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Targeting RPS6K1 for Refractory Breast Cancer Therapy

Jayalakshmi Sridhar[1] • Rajesh Komati[2] • Satyendra Kumar[1]

[1]Department of Chemistry, Xavier University of Louisiana, Louisiana, USA;
[2]Department of Chemistry, Nicholls State University, Louisiana, USA

Author for correspondence: Jayalakshmi Sridhar, Department of Chemistry, Xavier University of Louisiana, 1 Drexel Dr., New Orleans, LA, USA. Email: jsridhar@xula.edu

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Abstract: In 2020, female breast cancer overtook lung cancer to become the most diagnosed cancer worldwide. Nearly 30% of women diagnosed with early-stage breast cancer have recurrent disease with resistance to therapeutics evidenced in 25% of cases. The hormone receptor positive (ER+ and PR+) and HER2+ breast cancers quickly develop resistance to the frontline therapeutics, namely, endocrine therapy and trastuzumab treatment. The overactivity of the PI3K/mTOR/S6K1 pathway has been shown to lead to multidrug resistant breast cancer. While PI3K and mTOR targeted therapeutics have shown promise, development of resistance and mutations in these proteins have limited the success of these agents. S6K1 kinase, a downstream effector whose activation leads to translation of ribosomal proteins, enhancement of mRNA biogenesis, and cap-dependent translation and elongation, is a critical player in the PI3K/mTOR pathway and the ER+ pathway. Inhibiting the activity of S6K1 can provide the needed therapeutic option for resistant/refractory breast cancer patients.

Keywords: human epidermal growth factor receptor 2; mammalian target of rapamycin; refractory breast cancer; ribosomal protein S6 kinase 1; RPS6K1

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INTRODUCTION

The ribosomal protein S6 kinase beta family of genes *RPS6KB1* and *RPS6KB2* encode several proteins that are serine threonine kinases (1). Alternate use mRNA translational AUG start codons on *RPS6KB1* is known to generate distinct isoforms of the protein: p70S6K1, p85S6K1, (2, 3), p60S6K1, and p31S6K1 (4, 5). p85S6K1, the larger isoform, includes the nuclear localization sequence (NLS) in the N-terminus with a 23 amino acid extension which was initially thought to be constitutively nuclear (5–7) but recent studies based on nuclear-cytoplasmic fractionation show its presence in the cytoplasm of breast cancer cells (5, 8). p70S6K1 is thought to be mostly localized in the cytoplasm but studies have shown it to accumulate in the nucleus leading to the conclusion that p70S6K1 may transit between the cytoplasm and nucleus of the cell (5, 9). The scant literature on the shorter isoform p31S6K1 only indicate it to be located in the nuclei of human normal fibroblasts (8). Through phosphorylation, dephosphorylation, ubiquitination and acetylation, S6K1 is involved in protein synthesis, cellular growth, metabolism, cell structure and organization, aging and adiposity, memory, immunity, and muscle hypertrophy (3). Two isoforms, p70S6K1 and p85S6K1, have been extensively studied as these are the targets for mammalian target of rapamycin (mTOR) phosphorylation and play an important role in cancer progression, enhanced cell viability, migration, and resistance to existing therapeutics (10).

S6K1 STRUCTURE AND REGULATION

S6K1 isoforms belong to the AGC serine/threonine protein kinase family. The shorter isoform p70S6K1 has 502 residues and the longer isoform p85S6K1 has 525 residues with the additional NLS 23 residues in the N-terminus. The kinase domains of both isoforms have identical sequences. Eight phosphorylation sites (residue numbers based on p70S6K1 sequence) have been identified in the catalytic domain (Thr229), linker region (Ser371, Thr389 and Ser404), and the putative autoinhibitory region (Ser411, Ser418, Thr421 and Ser424) (11–13) as shown in Figure 1A. The four residues in the autoinhibitory region need to be phosphorylated initially to expose the residues in the catalytic domain and the linker region for phosphorylation. PDK1 phosphorylates Thr229 on S6K1 which is in the activation loop of the kinase domain. Thr389 which is in the hydrophobic motif is the target for mTOR phosphorylation. Both of these phosphorylations are essential for the catalytic activation of the kinase (12). It has been proposed that in the autoinhibitory inactive state, the C-terminus pseudosubstrate domain of S6K1, which is basic in nature, interacts with the N-terminus, which is acidic, and blocks the key phosphorylation sites in the kinase domain (14). Initiation of activation is facilitated by a calcium-dependent priming step (15), followed by sequential phosphorylation of the C-terminus residues (Ser411, Ser418, Thr421 and Ser424) (16) inducing a conformational change opening up the phosphorylation sites on the T-loop, the turn motif, and hydrophobic motif. Phosphorylated T-loop induces critical conformational change to the active form of S6K1. Phosphorylated turn motif stabilizes the phosphorylated hydrophobic motif that

