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Targeting of protein translation as a new treatment paradigm for prostate cancer

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Abstract

Purpose of review—This overview will summarize some of the developments in the area of protein translation, including as they relate to the therapeutic targeting of prostate cancer.

Recent findings—Translational control, mediated by the rate-limiting eukaryotic translation initiation factor 4E (eIF4E), drives selective translation of several oncogenic proteins, thereby contributing to tumor growth, metastasis, and treatment resistance in various cancers, including prostate cancer. As an essential regulatory hub, several oncogenic hyperactive signaling pathways appear to converge on eIF4E to promote tumorigenesis. Several approaches that target the eIF4E-dependent protein translation network are being actively studied, and it is likely that some may ultimately emerge as promising anticancer therapeutics.

Summary—An array of inhibitors has shown promise in targeting specific components of the translational machinery in several pre-clinical models of prostate cancer. It is hoped that some of these approaches may ultimately have relevance in improving the clinical outcomes of patients with advanced prostate cancer.

Keywords

Prostate cancer; protein translation; eIF4F/eIF4E

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Conflicts of interest:

None

Introduction

Cancer cells are inherently capable of reprogramming the cellular proteome to adapt to a stressful tumor microenvironment. While deregulations in the expression and activity of translational regulators contribute to quantitative proteome reprogramming, selective translation of a subset of mRNAs that permits rapid and spatial production of certain proteins may contribute to tumor development and tumor progression [1,2]. Much of the research on translational control has focused on eukaryotic translation initiation factor 4E (eIF4E), the translational hub of several complex cancer signaling networks [3–6]. •

Translational control is a stringently regulated process consisting of four steps, namely: initiation, elongation, termination and ribosome recycling [7,8]. Translational control occurs predominately during initiation, the rate limiting step that is subject to extensive regulation [9,10]. Translation initiation complex (eIF4F)-, is a multicomponent complex containing several proteins including: eIF4E, which physically binds to a 5'-terminal cap structure, 7-MeGpppN (N is any nucleotide); eIF4A, an ATP-dependent helicase that unwinds secondary structures in the 5' UTR; and eIF4G, a scaffolding protein that serves a docking function in the assembly of eIF4F complex. Translation initiation functionally commences with the binding of eIF4E specifically to the 7-MeGpppN moiety in the 5'-cap structure. At this point, eIF4E interacts with the central scaffolding protein eIF4G, which in turn binds several additional factors, including the RNA helicase eIF4A, and poly (A) binding protein (PABP). This interaction results in the formation of a tripartite eIF4E:eIF4G:eIF4A core, termed the 'eIF4F complex'. The interaction of eIF4G with the eIF3 multi-component initiation factor is mandatory for the recruitment of 43S pre-initiation complex that encompasses the 40S ribosomal subunit and associated initiation factors [9–11]. Following assembly at the cap structure, the 43S pre-initiation complex scans along the 5' UTR of mRNA until it encounters the initiation codon, AUG. The movement of the scanning initiation complex along the mRNA can be stalled by the folded secondary structure within the 5'-UTR. eIF4A along with helicase accessory protein, eIF4B, serves to unwind such structures to facilitate scanning and ensuing translation of the mRNA. Once a suitable start codon has been located, the 60S large ribosomal subunit joins to form the 80S ribosomal complex. At this stage, the translation initiation complex leaves the now-complete ribosome for the commencement of translation elongation [12]. The interaction of eIF4G and PABP with the 5' and 3' ends of the mRNA brings about the circularization of the mRNA, facilitating the shunting of ribosomes from the termination codon to the mRNA 5'-cap to stimulate translation [13].

