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Review

EIF4EBP1 in Breast Cancer: Translational Control, Regulatory Networks, and Therapeutic Frontiers

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Abstract

Eukaryotic initiation factor 4E-binding protein 1 (EIF4EBP1/4E-BP1) is a pivotal translational regulator with context-dependent roles in breast cancer pathogenesis. Its phosphorylation status, dynamically controlled by mammalian target of rapamycin (mTOR), mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK), and AMP-activated protein kinase (AMPK) signaling, dictates a dualistic function: hypophosphorylated EIF4EBP1 suppresses oncogenesis by sequestering eIF4E and inhibiting cap-dependent translation of pro-tumorigenic mRNAs (e.g., cyclin D1 and c-MYC), while hyperphosphorylation promotes tumor progression and therapeutic resistance. EIF4EBP1 amplification (8p11-p12) is correlated with endocrine resistance and poor prognosis. EIF4EBP1 modulates cell cycle checkpoints, metabolic adaptation under stress, and resistance to cyclin-dependent kinase (CDK) 4 and 6 inhibitors and rapalogs via feedback loops (e.g., SGK3/Akt reactivation). Emerging therapeutic strategies, such as ATP-competitive mTOR inhibitors, bisteric compounds, and agents targeting polyamine metabolism or upstream kinases, exploit the dynamics of EIF4EBP1 phosphorylation. As a biomarker, phosphorylated EIF4EBP1 levels predict tumor aggressiveness and treatment failure, positioning it as a critical node for precision oncology. Future research must address spatial heterogeneity and leverage multi-omics/AI-driven approaches.

Keywords: breast neoplasms; mechanistic target of rapamycin; eukaryotic initiation factor-4E-binding protein 1; protein biosynthesis; biological markers

1. Introduction

Breast cancer (BC) is the most frequently diagnosed cancer and the leading cause of cancer-related death among women worldwide. According to the latest GLOBOCAN 2022 estimates, breast cancer accounted for 2,296,840 new cases and 666,103 deaths globally in the same year, representing 23.8% of all cancer cases in women and 15.4% of all cancer deaths among women [1,2]. The incidence of BC is increasing, particularly in developed countries and urban areas of China, where it has become a significant public health concern [3,4,5]. BC ranks first in incidence among cancers in women and second in cancer-related deaths, following lung cancer [6,7].

BC is classified on the basis of biological characteristics, molecular markers, and gene expression profiles. The main subtypes include hormone receptor-positive (HR+), human epidermal growth factor receptor 2-positive (HER2+), and triple-negative breast cancer (TNBC). HR+ BC, the most common subtype (60%–70% of cases), is sensitive to hormone therapies such as tamoxifen or aromatase inhibitors [8]. HER2+ BC, which accounts for approximately 25% of cases, is more aggressive but responds well to targeted therapies such as trastuzumab [9]. TNBC, which lacks hormone receptor and HER2 expression, is highly malignant and has limited treatment options and a poor prognosis [10]. Recent advancements in immunotherapy and targeted therapy offer hope for TNBC patients.

BC is driven by uncontrolled cell growth in mammary tissues and is influenced by molecular features, oncogenic pathways, and the tumor microenvironment, which play critical roles in progression and metastasis. Mutations in the phosphoinositide 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) pathway, particularly phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α (*PIK3CA*) mutation or phosphatase and tensin homolog (PTEN) loss, occur in more than 70% of cases and contribute to therapy resistance [11]. Inavolisib and inalizumab are novel and highly selective small-molecule inhibitors targeting the PI3K alpha isoform (p110α) with mutant-degrading activity [12,13]. They demonstrate trans-

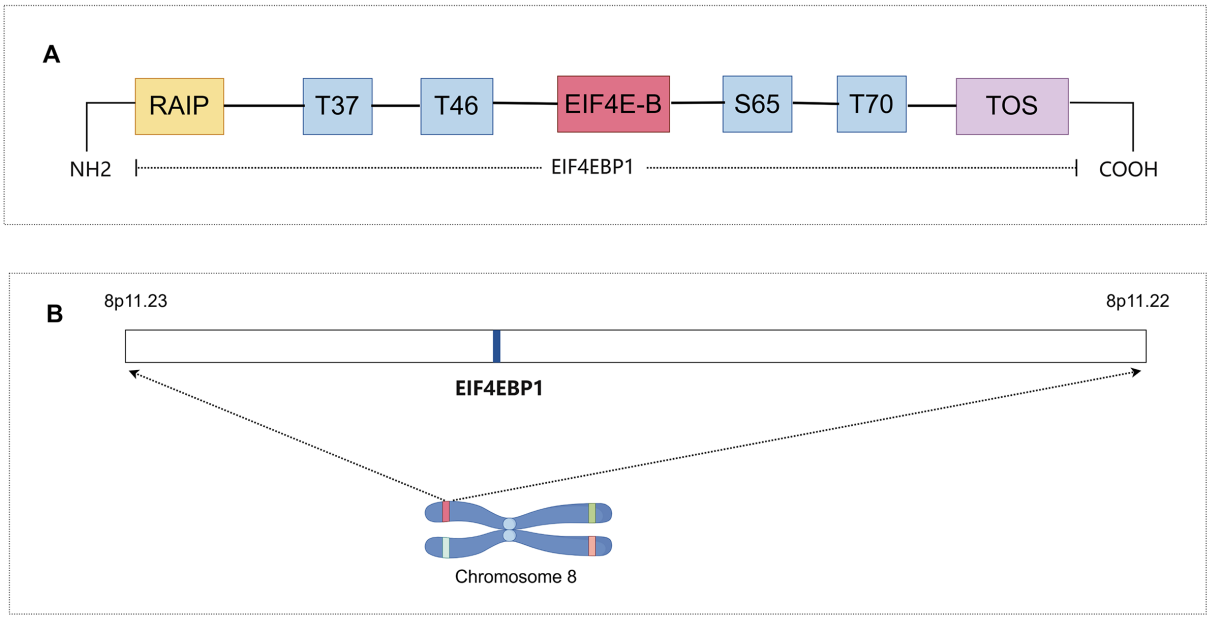


Fig. 1. Schematic representation of EIF4EBP1. (A) Protein structure. (B) Location of EIF4EBP1 on human chromosome 8. EIF4EBP1, Eukaryotic initiation factor 4E-binding protein 1.

formative potential in treating *PIK3CA*-mutated, hormone receptor-positive, HER2-negative advanced breast cancer, a setting frequently characterized by PI3K/Akt/mTOR pathway dysregulation that drives tumor progression and therapy resistance. Compared with the placebo, the phase 3 INAVO120 trial revealed that the combination of inavolisib with palbociclib and fulvestrant significantly improved the median progression-free survival (15.0 vs. 7.3 months; HR 0.43) and objective response rates (58.4% vs. 25.0%). Additionally, alpelisib (Piqray) has been approved by the FDA for the treatment of HR-positive, HER2-negative breast cancer with *PIK3CA* mutations [14]. Despite advancements in treatment modalities—including chemotherapy, surgery, radiotherapy, endocrine therapy, targeted therapy, and immunotherapy—BC remains a major health challenge because of high recurrence and mortality rates.

Ongoing research focuses on molecular mechanisms, early diagnosis, personalized treatment, and prognosis assessment. The development of novel therapies, such as immunotherapy targeting PD-L1/PD-1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA4), and precision medicine are crucial for improving treatment accuracy and patient outcomes. Effective prevention, diagnosis, and management strategies are essential for addressing the growing global burden of BC and optimizing the use of medical resources.

As a key translational repressor, eukaryotic translation initiation factor 4E binding protein 1 (EIF4EBP1) has significant implications in breast cancer research because of its central role in regulating oncogenic protein synthesis [15,16]. By competitively binding eukaryotic initiation factor 4E (eIF4E), EIF4EBP1 suppresses cap-dependent translation of malignancy-associated mRNAs encoding pro-survival, proliferative, and metastatic factors (e.g., cyclin D1, VEGF, and c-MYC). Clinically, elevated levels of phosphorylated EIF4EBP1 correlate with aggressive subtypes (e.g., HER2-positive breast cancer and triple-negative breast cancer), therapeutic resistance, and poor prognosis. Additionally, strategies to mimic its non-phosphorylated state (e.g., peptidomimetics and phosphorylation-resistant mutants) show promise in preclinical models for restoring translational control and suppressing metastasis. Thus, EIF4EBP1 serves as both a mechanistic nexus linking oncogenic signaling to translational reprogramming and a potential therapeutic vulnerability in breast cancer.

2. Structure of EIF4EBP1

The *EIF4EBP1* gene (official symbol: *EIF4EBP1*, eukaryotic translation initiation factor 4E-binding protein 1) is located on human chromosome 8 at cytogenetic band 8p11.23/8p11.22 [17,18]. Its genomic coordinates are chr8:38,030,534–38,060,365 (NCBI Gene ID: 1978) on GRCh38.p14. The gene comprises 3 exons and is oriented on the plus (forward) strand (Fig. 1B).

The protein structure of EIF4EBP1 is composed of several important domains that contribute to its function, which can be described in detail on the basis of its sequence and structural features: the eIF4E-binding domain, the C-terminal TOR signaling motif (TOS), and the N-terminal RAIP (Arg13, Ala14, Ile15 and Pro16) motif (Fig. 1A) [16].

