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Review

p70S6 Kinase as a Key Regulator of Cancer Cell Growth and Proliferation

Syed Tabia Geelani[1], Iram Rashid[2], Shafat A. Latoo[1,*]

[1]Department of Biochemistry, Cluster University, Srinagar, Jammu and Kashmir, India

[2]Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Srinagar, Jammu and Kashmir, India

[*]Corresponding author: Shafat A. Latoo, shafat1s@yahoo.co.in

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Abstract

p70S6 kinase 1 (p70S6K1), encoded by RPS6KB1, is a serine/threonine kinase within the PI3K/AKT/mTOR signaling network that regulates protein synthesis, cell growth, metabolism, and other processes relevant to cancer progression. Its activity is controlled by multisite phosphorylation involving mTORC1, phosphoinositide-dependent kinases-1 (PDK1), and additional regulatory inputs, and therefore changes in p70S6K phosphorylation or abundance may have context-dependent biological and clinical consequences. Increasing evidence links aberrant p70S6K signaling with epithelial–mesenchymal transition, cancer stemness, therapeutic resistance, angiogenesis, and metabolic adaptation in selected malignancies. In addition to cell-autonomous effects within tumor cells, emerging studies suggest that p70S6K signaling participates in interactions between tumor cells and components of the tumor microenvironment (TME), including immune cells, adipocytes, fibroblasts, and endothelial cells. These non-cell-autonomous functions represent an important and comparatively less explored dimension of p70S6K biology. Therapeutic approaches targeting this pathway include direct p70S6K inhibitors, dual or multitarget kinase inhibitors, upstream mTOR/PI3K/AKT pathway inhibitors, RNA-based approaches, and emerging computational and protein-degradation strategies. Importantly, these approaches differ substantially in target selectivity, pharmacological development, and clinical evidence and should therefore not be considered equivalent. This review integrates the molecular regulation and cancer-associated functions of p70S6K with current therapeutic strategies, with particular emphasis on tumor–microenvironment interactions, the distinction between direct and indirect pathway inhibition, and the translational barriers that have limited the development of p70S6K-directed therapies.

1. Overview

Uncontrolled cell proliferation, which is mostly caused by out-of-control signaling across intracellular pathways responsible for cell growth, metabolism, and survival, is a key feature of cancer. Once activated in cancer cells (a persistent activation of pro-growth signaling pathways), these pathways contribute to unchecked cell division and tumor development. Under physiological conditions, these pathways are typically well regulated based on various external cues (e.g., the availability of growth factors or nutrients). The PI3K/Akt/mTOR signaling axis, a key regulator of cellular proliferation and protein synthesis, is a crucial pathway that has been changed in several cancer types [1,2]. The RPS6KB1 gene encodes p70 ribosomal S6 kinase 1 (p70S6K1/S6K1), a member of the AGC family of serine/threonine kinases that functions as an important downstream component of the mTORC1 signaling network. Rather than representing the sole or primary mediator of mTORC1 function, p70S6K1 operates together with other mTORC1-regulated effectors, including 4E-BP1, to coordinate translational and growth-related responses. p70S6K1 activity is regulated through multiple phosphorylation events, including mTORC1-dependent phosphorylation of Thr389 and phosphoinositide-dependent kinases-1 (PDK1)-dependent phosphorylation of Thr229. Although phosphorylation of ribosomal protein S6 is a well-established consequence of p70S6K1 activation, S6 phosphorylation alone does not fully account for the diverse effects of p70S6K1 on protein synthesis, cell-cycle regulation, metabolism, cell motility, and tumor progression [3] As a kinase belonging to the AGC family, p70S6K shares many structural and regulatory traits with other kinases, such as Akt and PDK1. Initially, p70S6K was identified for its function in phosphorylating ribosomal protein S6, which is a part of the 40S ribosomal subunit. Numerous ribosomal biogenic and cell cycle-related mRNAs are translated more readily as a result of this phosphorylation [4].