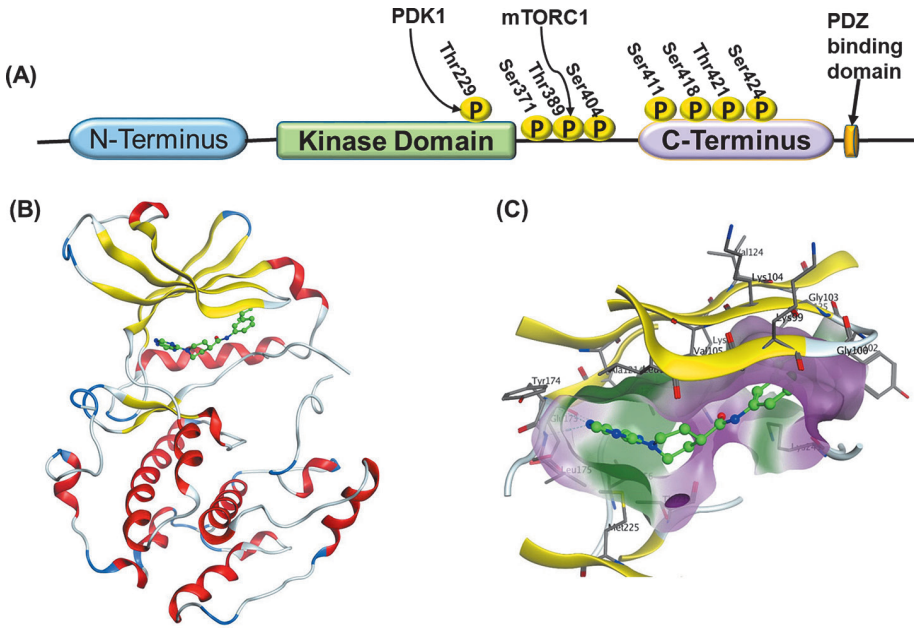

Figure 1. p70 S6K1 structure and schematic overview of S6K1 activating phosphorylation sites. **A,** p70S6K1 isoform, structure, and domain organization with phosphorylation sites. Residues phosphorylated by 3-phosphoinositide-dependent kinase 1 (PDK1) (Thr229) and mammalian target of rapamycin (mTORC1) (Thr389) are identified. **B,** The ribbon model of the kinase domain of S6K1 bound to the ligand 1-(9H-purin-6-yl)-N-[3-(trifluoromethyl)phenyl] piperidine-4-carboxamide adapted from reported crystal structure '3WF7.pdb'. **C,** Molecular surface depiction of the ligand binding pocket (3WF7.pdb) colored by lipophilicity (green) and hydrophilicity (purple) and the residues lining the pocket labeled in black.

binds to the N-lobe hydrophobic pocket (17, 18). The active conformation of the kinase domain bound to an inhibitor 1-(9H-purin-6-yl)-N-[3-(trifluoromethyl) phenyl]piperidine-4-carboxamide is shown in Figure 1B. The molecular surface map depicting the hydrophobic and lipophilic parts of the ATP-binding site (inhibitor replacing ATP) is shown in Figure 1C.

S6K1 AND BREAST CANCER

Breast cancer is the most prevalent cancer worldwide with 2.3 million new diagnosis and 685,000 deaths globally in 2020. In the United States, the estimated number of new breast cancer diagnosis is 281,550 with 43,600 deaths in the year 2021. There are four main types of breast cancer: luminal A (estrogen receptor [ER] and progesterone receptor [PR- positive status and corresponding human epidermal growth factor receptor 2 [HER2]-negative status); luminal B (ER, PR, and HER2-positive status); HER2-enriched (HER2+) with ER and PR-negative status; and the triple-negative (ER, PR and HER2-negative status). Triple-negative

breast cancer has the worst prognosis followed by the HER2+, luminal B, and luminal A. Luminal A is low-grade and has the best prognosis. The PI3K/AKT/mTOR pathway has a major role in cell metabolism, cell growth, cell proliferation, apoptosis and angiogenesis (19). This pathway is one of the most mutated pathways leading to altered protein functions and aberrant phosphorylation (Figure 2) (20, 21). Activation of mTOR is the hallmark of several cancers including breast cancer where it is highly deregulated and plays a key role on tumorigenesis (22).