A vast majority of eukaryotic mRNAs are translated in this cap-dependent manner where eIF4E plays a prime role [9,10]. However, the requirement for eIF4E varies dramatically among mRNAs. Under most circumstances, mRNAs with short 5' UTR and devoid of upstream AUGs (referred to as "strong mRNAs") are feebly translated by eIF4E. In contrast, mRNAs with long G/C-rich 5' UTRs, with the potential of forming stable secondary structures, and/or upstream AUGs (referred to as "weak mRNAs") are highly dependent on cap-mediated translation [14]. These mRNAs include growth factors and cytokines (e.g., fibroblast growth factor 2, insulin-like growth factor II, platelet-derived growth factor, TGF- β , VEGF, interleukin 15, Wnt/ β -catenin), protein kinases (e.g., Mos, Pim-1), transcription factors (e.g., Fos, Myc), polyamine biosynthetic enzymes (e.g., ornithine decarboxylase,

ornithine aminotransferase), inhibitors of apoptosis (e.g., survivin, Bcl-2, Bcl-XL), promoters of cell-cycle transit (e.g., Ras, Cdk 4, cyclin D1; cyclin D3 and mouse double minute 2) and matrix metalloproteinases. Thus, higher eIF4E levels result in inappropriate expression of key controllers of cell growth, survival, and proliferation without any effect on house-keeping genes [15,16]. ••

Regulation of cap-dependent protein translation

Regulation of cap-dependent translation chiefly occurs at the level of eIF4E and includes gene expression, sequestration and phosphorylation, among other processes [17]. Myc can transcriptionally activate the eIF4E gene through two Myc-binding sites (E-boxes) in the eIF4E promoter [18]. At the post-transcriptional level, eIF4E mRNA is stabilized by the transcriptional factor, HuR. Post-translationally, eIF4E can undergo proteasome-dependent degradation following ubiquitination at Lys-159 [19,20]. In addition, primary regulation of eIF4E activity is exerted through the PI3K/Akt/mTORC1/S6K/4E-BP–signaling axis [18]. This signaling axis is positively regulated by Ras and leads to hierarchical phosphorylation of the 4E-BPs, the well-studied eIF4E inhibitory proteins. While interaction between eIF4E and eIF4G is crucial for formation of the eIF4F complex and initiation of cap-dependent translation, 4E-BPs sharing a common eIF4E-binding motif with eIF4G compete for the same phylogenetically invariant dorsal surface of eIF4E, thereby sterically blocking the binding of eIF4G to eIF4E. This in turn prevents the assembly of 48S pre-initiation complex and restricts translation of mRNAs that are eIF4E dependent [21]. However, 4E-BPs can be phosphorylated by the nutrient sensor, mammalian target of rapamycin complex 1 (mTORC1). This results in the release of 4E-BPs from eIF4E, allowing eIF4G to bind to eIF4E. Free eIF4E can in turn associate with eIF4G to stimulate translation initiation. Thus, cellular levels of amino acids, hormones, and growth factors can directly influence translation initiation via mTOR mediated phosphorylation of 4E-BPs [22,23]. Other proteins such as Maskin and Cup can also associate with eIF4E on specific mRNAs through interactions with RNA-binding proteins to inhibit eIF4E [21].

In addition to regulation by mTORC1 signaling, eIF4E is subject to regulated phosphorylation at a single C-terminal residue, Ser209. This is mediated by the MAP kinase-interacting protein kinases (MNK), which are in turn activated by ERK and p38 MAPK pathways [24,25]. • Phosphorylation of eIF4E (the only validated in vivo substrate for MNKs) at ser209 is a prerequisite for the activity of eIF4E in cancer cells, whereas dispensable for normal development [26]. Mice and humans have two genes encoding MNKs, *Mknk1* and *Mknk2*. In humans, each gene undergoes alternate splicing that subsequently results in the production of two distinct proteins. The longer forms of the proteins are termed ‘MNK1a’ and ‘MNK2a’; and the shorter forms are referred to as ‘MNK1b’ and ‘MNK2b’. MNK1a is largely cytoplasmic in distribution and is tightly regulated by ERK/p38 MAPK signaling. MNK2a is distributed mostly in the nucleus and has a high basal activity. The C-termini of both MNK 1a and 2a isoforms contain a binding site for MAPKs, and the N termini comprise a polybasic sequence that binds eIF4G and importin. Presence of importin mediates entry of MNKs into the nucleus [27,28]. Thus phosphorylation of eIF4E at ser209 by MNKs is inevitable for its activation and initiation of cap dependent translation. Biophysical studies indicate that phosphorylated eIF4E binds less