Extensive research has demonstrated that a series of phosphorylation events that follow mTOR signaling closely regulates p70S6K function. It has been demonstrated that p70S6K overexpression or aberrant activation frequently occur in a variety of human malignancies. Increased protein synthesis, a quick transition from G1 to S phase, and an increased capacity

for cancer cells to proliferate indefinitely have all been linked to higher activation of p70S6K signaling [5,6]. In several malignancies, increased p70S6K expression, phosphorylation, or altered subcellular localization has been associated with aggressive disease characteristics, treatment resistance, or adverse clinical outcomes. However, the clinical significance of p70S6K appears to depend on tumor type, cellular context, the specific phosphorylation state examined, and the biological compartment in which p70S6K is detected. Thus, p70S6K should not be considered a uniformly predictive or prognostic marker across all cancer types.There is growing evidence that p70S6K contributes to processes other than protein translation that are important for the development of cancer, including cell motility, metabolic reprogramming, epithelial-mesenchymal transition, and altering the tumor microenvironment (TME). The pleiotropic character of p70S6K in cancer and the growth of cancer cells is supported by these many functions [1,7].

p70S6K has drawn more interest as a possible target for cancer treatment due to its crucial functions in the development and spread of tumors. The development of selective inhibitors specifically for p70S6K has accelerated recently, despite the fact that current therapies primarily use mTOR inhibitors as an indirect means of inhibiting p70S6K activity.

The biological effects of p70S6K1 extend beyond phosphorylation of ribosomal protein S6. Activated p70S6K1 phosphorylates multiple substrates involved in translational control, cell growth, metabolism, and cell-cycle regulation. Consequently, S6 phosphorylation is an important pharmacodynamic readout of p70S6K activity but should not be interpreted as the sole mechanism through which p70S6K1 regulates tumor-cell behavior. This distinction is particularly relevant when evaluating pharmacological studies, because inhibition of S6 phosphorylation may result from direct p70S6K inhibition or from suppression of upstream signaling through mTORC1 or other components of the PI3K/AKT/mTOR network.

Despite extensive investigation of the PI3K/AKT/mTOR pathway, several aspects of p70S6K biology remain insufficiently resolved. In particular, the context-dependent functions of p70S6K, the distinction between direct p70S6K signaling and effects caused by upstream mTORC1 inhibition, its contribution to tumor-microenvironment communication, and the determinants of therapeutic response remain incompletely defined. Accordingly, this review focuses not only on the canonical functions of p70S6K but also on its non-cell-autonomous activities and the challenges involved in translating p70S6K-directed strategies into clinically useful therapies.

Objectives:

The objective of this study is to investigate multiple ways by which p70S6K may act in tumor progression and metastasis. We aim to achieve this through several specific aims focusing on the following:

• Description of mechanisms that regulate p70S6K activation within the mTOR pathway;

• Examination of p70S6K involvement in cell cycle regulation and metabolic control contributing to cancer cell hyperproliferation;

• Analysis of p70S6K's role in oncogenic signaling pathways, such as the PI3K/Akt/mTOR pathway;

• Summary of clinical and experimental data supporting a relationship between aberrant p70S6K activity and tumor growth, progression, and malignant behavior;

• Evaluation of current data on inhibiting p70S6K as a potential therapeutic target by evaluating the use of kinase inhibitors in the treatment of cancer; and

• Identification of the existing research limitations, challenges, and gaps regarding how p70S6K contributes to tumorigenicity.

Scope:

This literature review will provide an extensive summary of the published scientific information concerning the p70S6K kinase and its role in regulating cancer cell growth. It is primarily focused on four key aspects:

(1) The biochemical and molecular processes that regulate activation and function of the p70S6K kinase;

(2) The p70S6K kinase's contribution to tumorigenesis and cancer progression, particularly with regard to growing and surviving cells;

(3) The interaction of the p70S6K kinase with the major signaling pathways that have been implicated as playing critical roles in cancer biology;

(4) The potential use of p70S6K as both a prognostic marker and as a target for therapeutic intervention.

2. Structure and Domains of p70S6 Kinase

The main downstream effector of the mammalian target of rapamycin complex 1 (mTORC1) signaling pathway is p70 ribosomal s6 kinase (p70S6K), which is a member of the AGC family of Ser/Thr kinases [8]. About 502 amino acids make up the human form of p70S6K, which has several regulatory phosphorylation sites that allow it to self-activate.