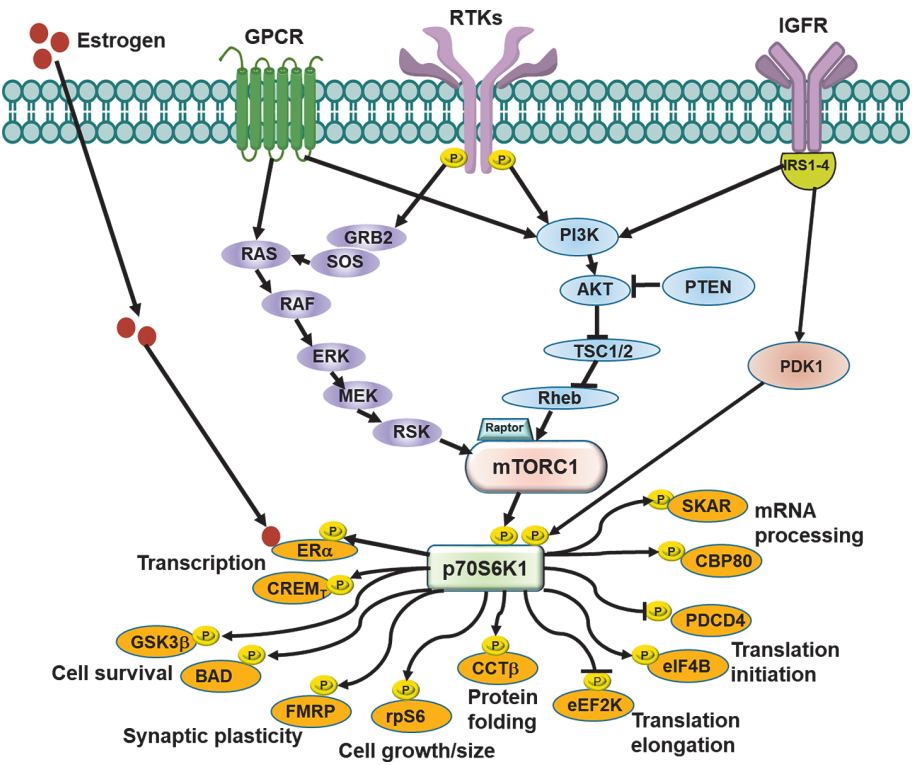

Figure 2. S6K1 is activated by coordinated phosphorylation by mTORC1 and PDK1. Growth factors, mitogens, and amino acids activate S6K1 through the PI3K/AKT/mTORC1, MAPK, IRS pathways. Activated S6K1 regulates several cellular processes by phosphorylation of substrates: mRNA processing via S6K1 Aly/REF-like target (SKAR), nuclear cap-binding protein subunit 1(CBP80); cap-dependent translation initiation via programmed cell death protein 4 (PDCD4) and eukaryotic translation initiation factor 4B (eIF4B); translation elongation via eukaryotic elongation factor 2 kinase (eEF2K); protein folding via T-complex protein 1 subunit beta (CCTβ); cell growth/size via ribosomal protein S 6 (rpS6); synaptic plasticity via fragile X mental retardation protein (FMRP); cell survival via glycogen synthase kinase β (GSK3β), Bcl-2-associated death promoter (BAD); transcription via transcription factors estrogen receptor alpha (ERα) and cAMP-responsive element modulator ($CREM_T$). ERK, extracellular-signal-regulated kinase; GPCR, G-protein coupled receptor; GRB2, growth factor receptor bound protein 2; IGFR, insulin growth factor receptor; IRS1-4, insulin receptor substrate 1–4; MEK, mitogen activated protein kinase kinase; PTEN, phosphatase and tensin homolog; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; RAF, rapidly accelerated fibrosarcoma; Rheb, Ras homolog enriched in brain; RAS, rat sarcoma virus; RTKs, receptor tyrosine kinases; RSK, ribosomal protein S6 kinase; SOS, son of sevenless; TSC1/2, tuberous sclerosis complex ½.