tightly to capped mRNA than non-phosphorylated protein [29]. MNKs can be dephosphorylated and deactivated by protein phosphatase 2A (PP2A). This action prevents MNK-mediated eIF4E phosphorylation and acts as a mechanism of negative regulation [30]. Figure 1 illustrates the mechanisms regulating eIF4E mediated cap dependent translation.

Role of eIF4E in prostate cancer

Mounting evidence continues to emphasize the significance of deregulated cap-dependent translation in several cancers, including that of the prostate gland. eIF4E, the core element of the translation machinery complex is positioned at the molecular nexus downstream of key oncogenic signaling pathways (e.g. Ras, PI3K/AKT/mTOR, and Myc) [18]. Hence, activation of eIF4E, which serves as a direct link between translation initiation and tumor development, plays a significant role in the development, progression, aggressiveness, and therapeutic resistance of prostate cancers. A study by Graff et al. [31] showed that both eIF4E and 4E-BP phosphorylation were elevated in 89 advanced prostate cancer patients which correlated with poor survival. In this same study, use of an antisense oligonucleotide specific to eIF4E markedly reduced the protein expression of eIF4E modulated mRNAs (Bcl2 and Mcl1) and enhanced apoptosis. Furic et al. [32], investigating the clinical importance of eIF4E in prostate cancer patients, observed a positive correlation between high Gleason scores and disease progression with eIF4E phosphorylation. They also performed tissue staining from BPH patients with no prostate cancer and compared them with malignant tissues. The results revealed increased eIF4E phosphorylation in the malignant tissues. Interestingly, they observed that MMP3, which is regulated by the MNK1/2-eIF4E translation complex, also positively correlated with eIF4E phosphorylation [32]. Pre-clinical studies in prostate cancer cells have shown that eIF4E phosphorylation initiated by MNK activation can lead to epithelial mesenchymal transition (EMT) and thus affect migration and invasion of these cells. EMT markers implicated in extracellular matrix degradation and remodeling such as MMP-2/3/9, in addition to Snail and N-cadherin, have been shown to be tightly regulated by the MNK-eIF4E axis [33]. Several other genes implicated in malignant prostatic disease, such as c-FLIP, cyclin D1, VEGF, c-Myc, HIF1 α and ornithine decarboxylase, are also regulated by eIF4E [34,35]. Bianchini et al. [36], previously showed that protein synthesis modulated by eIF4E phosphorylation significantly impacts cell cycle progression and prostate cancer growth. An in-depth study on eIF4E activity in relation to PTEN status revealed that loss of eIF4E phosphorylation resulted in significant decrease of 35 mRNAs, including CCL2 and CCL7, which are implicated in tumor progression. This combination of dysregulation is significant in prostate cancer as PTEN loss is known to cause early onset of prostate intraepithelial neoplasia and invasive disease [37]. Other studies have implicated eIF4E phosphorylation in the expression of stem cell factors such as Oct-4, Nanog, CD44 and β -catenin in several cancers, including prostate cancer. A recent study by Kwegyir-Afful et al. [33] showed that silencing of MNK1 resulted in a marked downregulation of eIF4E phosphorylation with resultant dramatic depletion of BMI-1, Nanog and β -catenin. Regulation of BMI-1 by the MNK-eIF4E axis is especially significant in prostate cancer as BMI-1 has been reported to be upregulated and implicated in docetaxel resistance [38]. Thus, accumulating evidence from pre-clinical and clinical

studies has revealed that the MNK1/2-eIF4E signaling axis may be a key target for therapeutic intervention of prostate cancer, and also other solid and hematological malignancies. Figure 2 outlines some of the potential advantages of targeting eIF4E mediated translation initiation in prostate cancer.