The eIF4E binding domain is the most critical region for the function of EIF4EBP1 [19]. This domain is respon-

sible for binding to the eIF4E protein, which is a key component of the eIF4F complex and is necessary for the recruitment of the ribosome to mRNA for translation initiation. The eIF4E-binding domain in EIF4EBP1 typically contains a conserved consensus sequence characterized by a short peptide motif, YXXXF (where Y represents tyrosine, X represents any amino acid and F is phenylalanine). This motif interacts directly with the cap-binding site of eIF4E, preventing the formation of the eIF4F complex and thereby inhibiting translation initiation. The high affinity of EIF4EBP1 for eIF4E under non-phosphorylated conditions ensures that translation is repressed under specific cellular conditions.

At the C-terminus, EIF4EBP1 contains a TOR signaling (TOS) motif, which is involved in the regulation of EIF4EBP1 by the mTOR pathway [20]. The TOS motif consists of a hydrophobic sequence that is recognized by the mTOR complex 1 (mTORC1). When mTORC1 is activated, it phosphorylates specific residues (T37/46/70 and S65) in the TOS motif of EIF4EBP1, promoting its dissociation from eIF4E. This phosphorylation event allows for the release of translational repression on eIF4E, thereby facilitating translation initiation. The C-terminal TOS motif is crucial for the regulation of EIF4EBP1 in response to mTOR signaling and is a key element in the cellular control of protein synthesis.

The N-terminal RAIP motif is also important for the regulation of EIF4EBP1 [21]. This region is involved in interactions with other proteins and signaling pathways, particularly under stress conditions. The RAIP motif, which consists of a conserved sequence, typically aids in mediating the binding of EIF4EBP1 to other regulatory proteins and can influence its stability or localization within cells. This motif may also play a role in the modulation of the function of EIF4EBP1 in various cellular contexts, such as during nutrient deprivation or growth factor signaling. The precise functions of the RAIP motif in EIF4EBP1 are still being explored, but it contributes to the overall dynamic regulation of EIF4EBP1 activity.

Phosphorylation of EIF4EBP1, which is primarily mediated by mTORC1, follows a hierarchical sequence: initial phosphorylation at Thr37/Thr46 primes subsequent modifications at Ser65/Thr70, ultimately inducing structural rearrangements that weaken eIF4E binding [22]. This sequential phosphorylation releases eIF4E, enabling eIF4F complex (composed of eIF4E, eIF4A, and eIF4G) assembly and promoting cap-dependent translation initiation [23]. By dynamically modulating this interaction, EIF4EBP1 regulates cellular processes such as proliferation, survival, and stress adaptation. Dysregulation of this mechanism, particularly through hyperactivation of mTORC1 or aberrant phosphorylation patterns, is implicated in oncogenesis and metabolic disorders, underscoring its role as a nexus for translational control and disease pathogenesis [24].

3. Regulation of EIF4EBP1

EIF4EBP1 is an important translational regulatory protein in eukaryotic cells. It inhibits the mRNA translation process by interacting with eIF4E. EIF4EBP1 plays a key role in processes such as cell growth, differentiation, and stress responses. Its signaling pathways involve primarily multiple upstream kinases, downstream targets, and associated regulatory networks (Fig. 2) [15,16].

3.1 The PI3K/Akt/mTOR Pathway

The PI3K/Akt/mTOR pathway is a crucial signaling cascade that regulates various cellular processes, such as growth, survival, metabolism, and protein synthesis [24,25,26]. This pathway is initiated when growth factors bind to their respective receptors on the cell surface, activating phosphoinositide 3-kinase (PI3K) and subsequently leading to the activation of Akt (also known as protein kinase B). Akt, once activated, then stimulates mTOR, a central regulator of cell growth proliferation, survival, and metabolism [26,27,28].

mTOR functions through two distinct multiprotein complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) [29]. mTORC1, which is sensitive to rapamycin, primarily regulates protein synthesis, ribosome biogenesis, and cell cycle progression by phosphorylating downstream effectors such as ribosomal protein S6 kinase 1 (S6K1) and EIF4EBP1 [30,31]. S6K1 phosphorylates ribosomal protein S6, and promotes ribosome synthesis and cell growth [31], whereas phosphorylation of EIF4EBP1 releases it from eIF4E, enabling the assembly of the eIF4F translation initiation complex and facilitating cap-dependent mRNA translation [22,23]. mTORC2, which is relatively resistant to rapamycin, regulates cell metabolism and survival by phosphorylating AGC family kinases, including Akt [32].

As a key target of mTOR, EIF4EBP1 plays a dual role in cancer [15,16]. As a tumor suppressor, in its inactive or hypophosphorylated form, EIF4EBP1 tightly binds to eIF4E, blocking its interaction with eIF4G. This mechanism reduces the synthesis of pro-growth and survival proteins, such as cyclin D1 and c-MYC, while promoting cell cycle arrest and energy conservation [33,34]. However, phosphorylation by mTORC1 inactivates EIF4EBP1, causing it to dissociate from eIF4E. This release allows for eIF4E to participate in the initiation of translation, thereby promoting protein synthesis and cancer progression. High levels of phosphorylated EIF4EBP1 (p-EIF4EBP1) are associated with poor prognosis in various cancers, including breast cancer. Interestingly, *EIF4EBP1* amplification and overexpression have also been linked to tumor aggressiveness, suggesting a potential oncogenic role [33,35,36].

3.2 Profile of the AMPK/TSC2/mTOR Pathway

AMP-activated protein kinase (AMPK) serves as a central energy sensor that regulates cellular metabolism and

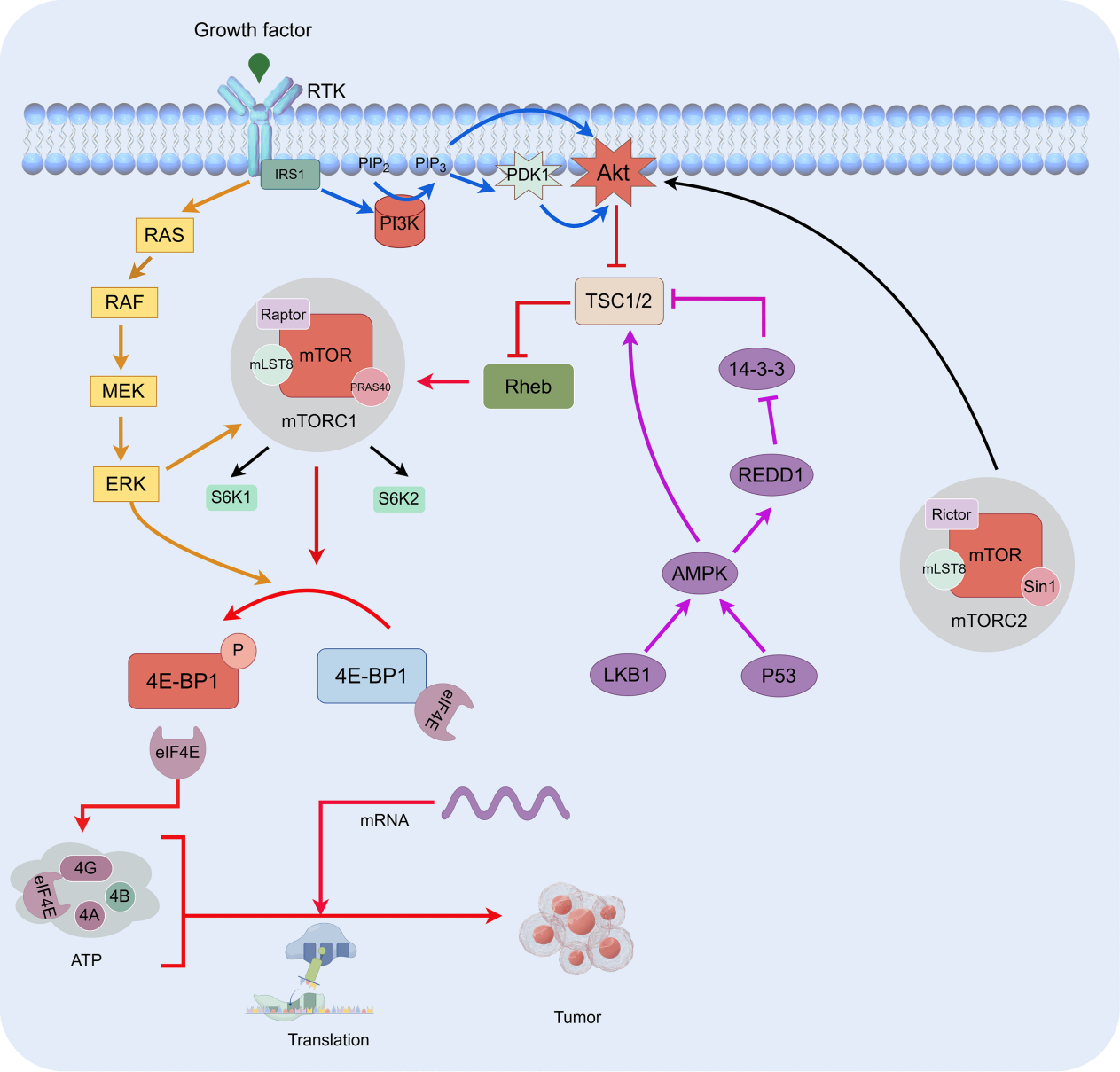


Fig. 2. Schematic proposal of the signaling pathways converging at EIF4EBP1. The arrows represent activation, and the bars represent inhibition.

protein synthesis, including the modulation of EIF4EBP1 [37,38]. The regulatory interplay between AMPK and EIF4EBP1 primarily occurs through the suppression of mTORC1 [39,40]. Under energy-deprived conditions, AMPK is activated by increased AMP/ATP ratios or upstream kinases such as liver kinase B1 (LKB1) [40]. Once activated, AMPK phosphorylates tuberous sclerosis complex 2 (TSC2) at Ser1387, enhancing its ability to inhibit Ras homolog enriched in the brain (Rheb), a critical activator of mTORC1 [41,42]. This inhibition of mTORC1 activity prevents the phosphorylation of EIF4EBP1 at canonical residues (Thr37/46, Ser65, and Thr70), thereby maintaining EIF4EBP1 in its hypophosphorylated, active state.