mTOR can associate with either Raptor or Rictor to form two distinct complexes mTORC1 or mTORC2 (23–25). Activated mTORC1 phosphorylates the key substrates p70S6K1 and elongation initiation factor (EIF)-4E binding protein 1 (4EBP1). Activated p70S6K1 promotes ribosome biogenesis and the translation of cell growth and cell division proteins including IRS1, CREMt, ERa, SKAR, FMRP, S6, BAD, GSK3, p21 and Cyclin D1 (26–32). mTORC1 is the downstream regulator of the PI3K/AKT signaling pathway which is activated in 60% of breast cancers (33–35). PI3K pathway indirectly activates mTORC1 mainly through AKT. Phosphorylation of tuberous sclerosis complex 2 (TSC2) by AKT results in its dissociation from TSC1/2 which is a negative regulator of mTORC1 activator RHEB. Additionally, AKT phosphorylates PRAS40 that is associated with Raptor and is an inhibitor of mTORC1 leading to dissociation of Raptor resulting in mTORC1 activation. ERK and RSK in the Ras-MAPK signaling pathway can also phosphorylate TSC2 which then initiates RHEB-mediated activation of mTORC1 (36). Other triggers for mTORC1 activation are intracellular ATP, glucose, and certain amino acids (leucine, arginine, and glutamine) (37).

RPS6KB1 gene amplification

The chromosomal region 17q22-17q23 is found to be often amplified in breast cancer (38). High copy number amplification of *RPS6KB1* gene (≥3 copies), which is in the 17q23 genomic region, is evidenced in 10.7% of breast cancer while some amount of amplification of the *RPS6KB1* gene is also seen in several other types of cancer (4, 38). Immunohistochemical analysis of normal human breast tissue, benign and malign breast tissues have clearly shown that S6K1 is overexpressed in cancerous breast tissues when compared to normal breast tissues (39, 40). A study of 368 patients indicated increased risk of locoregional recurrence in breast cancer with an associated p70S6K1 overexpression and established p70S6K1 as a prognostic marker for locoregional recurrence indicating a key role (41). In a study of the global whole genome mRNA levels of S6K1 overexpressed tumors using the publicly available van de Vijver cohort (n = 295) showed positive association with RPS6 and PI3KCA mRNA in the PI3K/AKT/mTOR pathway (42).

S6K1 and receptor tyrosine kinases in breast cancer

HER2, and epidermal growth factor receptor (EGFR) belong to the ERBB family of receptor tyrosine kinases (RTKs- EGFR, HER2, HER3 and HER4)) that stimulate the PI3K/AKT/mTOR/S6K1 pathways. Overexpression of HER2 is evidenced in 20–30% of breast cancers (43) with the HER2 gene amplification being the main cause. While ligand binding activates EGFR, HER2 does not directly bind to any ligands for activation. Homo- and heterodimerization induce autophosphorylation in the intracellular kinase domain of these receptors (44). HER2-targeted therapies include antibodies that prevent dimerization in the extracellular domains, such as trastuzumab and pertuzumab, and reversible/irreversible ATP-competitive inhibitors of the kinase domain (lapatinib/neratinib) (45). These therapeutics have greatly improved the 5-year survival rates of luminal A/B breast cancer patients. Resistance to these therapeutics develop often with intrinsic *HER2* alterations, constitutive activation of downstream PI3K pathway due to

the activating mutation of downstream proteins, overexpression other ERBB family members and RTKs such as insulin-growth factor receptor 1 (IGFR1), fibroblast growth factor receptor-4 (FGFR4), and inactivation of tumor suppressor proteins (46–51). About 70% of HER2-positive breast cancer patients develop *de novo* or acquired resistance to trastuzumab leading to refractory metastatic breast cancer (52, 53). It has been shown that intense trastuzumab treatment induces PDK1 and mTORC1 phosphorylated activation of S6K1 exclusively in trastuzumab resistant breast cancer cells leading to the suggestion that S6K1 can function as an early biomarker of trastuzumab resistance and a viable target for inhibition for the treatment of refractory breast cancer (54).