The TOR signaling (TOS) motif is found in the acidic domain of the initial portion of p70S6K, which has a regulatory function. In order to obtain mTOR-dependent phosphorylation-activation on the p70S6K, this motif must bind to raptor, one of the elements of the mTORC1 complex. All members of the AGC family have a core catalytic domain with a two-lobed structure that comes after the N-terminal domain of p70S6K The ATP binding pocket is made up of the N-lobe and C-lobe. Threonine-229 (Thr-229 is also present in the sequence of an activation loop (T-loop) as shown in Figure 1. To properly function on the catalytic activity of the p70S6K protein, PDK1 must phosphorylate Thr-229 [9].

Critical phosphorylation sites (Thr389 and Ser371) are found in the linker region of p70S6K, which connects the

kinase domain (KD) to the regulatory domain (RD). Phosphorylation of Thr389 by mTORC1 is essential for maintaining the active configuration of p70S6K and enabling its subsequent activation through PDK1 [10].

The S6 kinase family-specific C terminus of p70S6K has several serines (Ser411, Ser418, Ser421, and Ser424), each of which adds to the domain's autoinhibitory properties. The KD's enzymatic activity is inhibited during resting conditions because the domain is not phosphorylated at any serine site. However, when this domain is phosphorylated at many sites, the KD's autoinhibition is removed, allowing substrate to reach the catalytic core.

In response to environmental cues, p70S6K can perform roles linked to protein synthesis, cell growth, and metabolism thanks to its modular domain architecture and tightly regulated phospho-events.

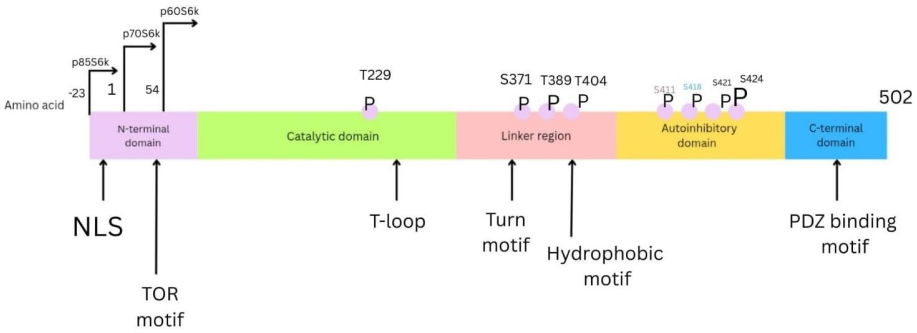


Figure 1. Structure and domain organization of S6K family of proteins.

3. PI3K/AKT/mTOR Signaling Pathway

The PI3K/AKT/mTOR pathway is an intracellular signaling cascade that regulates cell growth, metabolism, survival, and cell cycle progression. External stimuli that bind to receptor tyrosine kinases on the cell membrane, such as insulin, the IGF-1 hormone, EGF, and growth factors, initiate the pathway.

After a receptor is activated, the PI3K pathway is activated, causing PI3K to change phosphatidylinositol-4,5-bisphosphate (PIP_2) into phosphatidylinositol-3,4,5-trisphosphate (PIP_3), which acts as a docking point for signaling proteins known as downstream signaling molecules. Another signaling molecule, AKT, is recruited and activated when PIP_3 is present at the plasma membrane. AKT is activated by phosphorylating two additional molecules, PDK1 and mTORC2.

Among the many tasks that AKT carries out is the regulation of a number of downstream molecules that are essential for cell survival and cell cycle progression.

By suppressing cell cycle regulators like p27 and phosphorylating FOXO transcription factors, which results in their sequestration in the cytoplasm and decreases the transcription of pro-apoptotic genes, apoptotic signaling is suppressed. Furthermore, mTOR complex 1 (mTORC1), a crucial regulator of cellular metabolism and protein synthesis, is activated by AKT. Through the phosphorylation of downstream effectors, such as p70 ribosomal S6 kinase (p70S6K) and eukaryotic translation initiation factor 4E-binding protein 1 (4EBP1), mTORC1 controls mRNA translation and ribosomal biogenesis, enabling cell division and growth. Tumor suppressors like phosphatase and tensin homolog (PTEN) negatively control this signaling pathway by dephosphorylating PIP3, which stops AKT activation and maintains the signaling system's equilibrium.

The PI3K/AKT/mTOR (Figure 2) pathway is often dysregulated in cancers, and hyperactivation of the pathway results in enhanced proliferation and decreased apoptosis. Nonetheless, the route is crucial for physiological functions and is particularly necessary for stem cell maintenance when it is active regularly. By avoiding premature differentiation, PI3K/AKT/mTOR contributes to neural stem cell proliferation and self-renewal. Furthermore, the route plays a crucial part in the nervous system's long-term potentiation (LTP), indicating that it is essential to the development and operation of neurons.