In addition to mTORC1-dependent regulation, AMPK may influence EIF4EBP1 through alternative pathways. For instance, AMPK activation upregulates the expression of regulated development and DNA damage response 1 (REDD1), a stress-responsive protein that further suppresses mTORC1 activity by displacing TSC2 from 14-3-3 protein complexes [43,44]. Furthermore, AMPK activation indirectly modulates EIF4EBP1 phosphorylation via crosstalk with the PI3K/Akt pathway. AMPK inhibits Akt signaling by phosphorylating and inactivating insulin receptor substrate 1 (IRS-1), thereby reducing Akt-mediated activation of mTORC1.

Experimental evidence highlights the functional consequences of AMPK-EIF4EBP1 axis activation. For example, metformin, a pharmacological AMPK activator, induces AMPK-dependent dephosphorylation of EIF4EBP1, leading to reduced cyclin D1 levels and G0/G1 cell cycle arrest in breast cancer cells [45,46]. Similarly, the natural products resveratrol [47] and honokiol [48] activate AMPK, suppressing mTORC1-EIF4EBP1 signaling and inhibiting tumor growth. Notably, AMPK-driven EIF4EBP1 regulation is context dependent; under nutrient-rich conditions, AMPK activity may be overridden by growth factor signaling, but under metabolic stress, this pathway becomes dominant in prioritizing energy homeostasis over anabolic processes [38].

In summary, AMPK orchestrates EIF4EBP1 regulation through mTORC1 suppression, REDD1 induction, and cross-talk with other signaling cascades. This multilayered control ensures precise modulation of cap-dependent translation in response to cellular energy status, positioning AMPK-EIF4EBP1 as a critical nexus in balancing protein synthesis with metabolic demands.

3.3 The MAPK/ERK Pathway

The MAPK/ERK signaling pathway (mitogen-activated protein kinase/extracellular signal-regulated kinase pathway) is a critical intracellular signaling cascade that regulates cell proliferation, differentiation, survival, and metabolism. It is activated by extracellular signals such as growth factors, cytokines, and hormones, which bind to receptor tyrosine kinases (RTKs) on the cell surface. This binding triggers a series of phosphorylation events, starting with the activation of the small GTPase Ras, which then activates the kinase RAF. RAF phosphorylates and activates MEK, which in turn phosphorylates and activates ERK [24,49,50].

The MAPK/ERK pathway can indirectly influence EIF4EBP1 phosphorylation through its crosstalk with the PI3K/Akt/mTOR pathway [51,52]. ERK activation can increase mTORC1 activity, which directly leads to the inactivation of EIF4EBP1 and the release of eIF4E to participate in the translation initiation process and promote protein synthesis. In addition, ERK can relieve the inhibitory effect of EIF4EBP1 on eIF4E by directly phosphorylating multiple sites of EIF4EBP1 (such as Thr37, Thr46, and Ser65).

In cancer, hyperactivation of the MAPK/ERK pathway often leads to increased phosphorylation of EIF4EBP1, promoting the translation and synthesis of proteins involved in cell growth, survival, and proliferation. This contributes to tumor progression and resistance to therapies.

4. Role of EIF4EBP1 in Breast Cancer

4.1 Cell Cycle Regulation and Translational Control of Tumor Progression

4.1.1 EIF4EBP1 is a Pivotal Regulator of Cell Cycle Progression

The eukaryotic cell cycle is tightly regulated by cyclins and cyclin-dependent kinases (CDKs), which orchestrate progression through distinct phases (G1, S, G2, M). Cyclins bind to and activate CDKs, forming complexes that phosphorylate target proteins to drive phase-specific transitions. For example, cyclin D1 partners with CDK4/6 during the G1 phase to phosphorylate the retinoblastoma (Rb) protein, facilitating the G1/S transition through the release of E2F transcription factors. Conversely, CDK inhibitors such as $p27^{Kip1}$ bind to cyclin-CDK complexes (e.g., cyclin E/CDK2) to block kinase activity, inducing cell cycle arrest. Dysregulation of cyclin-CDK dynamics—through overexpression of cyclins, loss of CDK inhibitors, or aberrant signaling—is a hallmark of cancer, making these pathways critical therapeutic targets [53,54].

EIF4EBP1 critically regulates cell cycle progression by modulating cap-dependent translation. In the G1 phase, EIF4EBP1 controls cyclin D1 and $p27^{Kip1}$ levels to enforce arrest (Fig. 3). Jiang et al. [55] demonstrated that a constitutively active EIF4EBP1 mutant (EIF4EBP1-5A) induces G1 arrest in MCF-7 cells by downregulating cyclin D1 and upregulating $p27^{Kip1}$ through enhanced cap-independent translation of the latter. This increased $p27^{Kip1}$ binds to cyclin E/CDK2, suppressing CDK2 activity. A previous study reported that EIF4EBP1 is essential for rapamycin-induced cyclin D1 reduction in MCF-7 cells, with EIF4EBP1 knockdown abolishing this effect [56]. Leucine starvation further suppressed EIF4EBP1 phosphorylation and cyclin D1 expression more effectively than rapamycin did in HEK293 cells. Foster's group revealed that complete G1 arrest by rapamycin in MDA-MB-231 cells requires dual inhibition of S6K and EIF4EBP1: low doses (nM) inhibit S6K to activate Transforming Growth Factor-beta (TGF-β) signaling, whereas high doses (μM) suppress EIF4EBP1 phosphorylation, leading to Rb dephosphorylation and cyclin D1 downregulation [57,58]. A previous study corroborated these findings, showing that EIF4EBP1 knockdown in ER+ breast cancer cells reduces cyclin D1 expression, increases p27 expression, and induces G1 arrest [59].

Resistance to CDK4/6 inhibitors (e.g., palbociclib) in HR+/HER2- breast cancer is driven by PI3K/mTOR hyperactivation. A previous study demonstrated that compared with control cells, palbociclib-resistant cells exhibit elevated EIF4EBP1 phosphorylation, which enhances the translation of cyclin D1 and CDK4, fuelling resistance. Targeting PI3K/mTOR with BYL719 or everolimus reduces p-EIF4EBP1 levels, suppresses cyclin D1/CDK4 synthesis, and restores drug sensitivity. Clinical data confirm that post-palbociclib progression is correlated with elevated p-

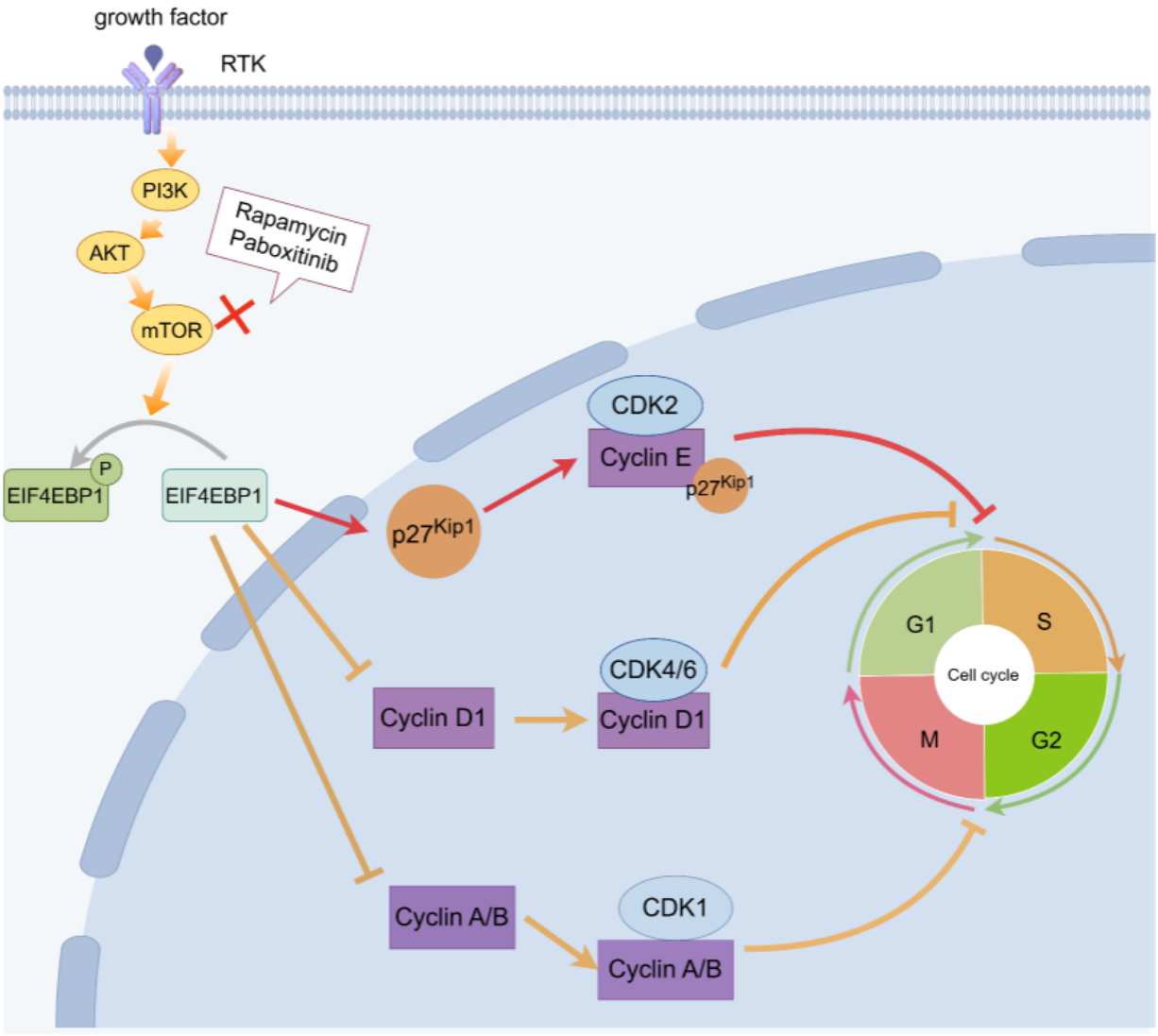


Fig. 3. Schematic representation of the effect of EIF4EBP1 on cell cycle progression. The arrows represent activation, and the bars represent inhibition.

