibitors; however, most of them eventually develop progression or recurrence. Estrogen-depleted cells rely on activation of mTOR signaling²⁸; as a result, inhibition of mTOR signaling sensitizes these cells to aromatase inhibitors.¹⁴³ Thus, there is cross-talk between estrogen receptor signaling and PI3K/Akt/mTOR signaling, and the latter is responsible for the development of resistance to aromatase inhibitors. Striking results were seen in a phase II study of the combination of the estrogen receptor antagonist tamoxifen with everolimus in comparison with tamoxifen alone in patients with hormone receptor–positive, epidermal growth factor receptor 2–negative, aromatase inhibitor–naïve metastatic breast cancer.¹⁴⁴ The 6-mo rate of clinical benefit was 61% with the combination and 42% with tamoxifen alone, and the risk of death was 55% lower with combination therapy than with tamoxifen alone. In another phase II trial, 270 postmenopausal women with operable estrogen receptor–positive breast cancer received neoadjuvant treatment with letrozole (a nonsteroidal aromatase inhibitor) with or without everolimus. Greater inhibition of cell proliferation and better clinical response rates were observed in the combination arm (response rates of 68.1% with letrozole alone and 59.1% with the combination; $P = 0.062$, one-sided $\alpha = 0.1$).¹⁴⁵ The aromatase inhibitor exemestane inhibits estrogen synthesis. Recently, the BOLERO-2 phase III trial included 724 patients with hormone receptor–positive advanced breast cancer that had previously been treated with nonsteroidal aromatase inhibitors and had progression or recurrence, and/or with advanced disease.^{146,147} Patients were assigned into exemestane and exemestane plus everolimus groups. According to an assessment by local investigators, median PFS times were 6.9 mo in the combination group and 2.8 mo in the exemestane-only group (HR, 0.43; 95% CI, 0.35–0.54; $P < 0.001$) (Fig. 2A). According to an assessment by an independent committee, the median PFS times were 10.6 mo for the combination and 4.1 mo for exemestane only (HR, 0.36; 95% CI, 0.27–0.47; $P < 0.001$) (Fig. 2B). Thus, adding everolimus to exemestane improved PFS in these patients. A phase III study that was similarly planned but targeted nonsteroidal aromatase inhibitor–naïve patients with temsirolimus was terminated owing to a lack of responses at

the interim analysis.¹⁴⁸ Letrozole alone or with temsirolimus was offered as a first-line therapy to 1,112 patients; no difference in PFS between the groups was observed.

ATP-competitive inhibitors of mTOR—the mTOR kinase inhibitors—are potent inhibitors of mTORC1 and mTORC2; these inhibitors include Ku-0063794, PP30, Torin1, WYE-132, and WYE-354 in preclinical settings and AZD2014, AZD8055, MLN0128, OSI-027, and PP242 in clinical trials. They more effectively inhibit mTOR preclinical studies, resulting in dephosphorylation of 4E-BPs and impairment of translation initiation. They also inhibit Akt phosphorylation by directly inhibiting mTORC2. Clinical trials are ongoing to determine the efficacy