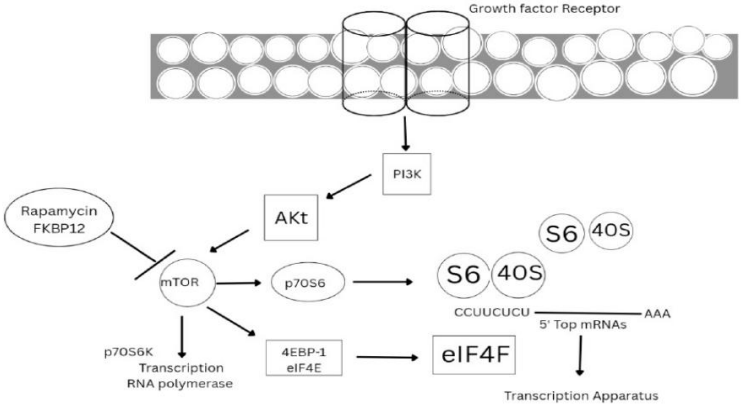


Figure 2. PI3K, AKT, p70S6K and mTOR signaling cascade.

4. Functions of p70S6K in Cancer

Initially discovered as a crucial regulator of mitogen-stimulated protein synthesis, p70S6K is specifically engaged in the translation of a particular class of mRNAs that have a 5′ terminal oligopyrimidine (TOP) sequence [11]. In model animals like mice and Drosophila, it has been demonstrated that experimental interruption of p70S6K activity greatly suppresses organismal growth [12,13]. By affecting several molecular signaling pathways, p70S6K has been shown in later research to be crucial in regulating the growth and survival of cancer cells [2]. Furthermore, fresh research indicates that p70S6K signaling contributes to the development of cancer via a number of recently discovered functional mechanisms (Table 1).

Table 1. Aberrant expression/activation of p70S6K in different cancers.

Cancer	p70S6K Alteration	Biological/clinical context
Astrocytoma	Increased p70S6K activity expression	Tumor progression
Non-small-cell lung cancer	Increased phosphorylated p70S6K	EGFR-TKI resistance
Breast Cancer	Increased phosphorylated p70S6K	Endocrine therapy response/resistance
Vascular tumor	Hyperactivation	IHC
Gastric cancer	Subcellular localization	IHC
Liver cancer	Hyperactivation	IHC

4.1 EMT and Cancer Stemness

The epithelial-mesenchymal transition (EMT), which allows epithelial cells to take on mesenchymal traits, is an essential biological process involved in both adult tissue repair and embryonic development [14]. A growing body of research indicates that p70S6K activation is essential for EMT and cancer stem-like characteristics, especially during ovarian cancer invasion and metastasis. HGF/c-Met pathway activation promotes p70S6K signaling, which in turn raises matrix metalloproteinase-9 (MMP9) expression and proteolytic activity, promoting EMT-associated phenotypic changes and tumor cell invasiveness [15]. Furthermore, p70S6K promotes the mesenchymal transition by upregulating Snail, a transcriptional repressor of E-cadherin [16].

By stabilizing actin filaments and triggering Rho-family GTPases, such as Rac1 and Cdc42, which encourage cancer cell migration, p70S6K also controls cytoskeletal architecture [17-19]. Additionally, via interfering with Dicer and tristetraprolin's interaction, p70S6K regulates microRNA synthesis and promotes the maturation of miR-145. Increased N-cadherin expression and the development of three-dimensional tumor spheroids are two outcomes of this process [20]. Additionally, p70S6K supports spheroid–peritoneal contacts during metastatic progression by facilitating spheroid attachment and colonization via the P-cadherin/integrin β1 signaling pathway [21]. Studies showing p70S6K's role in hematopoietic stem cell self-renewal and leukemia development lend more credence to these conclusions, suggesting a wider role for p70S6K in controlling cancer stemness [22].

4.2 Resistance to Drugs

Cancer cell lines that show resistance to a variety of chemotherapeutic drugs, such as paclitaxel, erlotinib, pemetrexed, cisplatin, and doxorubicin, have often been found to demonstrate upregulation of the Akt/mTOR/p70S6K signaling axis [23,24]. In patients with hormone receptor-positive breast cancer, increased phosphorylation of p70S6K has also been connected to poor clinical outcomes and resistance to endocrine therapy [25].