EIF4EBP1, cyclin D1, and CDK4 levels, highlighting the therapeutic potential of dual PI3K/mTOR inhibition [60].

Beyond G1 regulation, EIF4EBP1 influences G2/M arrest via CDK1-dependent mechanisms. Paclitaxel (PTX) induces EIF4EBP1 hyperphosphorylation in MDA-MB-231 cells, which is correlated with G2/M arrest and cyclin B-CDK1 activation. Pharmacological CDK1 inhibition or cyclin B silencing abrogates PTX-induced EIF4EBP1 phosphorylation, a response that is conserved across breast, ovarian, and thyroid cancers, suggesting a universal mechanism for the use of microtubule-targeting agents [61].

Therapeutic strategies must address the feedback loops and dual roles of EIF4EBP1. While mTOR inhibitors (e.g., rapamycin) suppress EIF4EBP1 phosphorylation to induce G1 arrest, resistance via PI3K/mTOR reactivation necessitates combination therapies [57,58]. High-dose rapamycin or dual PI3K/mTOR inhibitors (e.g., everolimus + LY294002) mitigate compensatory Akt activation [62]. Additionally, targeting CDK1 or cyclin B may enhance the efficacy of microtubule-targeted therapies by modulating EIF4EBP1 phosphorylation.

In conclusion, EIF4EBP1 plays a crucial regulatory role at various stages of the cell cycle by modulating cyclin D1, $p27^{Kip1}$, and CDK activity. Additionally, it is involved in the development of therapeutic resistance in cancer. Its regulatory functions at multiple key points of the cell cycle, combined with its role in the PI3K/mTOR signaling pathway, suggest that targeting these pathways and downstream CDKs could lead to the development of new therapeutic strategies aimed at restoring normal cell cycle control and overcoming resistance. Therefore, EIF4EBP1 offers new insights for the treatment of cancers such as breast cancer and serves as a promising therapeutic target.

4.1.2 The Dual Role of EIF4EBP1 in Breast Cancer: Tumor Suppression and the Oncogenic Paradox

EIF4EBP1 plays complex roles in breast cancer progression, oscillating between tumor suppression and oncogenic drive depending on its phosphorylation status and genomic context. A previous study demonstrated that phosphorylation of the Akt/mTOR/EIF4EBP1 axis increases progressively from normal breast epithelium to invasive tumors and is correlated with ErbB2 overexpression [27]. As a tumor suppressor, EIF4EBP1 antagonizes eIF4F complex-driven oncogenic translation by sequestering eIF4E. However, sustained hyperphosphorylation in breast cancer disrupts this interaction, unleashing eIF4E to assemble the eIF4F complex, which enhances the translation of pro-survival (e.g., Bcl-XL) and oncogenic (e.g., cyclin D1) mRNAs while conferring apoptosis resistance through both mTOR-dependent and noncanonical pathways. The hypophosphorylated form of EIF4EBP1 potently suppresses tumorigenesis, as evidenced by reduced proliferation and clonogenicity in cells expressing phosphorylation-defective mutants (e.g., A37/A46). Conversely, loss of functional hypophosphorylated EIF4EBP1 during cancer evolution aligns with selective pressures that favor apoptosis resistance, underscoring its phosphorylation-dependent regulatory duality [63].

This paradox extends to EIF4EBP1 overexpression in cancers, including TNBC. Amplification of the 8p11-p12 genomic region, harboring the *EIF4EBP1* gene, occurs in 20–30% of metastatic ER+ breast cancers and is linked to endocrine resistance [36,59]. While EIF4EBP1 overexpression typically results in hyperphosphorylation—driving oncogenic translation—its knockdown in luminal breast cancer cells (e.g., SUM-44 and Cama-1) induces G1 arrest, cyclin D1 downregulation, and p27 upregulation, highlighting its context-dependent role. A previous study further reported that FGFR1 co-amplification at 8p11 promotes PI3K-mediated EIF4EBP1 phosphorylation (Thr37/46, Ser65, and Thr70), inactivating its tumor-suppressive function and enhancing eIF4E-driven oncogenesis [33]. Strikingly, *EIF4EBP1*-amplified tumors exhibit sensitivity to FGFR1/PI3K inhibitors (e.g., BGJ398 and BKM120), whereas CRISPR-mediated *EIF4EBP1* deletion accelerates tumor growth and diminishes the therapeutic response, revealing its dual role as both an oncogenic driver and a therapeutic vulnerability.

The expanding landscape of EIF4EBP1 research illuminates its dualistic role as both a molecular rheostat and a vulnerability node within oncogenic networks, governed by context-dependent phosphorylation dynamics and crosstalk with divergent signaling cascades. Karni's seminal discovery of isoform-specific S6K1 regulation (Iso-2 vs. Iso-1) underscores a paradigm wherein mTORC1 signaling bifurcates to either hyperphosphorylate EIF4EBP1 (pro-oncogenic) or suppress its phosphorylation (tumor-suppressive), contingent on isoform stoichiometry and Ras-driven transformation states [64]. This duality positions EIF4EBP1 at the epicenter of translational plasticity, where its phosphorylation status dictates the synthesis of metastasis-promoting effectors (e.g., MMPs and Snail) versus tumor-suppressive micropeptides such as CIP2A-BP. Zhou's work in TNBC further entrenches EIF4EBP1 as a TGF-β/Smad effector that paradoxically connects immunosuppressive signaling and metabolic reprogramming—a dichotomy resolved by its capacity to repress LINC00665-dependent CIP2A-BP suppression, thereby licensing PI3K/Akt/NF-κB-driven invasion [65].

Emerging therapeutic paradigms targeting EIF4EBP1 phosphorylation exploit its role as a translational gatekeeper but confront inherent complexities. Zacksenhaus's synthetic lethality strategy—combining EIF4EBP1 depletion with eEF2K inhibition—reveals a metabolic Achilles' heel in TNBC, where glutamine deprivation unmasks an irreconcilable conflict between pro-proliferative protein synthesis (c-MYC, cyclin D1) and energy homeostasis [66]. Additionally, it was demonstrated that collagen XVII (COL17) suppresses EIF4EBP1 phosphorylation (Thr37/46), disrupting Akt/mTOR signaling and impairing proliferation [67]. In TNBC, combined CDK12/13 and EGFR inhibition prevents EIF4EBP1 phosphorylation (T37/T46/S65/T70), destabilizing MYC and MCL-1 via translational repression and proteasomal degradation. CRISPR screens revealed that the CCR4-NOT complex (e.g., CNOT1) is essential for enabling EIF4EBP1 dephosphorylation, with the loss of CNOT1 restoring MYC stability and therapeutic resistance [68]. This finding underscores the necessity of multilayered targeting, as exemplified by Peruzzi's observation of EIF4EBP1–c-MYC coregulation, in which miR-3189-3p-mediated EIF4EBP1 suppression disrupts a feedforward loop driving MYC-dependent anabolism [34]. In TNBC, miR-3189-3p directly targets the 3′UTR of EIF4EBP1, leading to its downregulation, which disrupts a critical feedforward loop that sustains MYC-driven anabolic metabolism. EIF4EBP1 normally promotes MYC translation by sequestering eIF4E, and its suppression paradoxically reduces MYC protein levels, impairing glycolysis, nucleotide synthesis, and ribosomal biogenesis—key processes for cancer cell proliferation. This disruption enhances chemotherapy sensitivity and inhibits TNBC cell proliferation, migration, and invasion.