Therapeutic targeting of cap-dependent translational complex

Considerable efforts have been made over the past decade to target eIF4E directly or indirectly for cancer therapy. eIF4E-targeted strategies comprise of targeting eIF4E synthesis; antagonizing eIF4E-to-cap and eIF4E-eIF4G interactions; sequestering eIF4E; and inhibiting eIF4E ser209 phosphorylation. Figure 3 and Table 1 summarize agents that target key components of the eIF4F translational machinery. Graff et al. [39] made the first attempt to target eIF4E directly by developing an anti-sense oligonucleotide (ASO) against eIF4E. These ASOs decreased eIF4E proteins and had dramatic cytotoxic effects at nanomolar concentrations across a panel of human cancer cell lines. Further, intravenous ASO administration selectively reduced eIF4E expression and suppressed tumor growth in human tumor xenografts without affecting body weight, organ weight, or liver transaminase levels. A phase 1 dose escalation study with ASO LY2275796 in patients with advanced solid tumors demonstrated that LY2275796 was well tolerated at the 1000 mg dose level with mild toxicities [68]. An alternative strategy to directly diminish eIF4E activity is to use siRNA. eIF4E knockdown using specific siRNAs has been reported to suppress cell growth in endometrial adenocarcinoma and squamous carcinoma cells, and enhance chemosensitivity, in addition to suppressing colony formation, in triple negative breast cancer cells [69–72].

Another effective approach to inhibit eIF4E activity is to antagonize eIF4E/cap or eIF4E–eIF4G interactions using specific inhibitors. Compounds of this class disrupt the formation of the eIF4F complex, and therefore impair translation of eIF4E-sensitive mRNAs [73]. An example of an eIF4E/cap inhibitor is ribavarin (1-β-D-ribofuranosyl-1, 2, 4-triazole-3-carboxamide), an antiviral guanosine analogue [40]. Ribavarin binds to eIF4E at the functional site used by 7-methyl guanosine mRNA cap and hence competes with eIF4E:mRNA binding [74]. Ribavirin is reported to potently suppress eIF4E-mediated oncogenic transformation of murine cells *in vitro*, of tumor growth in a mouse model of eIF4E-dependent human squamous cell carcinoma *in vivo*, and of colony formation of eIF4E-dependent acute myelogenous leukemia cells derived from human patients [75]. A clinical trial with ribavirin has shown to reduce eIF4E activity and induce partial remission in some M4/M5 acute myeloid leukemia (AML) patients [76]. Further, ribavirin also has effects on solid tumors and inhibits growth of several breast cancer cell lines with elevated eIF4E levels [77,78]. Another cap-binding agonist includes 4Ei-1, a tryptamine phosphoramidate prodrug of 7Bn-GMP (a synthetic nucleotide derivative that blocks the binding of eIF4E to the mRNA cap) [41]. 4Ei-1 is shown to reduce proliferation, suppress colony formation and repress EMT in mesothelioma cells with minimal toxic effects [42]. An alternative class of promising inhibitors includes compounds that prevent eIF4E–eIF4G interactions. The classic example of this is 4EGI-1, a small molecule inhibitor identified through high-throughput fluorescence polarization assay. 4EGI-1 displaces eIF4G from eIF4E and effectively enhances the association of 4E-BP1 to eIF4E [43]. 4EGI-1 is also

reported to have potent anti-proliferative and pro-apoptotic activity in multiple myeloma cells, Jurkat and A549 lung cancer cell lines [43,79]. The small molecule inhibitor 4E1RCat, discovered by Cencic et al. [44], also interferes with the interactions between eIF4E and eIF4G or 4E-BP1, consequently suppressing cap-dependent translation. 4E1RCat can reverse doxorubicin resistance in the Eμ-Myc lymphoma mouse model by enhancing the proapoptotic action of DNA damage [44]. Other eIF4E-eIF4G inhibitors include quabain and perillyl alcohol. Quabain, a cardiac glycoside directly binds to eIF4E and disrupts eIF4E/eIF4G association in a panel of human cancer cells [45]. Perillyl alcohol, a secondary product of plant mevalonate metabolism, attenuates interactions between eIF4E and eIF4G in prostate cancer cells [46]. Flavaglines, a family of natural products from the genus *Aglaia*, are reported to inhibit translation initiation by modulating the activity of eIF4A, the DEAD-box RNA helicase subunit of eIF4F complex [47]. Silvestrol, a cyclopenta[b]benzofuran flavagline, exhibits significant anticancer activity in human prostate and breast cancer xenografts primarily by impairing the ribosome recruitment step in translation initiation [48].