Further clinical data from separate patient cohorts shows that increased p70S6K expression is linked to a worse prognosis, while nuclear accumulation of p70S6K and its phosphorylated form correlates with a worse therapeutic response to tamoxifen [26]. Furthermore, in patients with primary breast cancer following surgery, elevated levels of phosphorylated p70S6K have been linked to lower locoregional recurrence-free survival and higher radioresistance [27].

According to an analysis of a database of patients with NCSEL, patients treated with TKIs who had high levels of phosphorylated p70S6K demonstrated a statistically significant lower progression-free survival (PFS) compared with those that had low levels of phosphorylated p70S6K. Other experimental studies found that blocking EGFR resulted in p70S6K translocating to the nucleus, where it could form complexes with MDM2 in chemotherapy-resistant tumors. The restoration of sensitivity to EGFR-directed therapies by inhibition of p70S6K signaling provides a rationale for targeting p70S6K at the level of therapeutic intervention to overcome drug resistance [28].

4.3 Angiogenesis

Tumor growth and nutrient supply depend on angiogenesis, which is controlled by variables like hypoxia and VEGF. By increasing the expression of VEGF and HIF-1α, p70S6K stimulates angiogenesis in ovarian and prostate malignancies [29]. In breast cancer tissues and cell lines, similar correlations between

p70S6K activation and increased VEGF/HIF-1α levels have been documented [30,31]. Furthermore, in EBV-associated epithelial malignancies, p70S6K has been linked to vasculogenic mimicry via Akt/HIF-1α signaling [32]. Tumor angiogenesis has also been associated with endothelial p70S6K activity; hepatocellular carcinoma was shown to have higher levels of phosphorylated p70S6K than non-malignant liver tissues [33]. Moreover, mechanical fluid flow in endothelial cells can trigger Akt/mTOR/p70S6K signaling, which aids in vascular remodeling under pathological circumstances [34-36].

4.4 The Tumor Microenvironment (TME) and p70S6K

The dynamic interactions between cancer cells and surrounding stromal elements, such as endothelial cells, immune cells, adipocytes, and fibroblasts, make up the TME. Studies on upstream PI3K/Akt/mTOR signaling indicate that p70S6K may affect TME regulation either through tumor cell–mediated signaling or by intrinsic activity within stromal cells, despite the lack of direct evidence connecting p70S6K activation to TME remodeling.

4.5 Immune Cells

It has been demonstrated that p70S6K increases PD-L1 translation in gliomas with PTEN loss, impacting immune checkpoint regulation [37]. Further research indicates that by influencing proteasomal degradation pathways, p70S6K suppression may modify the stability of PD-L1 protein [38]. Furthermore, it has been shown that KDM5A-related epigenetic regulation modifies PD-L1 expression in mouse tumor models via PTEN/PI3K/p70S6K signaling [39]. Further evidence from tumor xenograft studies suggests that stromal cells' p70S6K promotes angiogenesis by helping tumor-associated macrophages produce VEGF [40]. Although more research is needed to determine its clinical significance, increased phosphorylated p70S6K expression has also been seen in tumor-infiltrating lymphocytes in breast cancer [41]. p70S6K's wider immunoregulatory role is demonstrated by its involvement in immunological signaling pathways outside of cancer, such as STING-mediated IRF3 activation and Th17 cell differentiation [42-44].

4.6 Adipocytes

Recent evidence suggests that obesity and tumor development are positively correlated. By releasing bioactive chemicals and signaling molecules, cancer-associated adipocytes promote tumor growth [45,46]. Increased inflammatory marker expression is correlated with enhanced p70S6K expression in adipose tissue during obesity [47]. Additionally, via controlling nuclear histone modification and epigenetic processes, p70S6K signaling promotes the expression of adipogenic genes and contributes to adipocyte development [48]. Through neural pathways, circulating amino acids in the liver may trigger mTOR/p70S6K signaling to affect lipid metabolism [49].