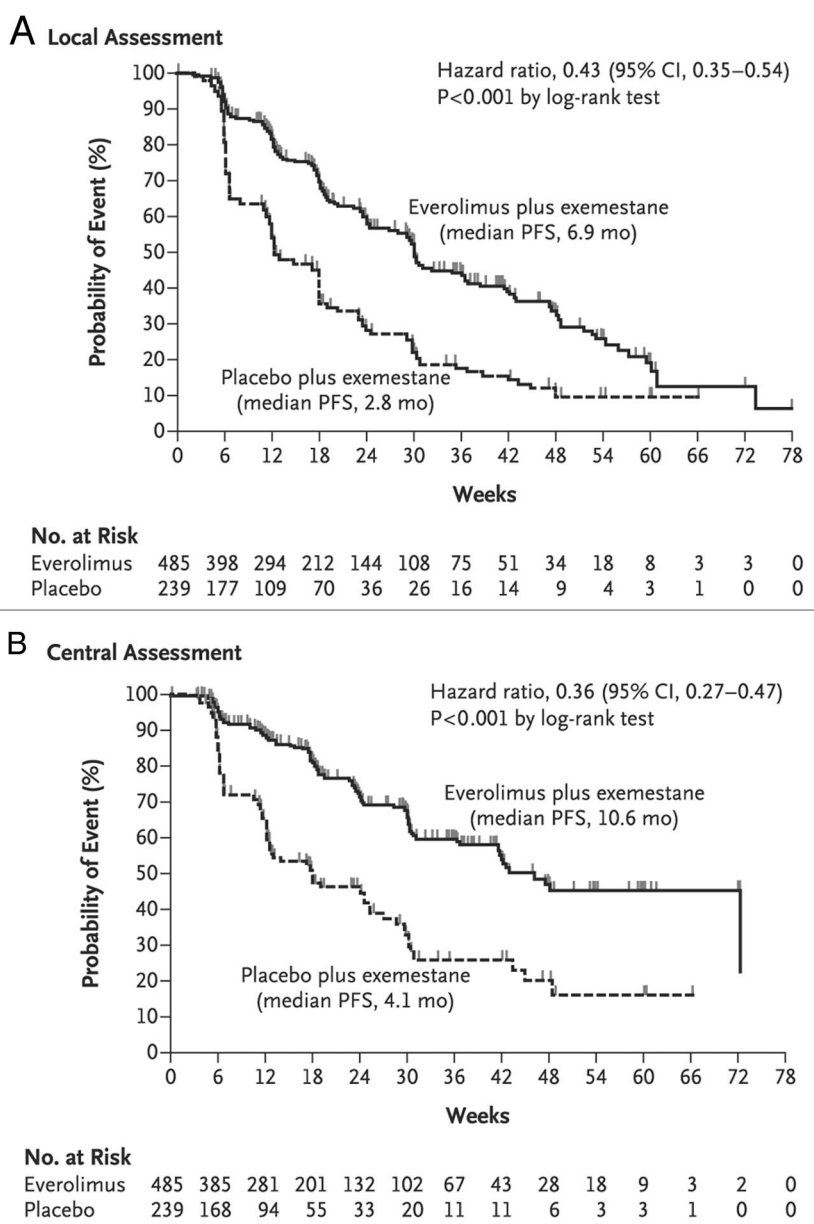


Figure 2. Kaplan-Meier estimates of progression-free survival rates. (A) Using radiographic studies, local investigators assessed the primary end point, progression-free survival. (B) A second assessment was conducted by an independent radiology committee. Reprinted from the New England Journal of Medicine 2012;366:520–9, with permission.

of mTOR kinase inhibitors as single agents and in combination therapy. Lastly, there are PI3K/mTOR dual inhibitors, which are more effective than rapamycin but also may be more toxic. PI-103 and WJD008 have been used in preclinical studies.^{149,150} XL765 GDC-0980, GSK2126458, NVP-BEZ235, PF-04691502, PF-05212384, and LY3023414 are being tested in clinical trials. These inhibitors are more efficient than mTOR inhibitors in blocking Akt phosphorylation.¹⁵¹

Akt is associated with tumor cell survival, proliferation, and invasiveness, and its activation is one of the most frequent alterations in cancer. Akt directly phosphorylates and inactivates tuberous sclerosis 2, and tuberous sclerosis 2 was shown to inhibit S6K1 and activate 4E-BP1 through mTOR.¹⁵² Thus, activated Akt stimulates mTOR and promotes activation of its downstream targets. Akt inhibitors API-2, AR-42, AR-67, and SRI2668 have been tested only in healthy subjects, and AZD5363, and GSK690693 are being tested in clinical trials. Also, the Akt inhibitor MK2206 is being evaluated in patients with advanced breast cancer and in the neoadjuvant setting in patients with operable breast cancer.^{153,154} Other Akt-inhibiting compounds, such as VIII, KP372-1, and A-443654, are being used in preclinical studies.

Approximately 25% of breast cancers overexpress HER2, which is associated with poor prognosis in patients not treated with HER2-targeted therapy.¹⁵⁵ HER2 activates both the PI3K/Akt/mTOR and the RAS/MAPK pathways—one of several connections between those pathways. Rapamycin inhibition of mTORC1 was shown to activate an S6K-PI3K-Ras feedback loop, leading to MAPK activation.¹⁵⁶ In addition, oncogenic MAPK signaling activates mTORC1 through the RSK1/2-raptor and ERK1/2-raptor axes.^{157,158} Inhibitors of the RAS/MAPK pathway component MEK1/2, including AZD6244, CI1040, MEK162, PD0325901, and MEK162, are very promising in the treatment of solid cancer. MEK162 has been evaluated in phase III trials, and trametinib has been approved by the FDA for Raf-mutant metastatic melanoma. These two agents are being tested for the treatment of breast cancer in phase I trials: trametinib as a single agent or in combination therapy and MEK162 in combination therapy.