eIF4E activity can also be targeted by sequestering eIF4E. Phenethyl isothiocyanate (PEITC), a constituent in several edible cruciferous vegetables is demonstrated to inhibit cap-dependent translation in human prostate cancer cells by regulating the levels and phosphorylation of 4E-BP1 [49]. 4EBP-based peptides fused to an analogue of gonadotropin-releasing hormone are reported to bind to eIF4E, interfere with eIF4E-eIF4G interaction, and constrain cap-dependent translation in ovarian tumors [80]. Herbert et al. [81] reported that peptides based on conserved eIF4E-binding motifs linked to penetratin peptide-carrier sequence, resulted in rapid and dose-dependent apoptotic cell death in MRC5 cells. A eukaryotic expression vector pSecX-t4EBP1 containing phosphorylation defective 4E-BP1 and protein transduction domains, was shown to significantly inhibit tumor growth and enhance the radiosensitivity of breast carcinoma xenografts in BALB/C mice [82]. Yu et al. [83] demonstrated that combined translational deregulation by incorporating an eIF4E-UTR recognition sequence into a therapeutic gene, together with transcriptional dysregulation with a prostate-specific promoter, selectively destroys gene expression in prostate cancer cells while sparing normal cells.

Inhibitors of the upstream signaling pathway PI3K/Akt/mTOR cause dephosphorylation of 4E-BPs, resulting in inhibition of eIF4E. In particular, inhibitors of the mTOR pathway are therapeutically attractive since 4E-BPs are direct substrates of mTOR kinase [84]. Some of the well characterized compounds of this class include rapamycin (sirolimus) and its derivatives (rapalogues). Rapamycin inhibits mTORC1 mediated phosphorylation of 4E-BP1, which in turn sequesters eIF4E and restrains the initiation of cap-dependent translation [50]. Although rapamycin exhibited potent antitumor effects in experimental tumor models, it failed to demonstrate promise as an anticancer drug in clinical trials [85–87]. Hence, rapamycin analogues (rapalogues) with more favorable pharmaceutical characteristics such as RAD001 (Everolimus), CCI-779 (Temozolimus), AP23573 (Deforolimus), SAR943 (32-deoxorapamycin) and ABT-578 (Zotarolimus) have been developed [51, 52, 88, 89]. RAD001 and CCI-779 have been approved by the FDA for the treatment of advanced renal cell carcinoma [53,90]. CCI-779 also has substantial single-agent activity in certain haematologic malignancies such as mantle cell lymphoma [91]. In addition, rapamycin and

rapalogues have demonstrated efficacy in combination with other chemotherapeutics [92–94].