4.7 The Fibroblasts

A common stromal component of the TME, cancer-associated fibroblasts (CAFs) are linked to poor clinical outcomes [50]. Studies show that p70S6K activation in gastric cancer requires bidirectional signaling between tumor-derived TGF-β1 and CAF-derived lysyl oxidase at metastatic locations [51], despite the lack of direct evidence connecting p70S6K to CAF regulation. Additionally, it has been demonstrated that CAF-secreted factors increase mTOR/p70S6K signaling in HER2-positive breast cancer cells, decreasing their susceptibility to targeted treatments [52]. Through p70S6K-dependent pathways, inflammatory circumstances further activate fibroblasts and encourage their development into myofibroblasts [53,54]. Furthermore, S6K kinases have a role in stromal aging and tumor-supportive remodeling by phosphorylating the epigenetic regulator ZRF1, which controls fibroblast senescence [55,56].

5. p70S6K's Function as a Cancer Therapeutic Target

In addition to cancer, p70S6K has become a significant pharmaceutical target in other chronic conditions such diabetes mellitus and Parkinson's disease [57,58]. Inhibition of p70S6K has been suggested as a substitute tactic in cancer treatment to lessen a number of side effects linked to mTOR inhibitors. Impaired immunological responses, thrombocytopenia, hyperlipidemia, nephrotoxicity, altered insulin sensitivity, and hyperglycemia are some of these adverse consequences [59].

The significance of creating inhibitors that specifically target p70S6K is further highlighted by studies indicating the presence of mTOR-independent activation of p70S6K [60-62]. Currently, mTOR inhibitors like rapamycin (sirolimus) and its analogs, such as everolimus and temsirolimus, are the most widely used inhibitors in clinical oncology that indirectly influence p70S6K activity (Table 2) summarizes the number of p70S6K-targeted drugs that have advanced to preclinical and clinical testing stages.

Table 2. Pharmacological and emerging strategies targeting p70S6K signaling in cancer.

Category	Compound / strategy	Primary molecular target	p70S6K selectivity	Mechanism / relationship to p70S6K	Development stage	Mainai indication / study population	Key findings	Major limitations / status	Refs.
Direct p70S6 inhibition	PF-4708671	p70S6K1 / S6K1	Preferential / selective for S6K1	Direct inhibition of S6K1 activity and downstream S6 phosphorylation	Preclinical	Cancer cell and experimental models	Inhibited p70S6K-mediated signalling and demonstrated antitumor effects in experimental models	Has not progressed to clinical evaluation	[62]
Direct p70S6K inhibition	LY2584702	p70S6K	P70SK - directed	Direct inhibition of p70S6K signaliing	Phase I / PhaseIb	Patients with advanced solid tumors; combination studies with erlotinib or everolimus	Early clinical studies demonstrated limited antitumor activity; treatment - related toxicity and pharmacokinetics limitations were reported	Clinical development was discontinued	[63,64]
Dual /multi target inhibition	AT7867	AKT and p70S6K	Not selective for p70S6K	Simultaneous inhibition of AKT and p70S6K signaling	Preclinical	Colorectal cancer and human tumor xenograft models	Inhibited AKT/p70S6K signaling and suppressed tumor growth in experimental models	Broader kinase activity makes p70S6k-specific effects difficult to distinguish	[65,66]
Upstream pathway inhibition	Everolimus	mTORC1	Indirect effect on p70S6K	Inhibition of mTORC1 suppresss downstream p70S6K signaling	Clinical	Cancer treatment	Suppresss mTORC1 signaling and consequently reduces downstream p70S6K pathway activity	Not a direct p70S6K inhibitor; pathway feedback may limit sustained pathway suppression	[67]

5.1 Creation of Specific Small-Molecule p70S6K Inhibitors

The first known small-molecule inhibitor that precisely targets p70S6K was PF-4708671. Without appreciably altering S6K2 or other AGC kinases like Akt, RSK, and MSK at similar dosages, this substance inhibits IGF-1-induced phosphorylation of the S6 protein mediated by p70S6K [68]. Its successful use in cancer research at doses between 50 and 60 mg/kg was shown by *in vivo* investigations, and no toxicity was noted [63,69]. Nevertheless, PF-4708671 has not yet progressed to clinical trial evaluation despite being described more than ten years ago.