Triple-negative breast cancers involve several pathways leading to cell division, cell growth, cell migration, and metastasis. The most prominent among these pathways is the EGFR overexpression and activation resulting in increased resistance to conventional therapies (55). It has been shown that anti-EGFR targeted therapies are beneficial for triple-negative breast cancers but have failed to demonstrate significant clinical efficacy as a standalone therapy. This lack of significant efficacy has been attributed to the constitutive activation of PI3K/AKT/mTOR pathway due to other genetic aberrations. A combination therapy approach that co-targets multiple proteins in this pathway may achieve efficient therapeutic effect for triple-negative breast cancer (56). Recent studies on the inhibition of S6K1 with the specific inhibitor PF-4708671 have shown promising potent anti-metastatic effect on triple-negative breast cancer cell lines (57).

FGFR4, a member of the receptor tyrosine kinase (RTK) family, is overexpressed in 30% of breast cancers (58). FGFR in conjunction with HER2 regulates the activity of cyclin D1 through MAPK and AKT/S6K1 pathways (Figure 3).

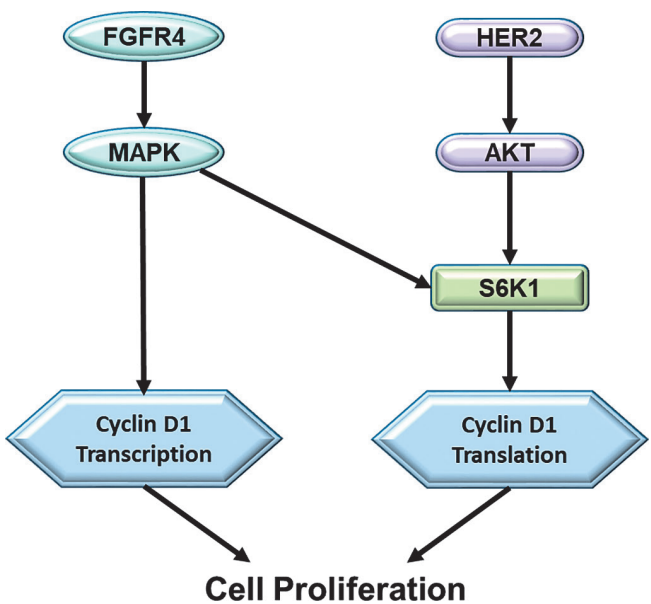

Figure 3. Model of regulation of cyclin D1 expression by collaboration between FGFR-4 and HER2 pathways leading to cell proliferation proposed by Koziczak and Hynes (61).

Based on the cell type and nature of the activating RTK, S6K1 stimulation occurs resulting in translational control of cyclin D1. Depletion of S6K1 by siRNA resulted in the reduction of S6 phosphorylation that led to a 20–30% decrease in cyclin D1 levels (59).

S6K1 and estrogen receptor alpha in breast cancer

Estrogen dependence is evidenced in 60% of breast cancers and targeted therapy with endocrine treatments such as antiestrogens and aromatase inhibitors have been frontline in clinical settings (60). Unfortunately, only 50% of ER+ breast cancers respond to endocrine treatments, and resistance develops eventually (60). The MAPK, PI3K and mTORC1 pathways have been implicated in resistance development in ER+ breast cancer leading to a deeper exploration of close interaction between the mTORC1/S6K1 and ER signaling (61). S6K1 can directly phosphorylate estrogen receptor alpha (ERα) on Ser167 in a ligand independent manner resulting in increased ERα transcriptional activity and enhanced cell proliferation (Figure 4) (62). Furthermore, estrogen induces the overexpression of S6K1 leading to the development and progression of breast cancer (63). The co-stimulatory relationship between ERα and S6K1 was evident in driving cell proliferation in low serum conditions with S6K1 able to partially rescue ERα knockdown (61, 64). Interestingly, S6K1 promoted ERα activation even in the absence of estrogen, leading to stimulation of cell proliferation and tumor transformation (61, 64, 65).