Other recent therapeutic strategies have focused on developing mTOR catalytic inhibitors that target both mTORC1 and mTORC2. Examples of this class of compounds include PP242, PP30, OSI-027, torin 1, AZD8055, WYE-125132, WYE-354, Ku-0063794, and palomid 529 [54–57, 95–97]. These second generation (catalytic) mTOR inhibitors can effectively minimize the feedback activation of Akt by mTORC2 to avoid offsetting their effects of sequestering eIF4E. Importantly, they inhibit 4E-BP phosphorylation more strongly than rapamycin and rapalogues [88]. Another potential class of mTOR kinase inhibitors is the dual PI3K/mTOR inhibitors. These inhibitors simultaneously target ATP binding sites of mTORC and PI3K with similar potency, and include SF1126, NVP-BEZ235, NVP-BGT226, PI103, XL765, and GNE-477 [59–61, 97–99]. These compounds can prevent PI3K pathway reactivation caused by the mTOR–p70S6K negative feedback loop, and thus have the potential to more thoroughly sequester eIF4E [58]. In contrast to conventional mTOR inhibitors, a novel esterified K β BA derivative, cinnamoyl-K β BA (C-K β BA), is reported to inhibit mTOR activity via downregulating the phosphorylation of p70 ribosomal S6 kinase, the major downstream target of mTORC1. C-K β BA mediated inhibition of mTOR signaling is shown to occur independently of mTOR upstream kinases (Akt and PDK1) and the negative regulators (TSC2 and PP2A), resulting in potent antiproliferative and proapoptotic effects in prostate cancer cells as well as in PC-3 prostate cancer xenografts [62]. Ligustrazine, a key component of the Chinese herb Chuanxiong, modulates the availability of eIF4E and subsequently inhibits cap-dependent translation in castration resistant prostate cancer (CRPC) chiefly through inhibition of mTOR activation [63].

Targeting MNKs to reduce eIF4E activity represents another potentially useful treatment strategy, and includes compounds that function as MNK degraders and MNK inhibitors. MNK degraders comprise of novel retinamides, galeterone (gal), and gal analogs (e.g., VNPT55) which have shown promise in inhibiting eIF4E activation and tumor growth in prostate, breast and pancreatic cancers [33,64–67]. MNK inhibitors, including CGP052088, CGP57380, cercosporamide, and 5-(2-(phenylamino)pyrimidin-4-yl)thiazole-2(3H)-one derivatives, have also been well studied [58]. The first preclinical proof of concept for novel MNK degrading agents (novel retinamides) was reported by our group [64]. • In this study, novel retinamides induced significant MNK degradation, resulting in the loss of phosphorylated eIF4E without any effects on the expression of total eIF4E levels in triple negative and Her-2 overexpressing breast cancer cells, and which was associated with apoptosis induction and inhibition of cell growth, colonization, invasion, and migration [64]. Novel retinamides (NRs) also caused degradation of MNK1 and MNK2, with subsequent reduction in phosphorylated eIF4E and downstream oncogenic programs in a series of androgen-sensitive (LNCaP), -insensitive (PC-3, C4–2B) and castration-resistant (22Rv1) human prostate cancer cells [65]. Amongst a series of NRs tested, VNLG-152 exhibited the highest efficacy in degrading MNKs, downregulating pEIF4E, and impeding eIF4E mediated oncogenic events in breast and prostate cancer cells [64,65]. C-4 heteroaryl 13-cis-retinamides were also found to induce MNK1/2 degradation via the ubiquitin–proteasome pathway, with resultant depletion of pEIF4E in human breast/prostate cancer cells *in vitro*

and MDA-MB-231 breast cancer/CWR22Rv1 prostate cancer xenografts *in vivo* [66]. By antagonizing the MNK-eIF4E axis, galeterone (gal) and its analog VNPT55 were found to profoundly inhibit migration and invasion in human prostate cancer cells and CWR22Rv1 tumor xenografts, possibly through modulation of several EMT- associated proteins such as snail, slug, N-cadherin, vimentin, and MMP-2/9 [33]. Gal and its analogs (VNPT55, VNPP414 and VNPP433-3 β) have also been recently found to downregulate MNK1/2 and pEIF4E with associated induction of G1 cell cycle arrest, caspase 3-mediated cell-death, and inhibition of cell migration/invasion in gemcitabine-sensitive and –resistant pancreatic ductal adenocarcinoma (PDAC) cells. Further, these agents strongly inhibit tumor growth in MiaPaca-2 tumor xenografts (61% to 92%) by depleting MNK1/2 and pEIF4E [67].