Eli Lilly and Company's LY2584702, another selective inhibitor, advanced to Phase I clinical trials in both cancer patients undertaking dose-escalation studies and healthy volunteers. Additionally, it was evaluated in conjunction with erlotinib and everolimus in a Phase Ib trial. These investigations showed low tumor response, restricted therapeutic effect, and toxicity issues with combination treatments [64]. LY2584702's clinical development for cancer treatment was terminated after a subsequent Phase I trial involving patients with advanced solid tumors was stopped due to the drug's poor pharmacokinetic properties and inability to induce tumor regression at the maximum tolerated dose [70].

Preclinical studies on efficacy and safety have been positive for a number of other prospective small-molecule p70S6K inhibitors, such as DG2 [65,71,72] and AT7867 [66,73]. Nevertheless, none of these substances have yet received Investigational New Drug (IND) approval status in spite of these discoveries.

5.2 Inhibition of the PI3K/Akt/mTOR Pathway Regulates p70S6K

To reduce p70S6K activity, a number of drugs that target the PI3K/Akt/mTOR signaling cascade have been investigated. In preclinical assessments, XL418, a dual inhibitor of Akt and p70S6K created by Exelixis, showed significant S6 phosphorylation inhibition, low off-target kinase activity, and acceptable ADME characteristics [74].

Eli Lilly's LY2780301 underwent early clinical testing and shown good tolerability, but limited anticancer effectiveness and poor correlation between medication plasma levels and p70S6K expression [75]. In patients with PI3K/Akt/mTOR pathway abnormalities, a later Phase II trial found moderate therapeutic effect and acceptable toxicity when coupled with gemcitabine [67].

Numerous studies have also been conducted on rapamycin and its analogs, or rapalogs. Despite rapamycin's potent immunosuppressive and anticancer effects, its poor solubility and pharmacokinetic constraints prompted the creation of better variants [59]. Everolimus and temsirolimus have shown encouraging clinical results and have been approved by the FDA for

the treatment of many cancer types, such as breast, kidney, and neuroendocrine tumors [76,77]. Furthermore, when coupled with conventional therapies for breast cancer, the dual p70S6K/Akt inhibitor M2698 demonstrated acceptable tolerability and partial therapeutic responses [78].

5.3 Biological and RNA-Based Strategies for p70S6K

RNA-mediated therapeutic approaches have become viable instruments for controlling the expression of p70S6K. Long non-coding RNAs and microRNAs have been linked to p70S6K signaling pathway modulation [79]. In ovarian cancer models, siRNA-based methods administered via nanoparticle systems have shown effective p70S6K suppression with less toxicity, despite the lack of direct p70S6K-targeted microRNA treatments [80]. Additionally, dendrimer-mediated delivery systems have demonstrated potential in targeting p70S6K-related pathways and other oncogenic signaling components [81].

5.4 Experimental and Computational Methods for Determining p70S6K Inhibitors

The utilization of high-throughput in silico methods to create selective p70S6K inhibitors with better pharmacological characteristics has been highlighted by recent developments in drug discovery. Several potential inhibitors have been found using integrated virtual screening techniques that combine pharmacophore modeling, molecular docking, genetic function approximation, and ligand clustering. This has produced about sixty compounds for further biological validation [82].

Several new p70S6K-targeting compounds have been found concurrently as a result of extensive computational screening of chemical libraries; some of these compounds have been structurally verified by crystallographic investigations. According to these investigations, a large number of inhibitors reduce kinase activity by occupying the ATP-binding pocket of p70S6K [83].

Using an AlphaScreenTM kinase assay, high-throughput biochemical screening revealed oxadiazole-substituted azabenzimidazole as a strong inhibitor that may prevent S6 phosphorylation at Ser235/236 [84]. In addition to traditional ATP-competitive inhibitors, thiophene urea compounds with high selectivity and potency against p70S6K were found through the investigation of non-traditional binding mechanisms [85]. Additionally, important amino acid residues necessary for efficient p70S6K inhibition have been identified by molecular docking studies, offering structural insights for logical drug design [86].

With computational analysis revealing FDA-approved substances like niclosamide and pyrvinium pamoate as potent inhibitors of p70S6K-mediated phosphorylation, drug repurposing techniques have also drawn attention. The potential of off-label usage was highlighted by these medicines' cytostatic effects in breast cancer models [82]. Additionally, ruthenium-containing organometallic compounds (EM5 and FL772) have demonstrated potent and highly selective inhibitory effects against p70S6K phosphorylation, indicating the emergence of metal-based medicinal methods [87].