In summary, EIF4EBP1 plays a critical context-dependent role in breast cancer, where its phosphorylation state, influenced by genomic factors, dictates its switch between tumor-suppressive and oncogenic functions. Its hypophosphorylated form inhibits the eIF4F complex, suppressing tumor growth, while hyperphosphorylation drives oncogenic translation programs. This dual role underscores the complex relationship between translation regulation and tumor progression, serving both as a buffer for genomic instability and as a potential tool for cancer promotion. *EIF4EBP1* amplification, especially in conjunction with the

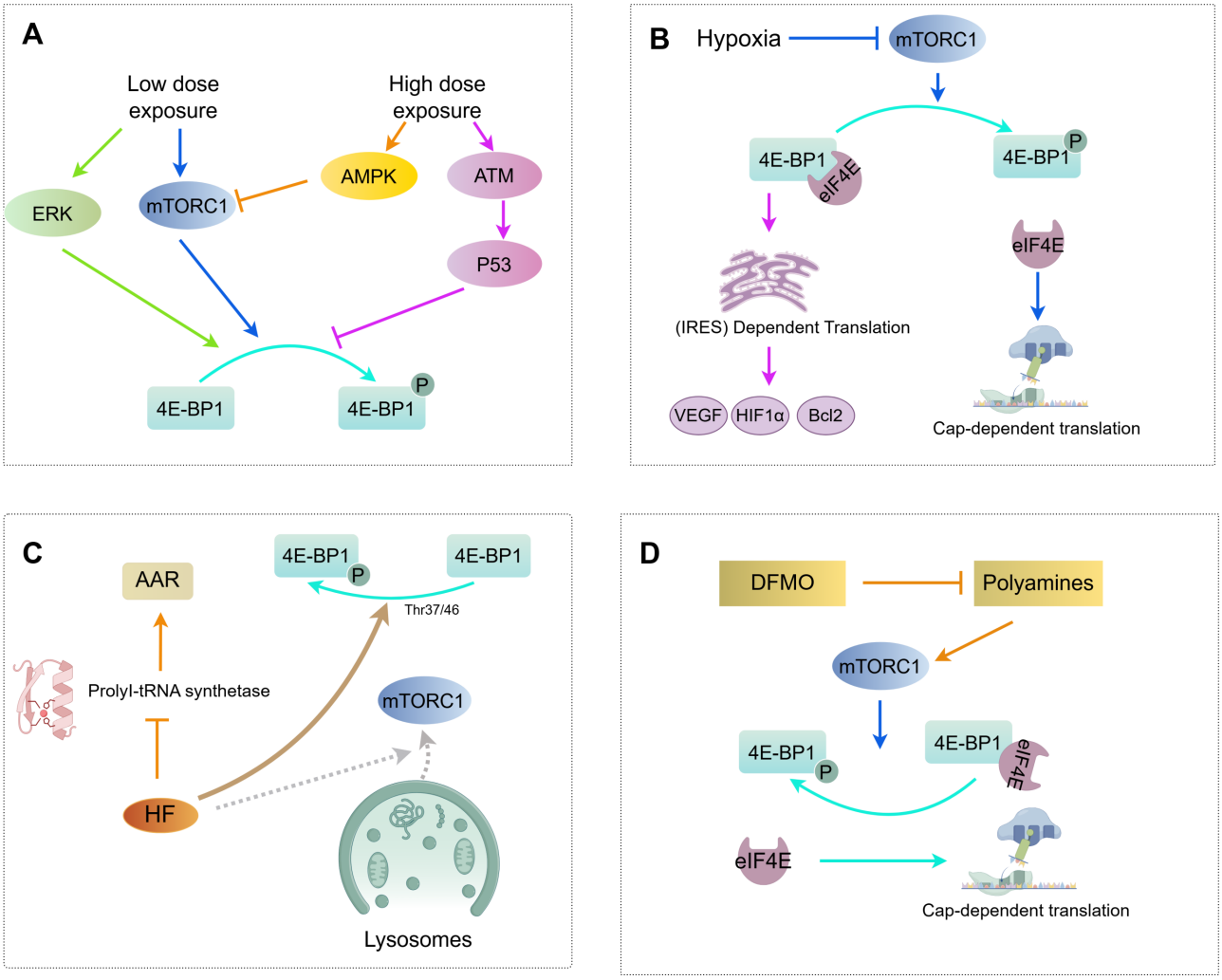


Fig. 4. Regulation of EIF4EBP1 by metabolic and environmental stressors. (A) Radiation exposure drives hierarchical phosphorylation of EIF4EBP1. (B) Hypoxia reduces EIF4EBP1 phosphorylation. (C) Context-dependent regulation of EIF4EBP1 in response to nutrient deprivation. (D) Polyamine depletion reduces EIF4EBP1 phosphorylation. The arrows represent activation, and the bars represent inhibition.

amplification of genes such as *FGFR1*, highlights the importance of genomic and epigenetic interactions in treatment resistance. Therapeutically, targeting its phosphorylation dynamics through upstream kinases or downstream effectors offers potential, although compensatory mechanisms and metabolic adaptations may limit efficacy. Future research should focus on understanding the functional heterogeneity of EIF4EBP1 across breast cancer subtypes to guide precision therapies based on phosphorylation status. Ultimately, EIF4EBP1 is pivotal for both tumor biology and therapeutic targeting in breast cancer.

4.1.3 Regulation of EIF4EBP1 by Metabolic and Environmental Stressors in Breast Cancer

Radiation exposure dynamically modulates EIF4EBP1 activity through phosphorylation and stability, influencing protein synthesis and cellular survival (Fig. 4A). Ultraviolet (UV) and ionizing radiation (IR) activate mTOR and ERK, driving hierarchical phosphorylation of EIF4EBP1 at Thr37/46, Ser65, and Thr70. However, prolonged stress—such as high-dose IR—triggers p53-mediated upregulation of Sestrin 1/2 and AMPK activation, inhibiting mTOR activity and leading to EIF4EBP1 dephosphorylation. This shift sequesters eIF4E, suppressing cap-dependent translation while stabilizing EIF4EBP1 via ATM/p53-dependent inhibition of proteasomal degradation, thereby linking DNA damage responses to translational control [69,70].

Hypoxia further reshapes translational regulation in advanced breast cancers (Fig. 4B). Under low oxygen, EIF4EBP1 and eIF4G are overexpressed, which is correlated with tumor size and hypoxia severity. Reduced mTOR activity hypophosphorylates EIF4EBP1, enabling it to sequester eIF4E. Concurrently, this promotes the

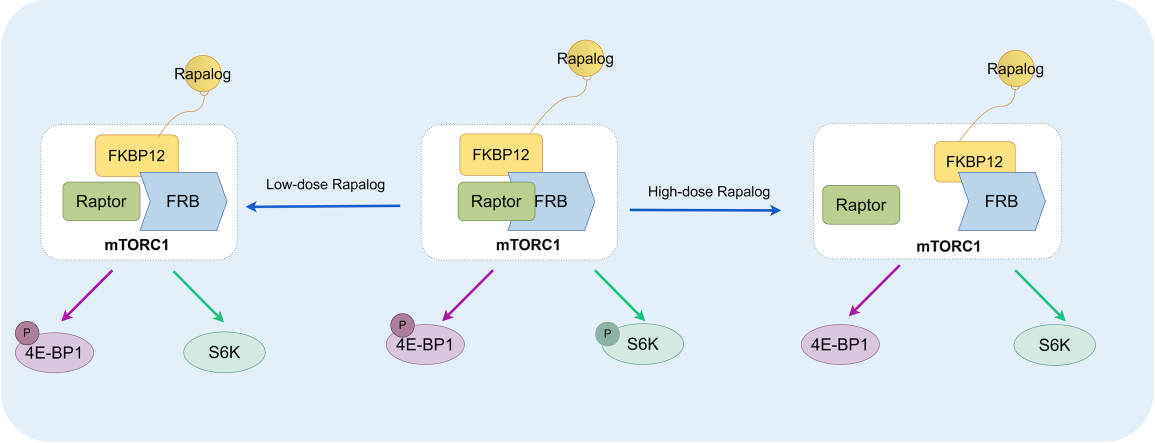


Fig. 5. Schematic representation of the dose-dependent inhibitory effect of rapalogs.

IRES-dependent translation of proangiogenic and survival factors such as VEGF, HIF1α, and Bcl2, facilitated by EIF4EBP1/eIF4G interplay. Remarkably, moderate hypoxia (5% O_2) is sufficient to activate this adaptive switch, ensuring tumor survival and angiogenesis through parallel translation pathways [71,72].

Nutrient deprivation affects EIF4EBP1 in a context-dependent manner (Fig. 4C). Amino acid starvation via Earle's balanced salt solution (EBSS) induces EIF4EBP1 hypophosphorylation, which globally represses protein synthesis [73]. In contrast, halofuginone (HF), which mimics proline starvation, uniquely preserves Thr37/46 phosphorylation, sustaining partial cap-dependent translation despite mTORC1 degradation. HF also induces autophagy, recycling cellular components for biosynthesis—a metabolic advantage over EBSS, which halts both translation and recycling. This dichotomy underscores how stress-specific mTOR modulation fine-tunes translational output.

Polyamines, which are critical metabolic regulators, increase mTORC1-driven EIF4EBP1 phosphorylation (Fig. 4D) [74]. Exogenous spermidine and spermine increase Thr37/46 phosphorylation and p70S6K activity in breast cancer cells, promoting eIF4E release and polysome formation for active translation. Conversely, polyamine depletion via DFMO reduces EIF4EBP1 phosphorylation, impairing translation initiation. A feedback loop in which mTORC1 supports polyamine synthesis, creating a vicious cycle of growth emerges. Targeting polyamine metabolism alongside mTORC1 inhibition synergistically suppresses tumor progression, suggesting therapeutic potential in breast cancers with dysregulated polyamine pathways.

Collectively, these findings highlight EIF4EBP1 as a nexus that integrates environmental, metabolic, and therapeutic stresses. Its phosphorylation status is dictated by mTOR, AMPK, and polyamine signaling, orchestrating translational adaptation and balancing survival and apoptosis. Strategic combinations, such as polyamine inhibitors with mTORC1 antagonists or hypoxia-targeted therapies, could exploit these pathways to disrupt cancer resistance, offering novel avenues for precision oncology.