Conclusion

Significant progress has been made in understanding the role of eIF4F- dependent pathways in mediating translational adaption, oncogenic transformation and malignant progression in several cancers, including that of the prostate gland. An array of inhibitors has shown tantalizing promise in targeting specific components of the translational machinery in prostate cancer models. However, knowledge on the role of these inhibitors is still in relative infancy, and their transition to the clinical setting will depend on extensive information on compound-mechanism hypothesis, compound-target engagement and pharmacodynamic activity. Thus, improved understanding of the existing bevy of inhibitors, and further discovery of novel molecules with improved efficacy to target the eIF4F translational complex, will facilitate the development of innovative clinical approaches to treating prostate cancers.

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KEY POINTS

- eIF4E-dependent pathways are a key hub in mediating translational adaptation, oncogenic transformation and malignant progression in prostate cancer.
- PI3K-Akt-mTORC1 signaling in response to extracellular stimuli results in phosphorylation of the translation repressors 4E-BPs which consequently dissociate from eIF4E, allowing the latter to form the “eIF4F translation initiation complex”.
- Mitogenic and stress signals activate eIF4E via components of the MAPK pathway including ERK and p38 MAPK, both of which converge to activate MNK1/2 that in turn phosphorylate eIF4E to cause translation initiation.
- Drugs targeting various components of the translation initiation machinery are in active development for a number of malignancies, including prostate cancer.

Figure 1. Mechanisms for the regulation of eIF4E mediated cap dependent translation and targeting strategies

PI3K pathway is activated in response to several extracellular stimuli resulting in the activation of downstream serine/threonine kinase, mTOR. mTOR associates with its binding partners and phosphorylates the translation repressors 4E-BPs, which consequently dissociates from eIF4E. Free eIF4E subsequently associates with eIF4A and eIF4G forming the “eIF4F translation initiation complex”. eIF4F consequently binds to m7G cap structure via the cap-binding protein eIF4E, promoting translation of numerous key oncogenic proteins. Mitogenic and stress signals can also activate eIF4E via components of the MAPK pathway including ERK and p38 MAPK. Both converge to activate MNK1/2, which bind to eIF4G and phosphorylate eIF4E at ser209 resulting in translation initiation. Drugs targeting cap dependent translation include (a) mTOR or dual PI3K/mTOR inhibitors; (b) eIF4E inhibitors; (c) inhibitors of eIF4E-4G interaction; (d) eIF4A inhibitors; (e) MNK degraders or inhibitors; (f) Inhibitors of eIF4E and Me⁷ G-capped mRNA interaction.

Figure 2. Therapeutic targeting of eIF4E inhibits growth and progression of prostate cancer irrespective of AR status.

Figure 3.
Molecular structures of agents targeting eIF4F translational initiation.

Table 1

Agents targeting eIF4F translation initiation

Target	Agent	Class	Reference
eIF4E synthesis	LY2275796	ASO	39
eIF4E-cap interaction	Ribavirin	Nucleoside analog	40
	7Bn-GMP, 4Ei-1	Small organic	41, 42
eIF4E-eIF4G interaction	4EGI-1, 4E1RCat, Quabain, Perillyl alcohol	Small organic	43, 44–46
eIF4A activity	Flavaglines, Silvestrol	Small organic	47, 48
4E-BPs regulator	PEITC	Small organic	49
mTORC1	Rapamycin	Antibiotic	50
	ABT-578, AP23573, CCI-779	Rapamycin analogues	51, 52, 53
mTORC1 and mTORC2	AZD8055, Ku-0063794, WYE-125132, Palomid 529	Small organic	54–56, 57
MNK inhibition	CGP57380, cercosporamide, 5-(2-(phenyloamino)pyrimidin-4-yl)thiazole-2(3H)-one derivatives	Small organic	58
PI3K-mTOR	SF1126, NVP-BEZ235, PI103	Small organic	59, 60, 61
p70 ribosomal S6 kinase	C-KbBA	Small organic	62
eIF4E availability	Ligustrazine	Small organic	63
MNK degradation	Novel retinamides, C-4 heteroaryl 13-cis-retinamides, Galeterone, VNPT55	Small organic	64–67