6. Research Deficits

The role of p70S6 kinase in the development of cancer has been thoroughly studied, but there are still a number of significant gaps that prevent us from fully comprehending its biological and clinical relevance. First, while the precise upstream regulatory mechanisms in various TMEs are still poorly understood, the majority of current research focuses on the downstream consequences of p70S6K activation on protein synthesis and cell proliferation. The impact of inflammatory signaling, hypoxia, and tumor-specific metabolic circumstances on p70S6K activation has not been thoroughly investigated.

Second, despite the fact that p70S6K has been linked to several cancer types, there aren't enough comparative studies looking at its functional roles and differential expression in various malignancies.

This limits our capacity to ascertain whether p70S6K behaves context-dependently based on tissue origin and genetic background or operates consistently as a proliferative driver.

The poor knowledge of p70S6K isoforms and their many biological roles represents another significant gap. Despite growing evidence that these isoforms may have distinct regulatory functions in tumor development, survival, and treatment resistance, most investigations fail to distinguish between p70S6K1 and p70S6K2.

“Although p70S6K has been associated with chemotherapy and targeted-therapy resistance in several experimental and clinical contexts, the molecular determinants of this association and its therapeutic significance remain incompletely define.

Furthermore, translational dependability is decreased because the majority of results are taken from in vitro models with little validation in in vivo systems and patient-derived samples.

Lastly, there aren't many standardized biomarkers based on p70S6K activity that may be applied to treatment classification or prognosis. This emphasizes the necessity of therapeutically significant research that connects molecular discoveries to patient outcomes.

7. Conclusions and Prospects for the Future

This review summarizes recent developments in therapeutic targeting approaches while highlighting the varied and growing roles of p70S6 kinase in controlling cancer cell proliferation and tumor progression. Given that p70S6K signaling functions at the nexus of oncogenesis, aging, and metabolic diseases, further research into this system may shed light on the molecular relationships between these ailments. Differentiating the direct biological roles of p70S6K from upstream regulators like mTOR is a significant research problem

since it is necessary to produce safer and more targeted therapeutic approaches.

The discovery of p70S6K-specific regulatory mechanisms may create new avenues for immunotherapy-based therapeutic approaches because mTOR inhibitors are known to have potent immunosuppressive effects. According to recent data, the mTOR–p70S6K axis can affect immune cell responses without reference to traditional S6 phosphorylation pathways

Despite a significant increase in the number of identified p70S6K substrates in recent decades, little is known about their functional significance in immuno-oncology and tumor-immune interactions. Additional research on p70S6K signaling in cancerous cells and elements of the TME may enhance the logical development of combination therapy strategies. Although computational drug discovery methods for p70S6K inhibitor identification have advanced, there are still few effective cell-based screening platforms that can capture cell-type-specific responses. Despite the development of intracellular detection technologies for phosphorylated S6 proteins utilizing sophisticated imaging techniques, its use in extensive drug screening is still neglected. Promising prospects for incorporation into high-throughput screening methods are presented by emerging biosensor-based technologies that can monitor real-time mTOR and p70S6K activity.

Due to the limited availability of appropriate binding pockets, the structural constraints related to kinase drug design continue to provide difficulties.

Targeted protein degradation techniques, such as proteolysis-targeting chimeras and associated molecular degraders, have drawn interest as an alternate tactic for the selective removal of carcinogenic proteins through proteasomal pathways. Thus, p70S6K degradation-based targeting is a promising treatment option. It is expected that new p70S6K-directed therapeutic approaches will surface and improve cancer treatment outcomes with further developments in molecular biology methods and drug development technology.

Taken together, the available evidence indicates that the therapeutic relevance of p70S6K depends on biological context, target dependency, pathway feedback, inhibitor selectivity, and appropriate patient selection. Future studies should therefore distinguish direct p70S6K inhibition from upstream pathway suppression and incorporate pharmacodynamic biomarkers that can establish target engagement. Improved molecular stratification and clinically validated biomarkers will be important for determining whether specific tumor contexts are sufficiently dependent on p70S6K signaling to benefit from selective intervention.

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SAL designed the review, STG and SAL collected the literature, STG, IR and SAL wrote the manuscript, SAL read, reviewed, and approved the manuscript.

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Competing Interests

The authors declare no conflict of interest.

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The authors declare that no generative artificial intelligence technologies were used when preparing this manuscript.

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