4.1.4 Regulation of EIF4EBP1 in the Therapeutic Resistance of Breast Cancer

Rapamycin and its analogs (rapalogs) bind to the immunophilin FKBP12, forming a complex that allosterically inhibits mTORC1 through interaction with its FRB domain (Fig. 5) [75]. This inhibition preferentially suppresses the phosphorylation of the substrate S6K but only weakly attenuates the phosphorylation of EIF4EBP1—a key mTORC1 target with four phosphorylation sites (Thr37, Thr46, Ser65, and Thr70). The sensitivity of these sites to rapamycin varies with dose: Thr70 phosphorylation is inhibited at concentrations sufficient to block S6K, whereas Thr37/46 and Ser65 require higher, apoptosis-inducing micromolar doses. At conventional nanomolar doses, rapamycin effectively suppresses S6K but does not significantly impact EIF4EBP1 phosphorylation, as residual mTORC1 activity is maintained at Thr37/46 phosphorylation. This incomplete inhibition contributes to therapeutic resistance, particularly in cells in which mTORC2 remains active, preserving Akt phosphorylation at Ser473 and sustaining pro-survival signaling. Furthermore, mTORC2-mediated Akt activation indirectly phosphorylates EIF4EBP1, enabling continued cap-dependent translation and tumor growth despite mTORC1 suppression.

Resistance to rapamycin is further exacerbated by feedback reactivation of the mTORC1/EIF4EBP1 axis. A previous study demonstrated that rapamycin-treated breast cancer cells exhibit transient EIF4EBP1 dephosphorylation, followed by re-phosphorylation driven by SGK3 and Akt. SGK3, activated via mTORC2 and hVps34-generated PI (3) P, phosphorylates TSC2 to reactivate mTORC1, sustaining cap-dependent translation and proliferation (Fig. 6) [76]. Phosphoproteomic analyses revealed that SGK3 acts independently and synergistically with Akt, with clini-

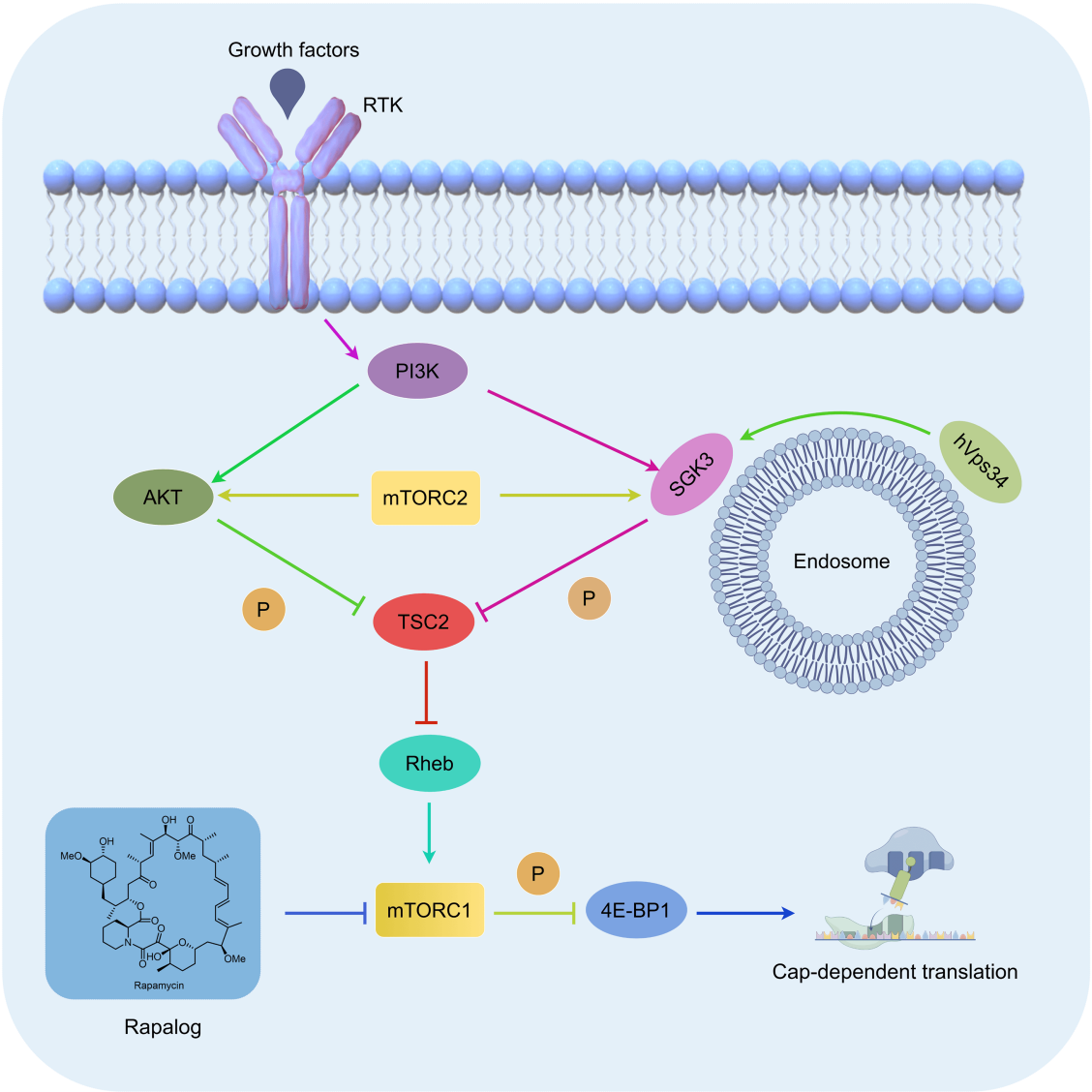


Fig. 6. Schematic representation of the feedback activation of SGK3 and Akt via TSC2. The arrows represent activation, and the bars represent inhibition. SGK3, serum/glucocorticoid-regulated kinase 3; AKT, protein kinase B; TSC2, tuberous sclerosis complex 2.

cal correlations linking elevated levels of phosphorylated EIF4EBP1 to SGK3 activity in patient samples. Combined inhibition of SGK3 and Akt nearly abolishes EIF4EBP1 rephosphorylation and enhances the efficacy of rapamycin, underscoring dual targeting as a strategy to overcome resistance.

The role of EIF4EBP1 extends to modulating sensitivity to other targeted therapies. In HER2-overexpressing breast cancer, lapatinib resistance is mediated by EIF4EBP1, as its knockdown sensitizes trastuzumab-refractory cells to lapatinib by reducing their viability [9]. Notably, this effect is specific to EIF4EBP1, as p70S6K inhibition does not alter the lapatinib response, and mTOR inhibition—affecting both targets—improves sensitivity. These findings position EIF4EBP1 as a critical node in resistance mechanisms beyond rapalogs.

The efficacy of ATP-competitive mTOR inhibitors, such as AZD8055 and BEZ235, is influenced by the EIF4EBP1 protein level. A previous study reported that high EIF4EBP1 expression is correlated with sensitivity to these inhibitors, as treatment enhances EIF4EBP1 binding to eIF4E, displacing eIF4G and disrupting the eIF4F complex [77]. In resistant, low-EIF4EBP1 cells, insufficient eIF4E sequestration permits translation and survival. Overexpression of EIF4EBP1 in resistant models restored inhibitor sensitivity without affecting baseline proliferation, highlighting its predictive value. This effect is mTOR-specific, as PI3K inhibitor responses remain unchanged, emphasizing the centrality of EIF4EBP1 abundance in mTOR-targeted therapeutic outcomes.

In summary, the phosphorylation status and expression levels of EIF4EBP1 intricately govern the response to

Table 1. Selected compounds that target the upstream regulators of eukaryotic initiation factor 4E-binding protein 1 (EIF4EBP1).

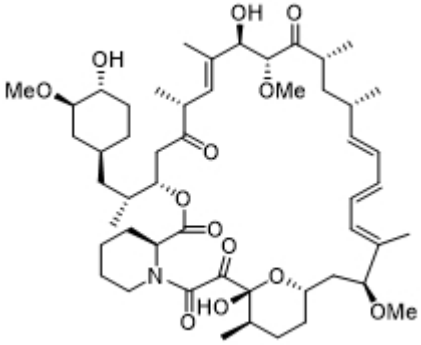
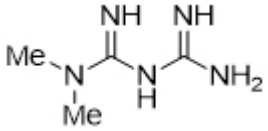
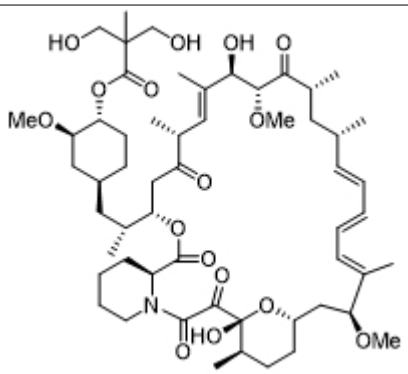
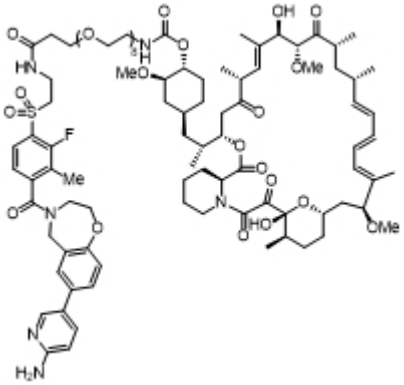
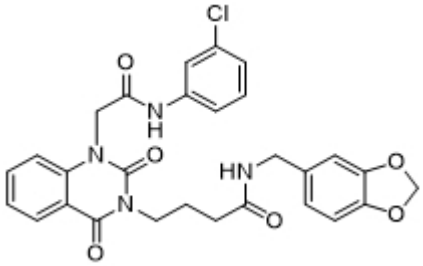
Name	Structure	Mechanism & target	Effect on EIF4EBP1
Rapamycin		Inhibitor of mechanistic target of rapamycin complex 1 (mTORC1)	Phosphorylation downregulation
Metformin		Activator of AMP-activated protein kinase (AMPK)	Phosphorylation downregulation
CCI-779		Inhibitor of mTORC1	Phosphorylation downregulation
RMC-6272		Inhibitor of mTORC1	Inhibitor of phosphorylation
WRX606		Inhibitor of mTORC1	Phosphorylation downregulation

Table 1. Continued.