Estrogen-related receptor alpha (ERRα), an orphan nuclear factor and a master regulator of cellular energy metabolism, is an essential regulator of tumor

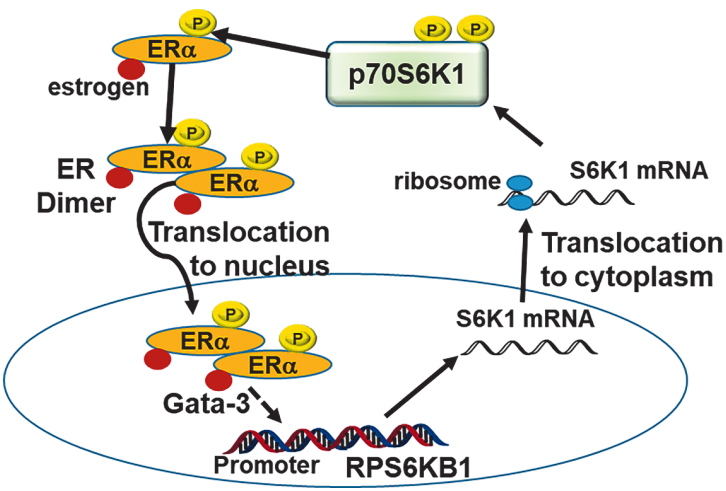

Figure 4. Positive co-regulatory mechanism of S6K1 and ERα. Estrogen binding and phosphorylation by S6K1 activates ERα leading to its dissociation of heat shock proteins (HSPs) and dimerization. ERα dimer translocates to the nucleus where it activates the promoter region of *RPS6KB1* and upregulates the transcription of S6K1 mRNA resulting in a positive feed-forward loop.

development as it provides for the energy needs of proliferating tumor cells (66, 67). ERRα expression is significantly increased in triple-negative breast cancer and ERα-negative breast cancers. MDA-MB-231 cells with reduced expression of ERRα showed increased expression levels of S6K1 mRNA and protein levels in conjunction with downregulation of ERα. ERRα was found to negatively regulate S6K1 expression by directly binding to its promoter, and inhibition of ERRα under low serum conditions resulted in increased expression of S6K1 due to increase in *RPS6KB1* gene expression (68).

TARGETING S6K1 FOR BREAST CANCER THERAPY

The importance of S6K1 in cell growth, cell proliferation, and metastasis is clearly evident in most types of breast cancers and thus S6K1 inhibition is emerging as a highly potential strategy for resistant/metastatic/refractory breast cancer. Frequent mutations in PI3K and PTEN lead to hyperactivation of mTOR and S6K1 (69, 70). Resistance to mTORC1 therapeutic rapamycin in cancer cells has been attributed to MAPK interacting kinase (MNK) which promoted subcomplex formation between MNK and mTORC1while decreasing the binding of DEPTOR (an mTOR inhibitor) to mTORC1 (71–74). Certain studies have hinted on S6K1 activation occurs by the action of eIF4E which is activated by MNK upon prolonged exposure to rapamycin (75). S6K1 hyperactivation has also been evidenced in breast cancers with mutations in IGF-1R, HER2, and FGFR (76). Additionally, *RPS6KB1* gene gain in ER+ breast cancer cells were a predictor of poor prognosis with S6K1 indicated as an important kinase for the growth of long-term estrogen deprived MCF7/LTED cells (77). All of these studies indicate that therapeutic intervention using S6K1 inhibitors can help for breast cancer cells that are resistant to current therapeutics.

In response to the evidenced role of S6K1 in resistant and refractory cancers, pharmaceutical companies have launched drug discovery efforts for S6K1 ATP-competitive inhibitors. Several compounds have been identified as S6K1 inhibitors belonging to the structural classes of indazoles, imidazoles, benzimidazoles, ureas, thiones, phenylpyrazoles, pyrozolopyrimidines, isoindolinones and organometallics (Figure 5).

PF-4708671

Pfizer developed the first specific S6K1 inhibitor PF-4708671 (IC_{50} of 0.160 μM), a benzimidazole derivative, along with 77 other protein kinases including 13 AGC kinase family members and its closest homolog S6K2 (IC_{50} = 65 μM) (78). RSK1, RSK2 and MSK1 were the other kinases inhibited by PF-4708671 (IC_{50} = 4.7 μM, 9.2 μM and 0.95 μM, respectively). PF-4708671 decreased phosphorylation of ribosomal protein S6 in HEK-293 cells. PF-4708671 has been used as the standard S6K1 inhibitor for the investigation of the role of S6K1 in several cancers. PF-4708671 in combination with tamoxifen was shown to be highly effective against ER+ MCF7 cells that had overexpression of S6K1 (79) and enhanced cell