The regulation of eIF4E forms another node of convergence between the PI3K/Akt/mTOR and RAS/MAPK signaling pathways. First, the PI3K/Akt/mTOR pathway phosphorylates 4E-BPs, liberates eIF4E, and allows eIF4F formation. Second, MAPK-interacting kinases 1 and 2 phosphorylate eIF4E, a modification that is required for eIF4E-dependent cell survival. Thus, mTOR and Mnk inhibition may inhibit cell proliferation. Indeed, in a panel of six cell lines, five showed a reduction in proliferation in response to treatment with Mnk kinase inhibitor N3-(4-fluorophenyl)-1H-pyrazolo-[3,4-d]pyrimidine-3,4-diamine (CGP57380).¹⁵⁹ The only unresponsive cell line had no detectable baseline eIF4E phosphorylation. The antifungal agent cercosporamide is an orally bioavailable Mnk inhibitor, particularly of Mnk2.¹⁶⁰ In cancer cell lines of various origins, cercosporamide blocked proliferation; mouse experiments showed dephosphorylation of eIF4E 30 min after cercosporamide administration. Thus, the published literature suggests that suppressing Mnk

function has potential in cancer treatment, like other approaches inhibiting eIF4E activity.

Obesity and diabetes are associated with increased breast cancer risk.¹⁶¹ Metformin is an anti-diabetic drug that exerts anti-cancer effects. For instance, patients with breast cancer and diabetes on metformin and neoadjuvant chemotherapy have a higher pathologic complete response rate than either breast cancer patients with diabetes receiving neoadjuvant chemotherapy but not metformin or nondiabetic breast cancer patients.¹⁶² The insulin-independent mode of action is not clear, but metformin activates adenosine monophosphate-activated protein kinase, which inhibits the mTOR pathway.¹⁶³ The dose of metformin needed to inhibit mTOR is not known; however, in vitro co-administration of metformin and everolimus with chemotherapeutic agents increased inhibition of cell proliferation.¹⁶⁴ A meta-analysis seven clinical studies assessed whether metformin is associated with decreased breast cancer risk and suggested that metformin is protective among postmenopausal breast cancer patients with diabetes, these patients have a lower risk of developing invasive breast cancer.¹⁶⁵ A neoadjuvant window of opportunity study of metformin in women with newly diagnosed, untreated, non-diabetic breast cancer who were waiting for surgery resulted in significant decreases in insulin, leptin, and C-reactive protein levels, a decrease in Ki67 staining of tumor tissue, and an increase in terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling staining.¹⁶⁶ These cellular changes were consistent with the anti-cancer effect of metformin. Several clinical trials are evaluating metformin administration in combination treatments for early and metastatic breast cancer. Further research is needed to identify the mechanisms of metformin's anti-tumor action and which cancer patients will benefit from metformin treatment.

Omacetaxine mepesuccinate was recently approved by FDA to treat chronic myeloid leukemia patients for resistance or tolerance to two or more tyrosine kinase inhibitors.^{167,168} Data pooled from two phase 2 trials showed hematologic response in 69% and major cytogenetic response in 20% of patients.¹⁶⁸ Median duration of hematologic response and major cytogenetic response were 12.2 mo and 17.7 mo, respectively. This is a novel approach to treat patients with chronic myeloid leukemia, and clinical trials are evaluating omacetaxine for different types of cancer and in drug combinations.

Conclusion

Emerging data show the importance of the dysregulation of translation in the development and progression of cancer. The first step of translation, translation initiation, appears to have a significant role in many cancer lineages, including breast cancer. Several agents target components of translation initiation, and many other agents target the components of the signaling pathways that regulate translation initiation. Most of these agents are in clinical trials, and some already have been approved for clinical use in cancer. As single agents or in combination treatments, they can inhibit tumor growth and prevent or overcome resistance to treatment. Further clinical studies will allow us to determine the

best approach to personalizing treatment in breast cancer patients with translational dysregulations.

Disclosure of Potential Conflicts of Interest

The authors have no disclosures.

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