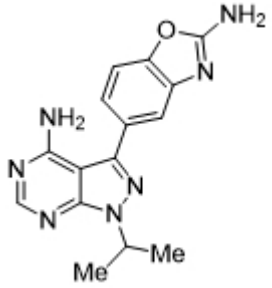
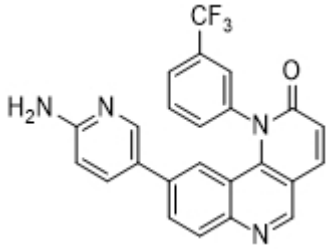
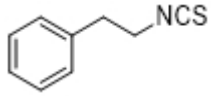
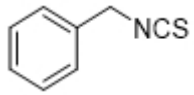
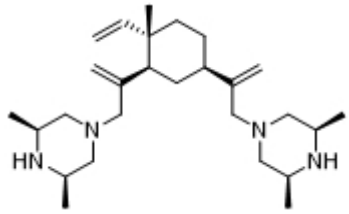
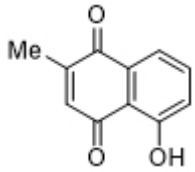
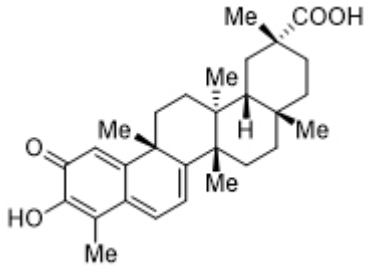
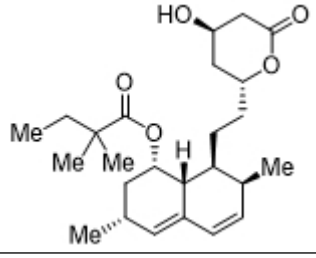
Name	Structure	Mechanism & target	Effect on EIF4EBP1
MLN0128		ATP-competitive inhibitor of mTOR	Phosphorylation downregulation (Thr37/46, Ser65)
Torin 2		ATP-competitive inhibitor of mTOR	Phosphorylation downregulation (Thr37/46, Ser65)
PEITC		Inhibitor of mTORC1	Phosphorylation downregulation (Ser65)
BITC		Inhibitor of mTORC1	Phosphorylation downregulation (Ser65)
IIi		Inhibitor of mTORC1	Phosphorylation downregulation
Plumbagin		Inhibitor of phosphoinositide 3-kinase (PI3K)/AKT serine/threonine kinase (Akt) signaling pathway signaling	Phosphorylation downregulation
Celastrol		Inhibitor of PI3K/Akt signaling	Phosphorylation downregulation
Simvastatin		Inhibitor of PI3K/Akt signaling	Phosphorylation downregulation

Table 1. Continued.

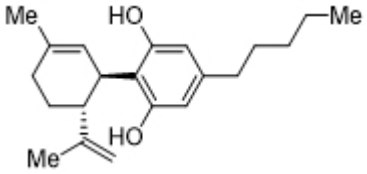
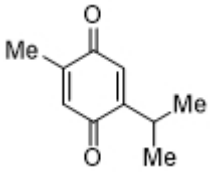
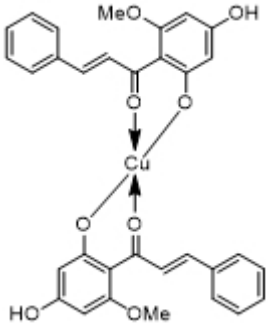
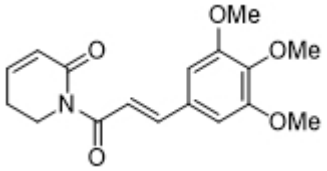
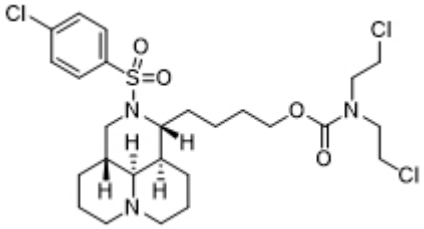
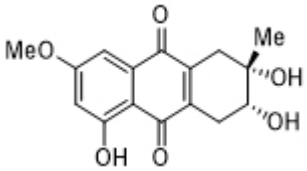
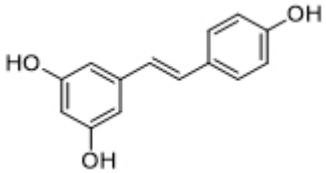
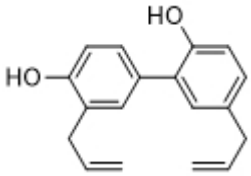
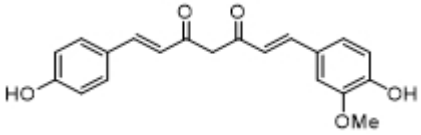
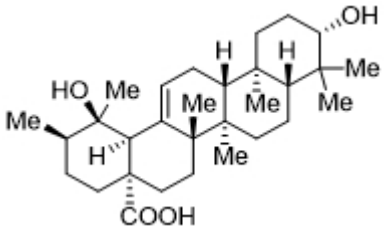
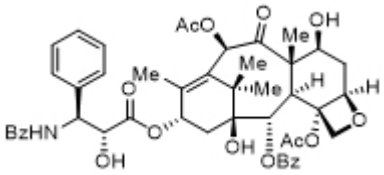
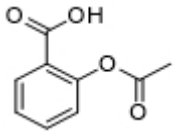
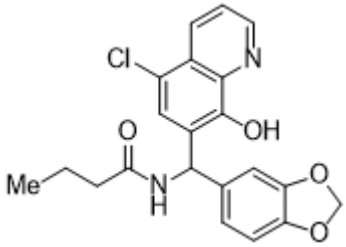
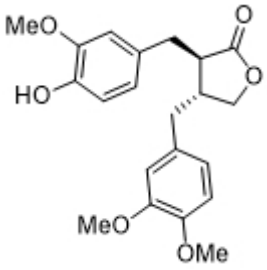
Name	Structure	Mechanism & target	Effect on EIF4EBP1
Cannabidiol		Inhibitor of Akt/mTOR signaling	Phosphorylation downregulation
Thymoquinone		Inhibitor of Akt	Phosphorylation downregulation
Cu^{2+}–cardamonin complex		Inhibitor of Akt	Phosphorylation downregulation
PPLGM		Phosphorylation downregulation of Akt at Ser 473	Expression downregulation
Sophoridine derivative		Inhibitor of AKT phosphorylation at Ser 473	Phosphorylation downregulation
Altersolanol B		Downregulation the levels of p-AKT (Ser473, Thr308)	Phosphorylation downregulation
Resveratrol		Activator of AMP-activated protein kinase (AMPK)	Phosphorylation downregulation (Thr37/46)
Honokiol		Activator of AMPK	Phosphorylation downregulation (Thr37/46)

Table 1. Continued.

Name	Structure	Mechanism & target	Effect on EIF4EBP1
Demethoxycurcumin		Activator of AMPK	Phosphorylation downregulation (Thr37/46)
Pomolic acid		Activator of AMPK	Phosphorylation downregulation
Paclitaxel		\	Induces CDK1-dependent EIF4EBP1 hyperphosphorylation
Aspirin		Downregulation of regulated in development and DNA damage responses 1 (REDD1)	Phosphorylation downregulation
YUM70		Inhibitor of mTOR	Expression upregulation and phosphorylation downregulation
Arctigenin		Inhibitor of EIF4EBP1	Expression downregulation

mTOR inhibition in breast cancer. While the partial efficacy and resistance mechanisms of rapalogs underscore the challenges of mTORC1-selective targeting, combinatorial approaches against SGK3/Akt or strategies leveraging EIF4EBP1 overexpression offer promising avenues. These insights suggest the need for personalized therapeutic regimens informed by EIF4EBP1 dynamics to optimize mTOR pathway inhibition and circumvent resistance.

4.2 Therapeutic Agents of EIF4EBP1 and its Phosphorylation

In breast cancer, a considerable body of literature reports on small-molecule agents capable of pharmacologically modulating 4EBP1 phosphorylation, both directly and indirectly (Table 1). Rapamycin and its structural analogs (rapalogs) primarily target mTORC1 by binding to the FKBP12-rapamycin binding domain, leading to the dephosphorylation of EIF4EBP1. CCI-779, an ester derivative of rapamycin, suppresses mTOR activity, reduces EIF4EBP1 phosphorylation (Thr37/46/70, Ser65), and disrupts its dissociation from eIF4E, thereby downregulating cyclin D1 and c-MYC while upregulating p27 to induce G1 arrest [78]. Notably, rapalogs such as everolimus inhibit mTORC1 substrates (p70S6K and EIF4EBP1) but may paradoxically activate mTORC2-dependent Akt phosphorylation through feedback loops. In contrast, bi-steric inhibitors such as RMC-6272 and RMC-4529 demonstrate enhanced efficacy by potently blocking both mTORC1 sub-

strates (EIF4EBP1 and S6K) at low nanomolar concentrations without significantly inhibiting mTORC2 at higher doses, thereby inducing apoptosis in ER+/HER2- breast cancer cells via EIF4EBP1-mediated MCL1 suppression [79,80]. WRX606, a non-rapalog allosteric mTORC1 inhibitor, uniquely suppresses the phosphorylation of both S6K and EIF4EBP1 while preserving partial cap-dependent translation, minimizing cytotoxicity in noncancer cells [81].