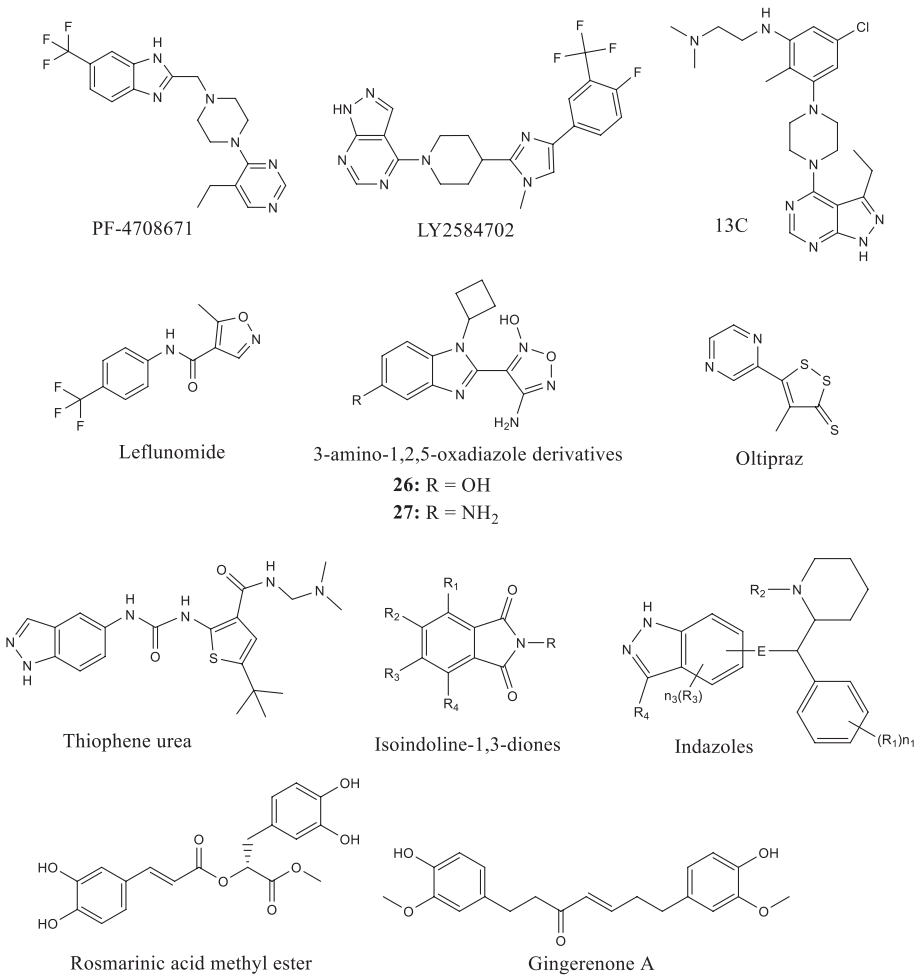

Figure 5. Structures of reported S6K1 ATP-competitive inhibitors.

death in glucose-starved MCF7 cells via downregulation of anti-apoptotic proteins Mcl-1 and survivin (80). The inhibitory effect of PF-4708671 on the AKT/mTOR/S6K1 pathway led to the inhibition of cell migration in triple-negative MDA-MB-231 cells and inhibition of local relapse in mice models (57, 81).

FS-115

The structure of the compound FS-115 has not been disclosed. FS-115 is reported to be a specific inhibitor of S6K1 (IC_{50} = 0.035 μM), S6K2 (IC_{50} = 2.06 μM), and AKT2 (IC_{50} = 23.8 μM). FS-115 showed high efficacy in the growth inhibition of

the triple-negative MBA-MD-231 cells with good pharmacokinetic and pharmacodynamics profile (82). Initial preclinical trials have indicated FS-115 is well tolerated in breast cancer patients with efficient suppression of distant metastasis formation (82).

LY2584702

Eli Lilly identified a 4-aminopyrazolopyrimidine molecule LY2584702, an inhibitor of p70S6K1, as an anti-tumor agent in advanced solid tumors in phase I and phase II trials (83, 84). LY2584702 was used to study the effect of S6K1 inhbition on non-small cell lung cancer (NSCLC) to establish phosphorylated S6K1 levels as prognostic marker for NSCLC patients. LY2584702 was found to suppress proliferation of NSCLC cells *in-vitro* (85).

Other heterocycles and urea derivatives

A series of pyrazolopyrimidines developed at Exelixis and derivatives exhibited selectivity for S6K1 (IC_{50} = 0.002 μM), Rsk2, PKA, AKT1 and AKT2 (IC_{50} values of 0.068, 0.042, 0.371 and 3.021 μM, respectively). Initial *in-vivo* xenograft studies on PC3 prostate cancer cell lines showed promising efficacy (86). The active ingredient of the immunosuppressive drug leflunomide, an isoxazole derivative A77 1726, inhibited S6K1 with an IC_{50} value of 0.080 μM. It was shown that A77 1726 exerted anti-proliferative effects in lymphocytes and tumor cells, and induced autophagy in part by inhibiting S6K1 activity (87). A series of 3-amino-1,2,5-oxadiazole derivatives developed by Vertex pharmaceuticals and Biofocus were found to be potent and selective inhibitors of S6K1. Two of these derivatives the 5-hydroxy-4-(benzimidazol-2-yl)-1,2,5-oxadiazol-3-amine and 5-amino-4-(benzimidazol-2-yl)-1,2,5-oxadiazol-3-amine (derivatives 26 and 27) exhibited <0.001 μM IC50 values with good selectivity over other AGC kinases (88).

Oltipraz belonging to a novel class of 1,2-dithiole-3-thiones were developed as S6K1 inhibitors by Sang Geon Kim's research group (89). Oltipraz inhibition of S6K1 was in conjunction with a H_2O_2 scavenging effect that resulted in HIF-1α activity inhibition and HIF-1α dependent tumor growth (90). The cancer therapeutic potential of oltipraz was explored extensively in *in-vivo* studies where oltipraz was found to induce diverse phase 2 enzymes, thereby decreasing the formation of carcinogen-DNA adducts (91). Phase 1 and 2 clinical trials indicated beneficial effects of oltipraz having diverse pharmacologic effects including reduced tumor growth (92). A series of thiophene urea derivatives that were initially identified as p39 inhibitors with an off-target activity against S6K1 were subjected to structure optimization studies that led to the development of a potent S6K1 inhibitor (IC_{50} = 0.015 μM) with excellent selectivity for S6K1 over 43 other kinases (93). Pharmacokinetic studies on thiophene urea derivatives indicated only moderate bioavailability and microsomal stability (94).

Derivatives of isoindoline-1,3-diones have been patented as S6K1inhibitors by Sridhar research lab (95). Derivatives of the isoindoline-1,3-dione series exhibited specific inhibition of S6K1 (IC_{50} values of 1–5 μM), WEE1, and PLK3 kinases

from a panel of 120 kinases. These compounds inhibited growth of multiple breast cancer cell lines that were ER+, HER2+ and triple-negative. Derivatives of indazoles have been patented by Sanofi-Aventis (96) as S6K1 inhibitors. Specificity and potency information for the indazole derivatives are not yet available. The search for natural products that are S6K1 inhibitors have resulted in the identification of rosmarinic acid methyl ester (RAME) (97) and gingerenone A (Gin A) (98) as S6K1 inhibitors with therapeutic potential for cancer and insulin resistance. RAME fully inhibited S6K1 activity at a concentration of 80 μM. RAME was also shown to induce autophagy and apoptosis in cervical cancer cells (97). Gin A was found to decrease S6 phosphorylation in a dose dependent manner and overcomes insulin resistance and enhanced insulin-stimulated glucose uptake in 3T3-L1 adipocytes and L6 myotubes (98). Organometallics complexes based on the core structure of staurosporine were developed as S6K1 inhibitors (99). The best complex, FL772, inhibited S6K1 (IC_{50} = 0.0073 μM) with >65% inhibition of 26 out of 456 kinases. FL772 was only able to inhibit S6 phosphorylation in budding yeast but not in 293T and $BRAF^{V600E}$ mutant melanoma cells.

CONCLUSION

Over the past two decades, enormous insight has been obtained on the role of S6K1 as regulator of cell growth and proliferation. Targeting S6K1 for therapeutic intervention in resistant and refractory breast cancer is promising. Several pharmaceutical companies and research groups have begun exploring the use of ATP-competitive inhibitors of S6K1 in treatment of cancers. Further studies are still needed to understand the overall function of S6K1 in different types of breast cancer to achieve complete success as therapeutics.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to research, authorship and/or publication of this manuscript.

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