Other mTOR inhibitors act via distinct mechanisms. ATP-competitive inhibitors such as sapanisertib (MLN0128) [82,83] and torin 2 [84] inhibit both mTORC1 and mTORC2, effectively reducing EIF4EBP1 phosphorylation (Thr37/46, Ser65) and overcoming rapamycin resistance. Phenethyl isothiocyanate (PEITC) and benzyl isothiocyanate (BITC) suppress mTORC1 activity, directly decreasing EIF4EBP1 phosphorylation (Ser65) and p70S6K activity [85]. Compounds such as tanshinone IIA and 13,14-bis(cis-3,5-dimethyl-1-piperazinyl)-β-elemene (IIi) [86] inhibit mTORC1 signaling, reducing EIF4EBP1 phosphorylation and downstream HIF-1α/VEGF expression.

Agents targeting upstream pathways include PI3K/Akt/mTOR inhibitors such as plumbagin [87], celastrol [88], simvastatin [89], cannabidiol [90], thymoquinone [91], and the Cu^{2+}–cardamonin complex [92], which suppress PI3K/Akt signaling, leading to mTOR inactivation and reduced EIF4EBP1 phosphorylation. PPLGM [93] and its sophoridine derivative [94] exert potent anticancer effects in TNBC cells by decreasing the phosphorylation of Akt at the Ser473 residue to inhibit PI3K/Akt and mTOR activity and significantly decreasing the expression of p70S6K1 and EIF4EBP1. Altersolanol B [95] downregulates the levels of p-Akt (Ser473, Thr308) and p-4E-BP1, while total protein levels remain unchanged. Metformin [62,96,97] and AMPK activators (resveratrol [47], honokiol [48], demethoxycurcumin [98], pomolic acid [99]) inhibit mTOR via AMPK-mediated phosphorylation, downregulating EIF4EBP1 (Thr37/46). Paclitaxel uniquely induces CDK1-dependent EIF4EBP1 hyperphosphorylation, which is reversible by treatment with CDK inhibitors (e.g., purvalanol A) [61].

Drugs with translational or epigenetic effects include 4EGI-1, which inhibits the eIF4E/eIF4G interaction and independently suppresses mTORC1, reducing EIF4EBP1 phosphorylation [100]. Valproic acid combined with tamoxifen restores ESR1 function and inhibits EIF4EBP1 phosphorylation [101]. Aspirin and salicylic acid reduce EIF4EBP1 phosphorylation via REDD1 downregulation [102], whereas YUM70 upregulates EIF4EBP1 expression and inhibits its phosphorylation via mTOR suppression, reducing c-MYC translation [103]. Arctigenin directly downregulates EIF4EBP1 expression, reversing epithelial to mesenchymal transition (EMT) and metastasis in TNBC [104].

These findings highlight diverse pharmacological strategies to modulate EIF4EBP1, with rapalogs and mTOR inhibitors primarily targeting phosphorylation, while upstream pathway modulators and translational regulators offer complementary mechanisms to disrupt oncogenic translation and improve therapeutic outcomes.

4.3 EIF4EBP1: A Clinically Relevant Prognostic Biomarker in Breast Cancer

EIF4EBP1 has been identified as a critical prognostic marker in breast cancer, especially in patients with HER2/neu overexpression or amplification [105]. Increased expression and phosphorylation of EIF4EBP1 correlate with poor prognosis [35,36,106,107,108,109], higher tumor grade [110], and resistance to endocrine therapy [2,59,111], including tamoxifen [112]. High levels of phosphorylated EIF4EBP1 are associated with features such as increased tumor size, increased lymph node metastasis, and increased risk of locoregional recurrence, indicating its role in aggressive tumor behavior [105,113].

The phosphorylation status of EIF4EBP1 is linked to tumor progression, with increased p-EIF4EBP1 levels predicting poor disease-free survival (DFS) [27], progression-free survival (PFS) [113], and distant recurrence-free survival (DRFS) [113,114]. High cytoplasmic expression of p-EIF4EBP1 is particularly predictive of poor outcomes, whereas nuclear p-EIF4EBP1 does not have a similar correlation [36,114]. Additionally, the EIF4EBP1/eIF4E ratio serves as a prognostic indicator, with a lower ratio (indicating hyperphosphorylation) linked to mTOR inhibitor resistance and aggressive tumor behavior [51].

Moreover, the role of EIF4EBP1 in endocrine resistance has been highlighted, with its expression being associated with a diminished response to therapies such as tamoxifen [2]. In tamoxifen-resistant breast cancer cells, high levels of EIF4EBP1 correlate with both poor prognosis and increased metastasis. Furthermore, the presence of EIF4EBP1 in the 8p11-p12 genomic locus, which is frequently amplified in breast cancer, further supports its role as a marker for endocrine therapy resistance [2,33,59].

Recent studies have also explored the involvement of EIF4EBP1 in autophagy-related gene models, in which it was shown to be associated with poor prognosis. Its overexpression, along with that of other markers such as S6K2, suggests a synergistic effect in promoting tumorigenesis [106,107,115,116,117].

In summary, EIF4EBP1 serves as a critical biomarker for assessing prognosis, treatment response, and resistance in breast cancer.

5. Conclusion and Future Perspectives

The current understanding of the role of 4E-BP1 (EIF4EBP1) in breast cancer pathogenesis and therapy highlights both the progress and persistent challenges that hinder translational advancements. While the dual role of 4E-BP1 as both a tumor suppressor and oncogenic effector is well documented, the field has often relied on oversimplified mechanistic models. Most studies attribute the

functional dichotomy of 4E-BP1 to its phosphorylation status, neglecting the spatial, temporal, and isoform-specific dynamics that fine-tune its activity in heterogeneous tumor microenvironments (TMEs). For instance, the commonly emphasized hierarchical phosphorylation model (Thr37/46 $\rightarrow$ Ser65/Thr70) overlooks noncanonical phosphorylation sites, such as Ser83, and their interaction with metabolic stress. This reductionist approach perpetuates conceptual redundancy, exemplified by the repetitive association between hyperphosphorylation and poor prognosis without addressing context-specific signaling mechanisms.

Therapeutic strategies targeting 4E-BP1 phosphorylation, such as the use of rapalogs and mTOR inhibitors, show promise but are hindered by methodological stagnation. These strategies remain clinically ineffective because of issues such as feedback reactivation, such as SGK3/Akt-driven rephosphorylation, and off-target effects. While combinatorial approaches (e.g., PI3K/mTOR + CDK4/6 inhibition) show preclinical potential, their translation is limited by an overemphasis on canonical pathways, often ignoring emerging regulators such as the CCR4-NOT complex or metabolic vulnerabilities such as polyamine dependency.

To transcend these limitations, the field must prioritize mechanistic depth beyond bulk phosphorylation analyses. Single-cell phosphoproteomics and ribosome profiling are essential for mapping site-specific regulation of mRNA subsets (e.g., pro-survival vs. metastatic transcripts) and elucidating non-phosphorylative modifications (ubiquitination and acetylation). Subtype-specific vulnerabilities, particularly in HER2-low or HER2-inflammatory breast cancers, demand organoid-based platforms to capture TME-driven plasticity. Moreover, the metabolic–epigenetic crosstalk of 4E-BP1—such as its potential role in chromatin accessibility during nutrient stress—requires urgent exploration. Therapeutic innovation must shift from mTOR-centric approaches to novel modalities such as PROTACs, RNA-based stabilization of hypophosphorylated isoforms, or polyamine disruptors, integrated with spatiotemporal pharmacodynamic profiling to prevent resistance. Biomarker refinement necessitates multiplexed spatial technologies (e.g., CODEX) to resolve compartment-specific activity and systems-level omics integration for composite signatures (e.g., 4E-BP1/FGFR1 co-amplification with metabolic fluxes).

EIF4EBP1 research stands at a pivotal juncture, where mechanistic complexity intersects with AI-driven innovation. By transcending reductionist paradigms through multi-omics and spatially resolved technologies and harnessing AI to decode context-dependent signaling networks, the field can unlock EIF4EBP1's full potential as a translational control hub. This synergy between molecular biology and computational analytics promises to redefine precision oncology, delivering actionable strategies for aggressive or resistant breast cancer subtypes.

Author Contributions

WJL and LLH conceived the review topic, designed the literature-search strategy, collected and screened the literature, interpreted the evidence, and drafted the original manuscript. DDT contributed to literature collection and interpretation for EIF4EBP1 signaling and therapeutic mechanisms and prepared/optimized the figures and tables. HYM and WJW contributed to literature analysis, verification of key mechanistic statements, and critical revision of the manuscript. SBL and XHL designed the overall framework of the review, supervised the project, resolved the interpretation of controversial evidence, and critically revised the manuscript. All authors contributed to editorial changes, read and approved the final manuscript, and agree to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the manuscript preparation, ChatGPT and Deepseek were used solely for language polishing and grammatical refinement. After using this tool, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

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