mTOR Complexes and Their Role in Oncogenesis, Metastasis, and Targeted Drug Impediment

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ABSTRACT

mTOR, a serine-threonine kinase, functions as a core component of mTORC1 and mTORC2, which regulate cellular processes such as growth, protein synthesis, and autophagy in response to nutrient and growth factor signals. It is a central player in several signaling pathways, including PI3K/AKT, TSC1/TSC2/Rheb, AMPK/LKB1, and VAM6/RagGTPases. Dysregulated mTOR is implicated in oncogenesis and cancer progression, and while mTOR-targeted therapies make theoretical sense as a potential therapy, clinical trials have been disappointing. Further research is necessary to elucidate mTOR's precise role in cancer and the intricate mechanisms cancer cells employ to evade mTOR inhibition to develop more effective therapies.

Keywords: Cellular and Molecular Biology, Molecular Biology, mTOR Signaling, Oncogenesis, Metastasis, Drug Resistance

INTRODUCTION

In 1964, a team of Canadian scientists discovered Rapamycin on Rapa Nui Island, which exhibited impressive antifungal, immunosuppressive, and antitumor properties (Laplante & Sabatini, 2009). It was not until the early 1990s that mTOR, a crucial kinase targeted by Rapamycin, was identified as a "master regulator" of cellular metabolism that controls cell growth and division in response to nutrient availability and other signals (Sabatini et al., 1994; Liu & Sabatini, 2020). mTOR is part of the PI3K/Akt/mTOR pathway, which plays a vital role in many cellular processes and is frequently mutated in cancer (Dowling et al., 2010). Despite its significance in oncogenesis, the complexities

involved in developing targeted drugs against mTOR have impeded its use in cancer therapy. Further research is required to fill the gaps in our understanding of mTOR's regulation and function.

STRUCTURE OF mTOR COMPLEXES 1 & 2

In mammals, mTOR is a key regulator of cell metabolism and growth and exists in two distinct complexes—mTORC1 and mTORC2— (Figure 1A). Recent advances in cryo-electron microscopy have provided detailed insights into the assembly and regulation of these large complexes (~1 megadalton) (Chen et al., 2018). While both complexes share common core components—mTOR, mLST8, and DEPTOR (Figure 1B, 1C) (Kim et al., 2003),—the mTORC1-specific component RAPTOR is essential for the lysosomal localization of mTORC1 (Kim et al., 2002; Hara et al., 2002). RAPTOR also acts as a scaffold for DEPTOR, an interacting protein, and PRAS40, an mTORC1 inhibitor, thereby modulating mTORC1 activity (Liu & Sabatini, 2020). On the other hand, mTORC2 is comprised of two complex-specific components, RICTOR and mSIN1, which associate with DEPTOR and PROTOR1/2 to form the complex (Sarbassov et al., 2004; Frias et al., 2006; Jacinto et al., 2006). mSIN1 plays a critical role in the assembly of mTORC2 on the plasma membrane (Yuan & Guan, 2015), and recent crystallographic studies have shown that both mTOR complexes form dimers with a unique lozenge shape (Yuan & Guan, 2016; Stuttfeld et al., 2018). The co-crystal structures of FKBP12-rapamycin and PRAS40 with mTORC1 have shed light on the mechanism of mTORC1 inhibition by these compounds, which partially blocks the substrate entry to the kinase active site (Liu & Sabatini, 2020; Yang et al., 2013; Yang et al., 2017). Notably, RICTOR hinders the binding site for the FKBP12-rapamycin complex on mTOR, rendering mTORC2 resistant to rapamycin-mediated inhibition. Nevertheless, sustained exposure to rapamycin can indirectly affect mTORC2 signaling by sequestering mTOR into rapamycin-containing complexes, thereby preventing the formation of new mTOR complexes (Sarbassov et al., 2006; Lamming et al., 2012).

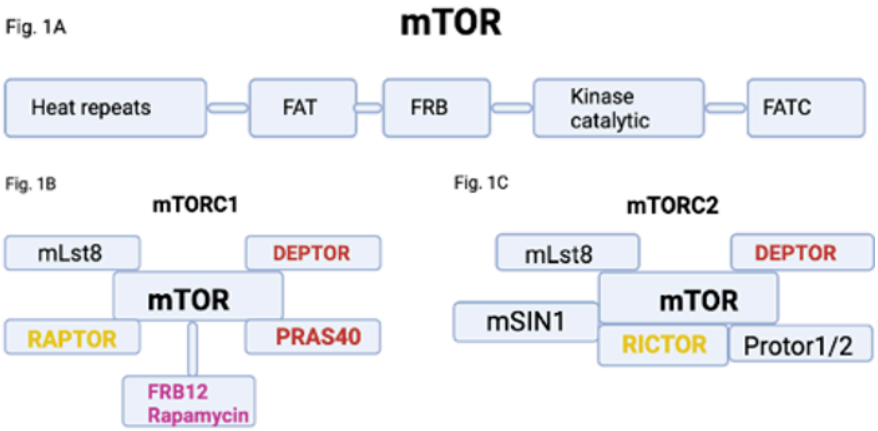


FIGURE 1A. Structure of mTOR, a common component of both complexes.

FIGURE 1B. mTORC1 subunits

FIGURE 1C. mTORC2 subunits

Upstream Regulators of mTORC1

mTORC1 integrates signals from Rheb and Rag GTPases, with Rheb regulating mTOR kinase activity and Rag controlling its localization (Figure 2). This ensures that mTORC1 activates anabolism only under optimal conditions for sustained growth (Liu & Sabatini, 2020).

A. Growth Factors

The binding of insulin/insulin-like growth factor-1 (IGF-1) to the tyrosine kinase receptor (RTK) initiates the recruitment of insulin receptor substrate (IRS1) and activates the phosphoinositide 3-kinase (PI3K), which generates phosphatidylinositol (3,4,5)-triphosphate (PIP3). Akt is then recruited to the plasma membrane by PIP3, where it is activated through phosphorylation by PDK1 and mTORC2 (Szwed et al., 2021). Growth factor signals converging on Tuberous Sclerosis Complex (TSC), a heterotrimeric complex composed of TSC1, TSC2, and TBC1D7 (Dibble et al., 2012), can result in the phosphorylation of TSC2 and inhibition of TSC by dissociating it from the lysosomal membrane where Rheb (Inoki, 2003; Tee et al., 2003) is located, which then activates mTORC1. Additionally, the Wnt and TNFα pathways can also activate mTORC1 by suppressing TSC1 (Du et al., 2019). Downstream components of the Ras/mitogen-activated protein kinase (MAPK) pathway, Akt, ERK, and RSK, can also stimulate mTORC1 signaling by suppressing TSC, thereby promoting anabolic processes.

B. Amino Acids

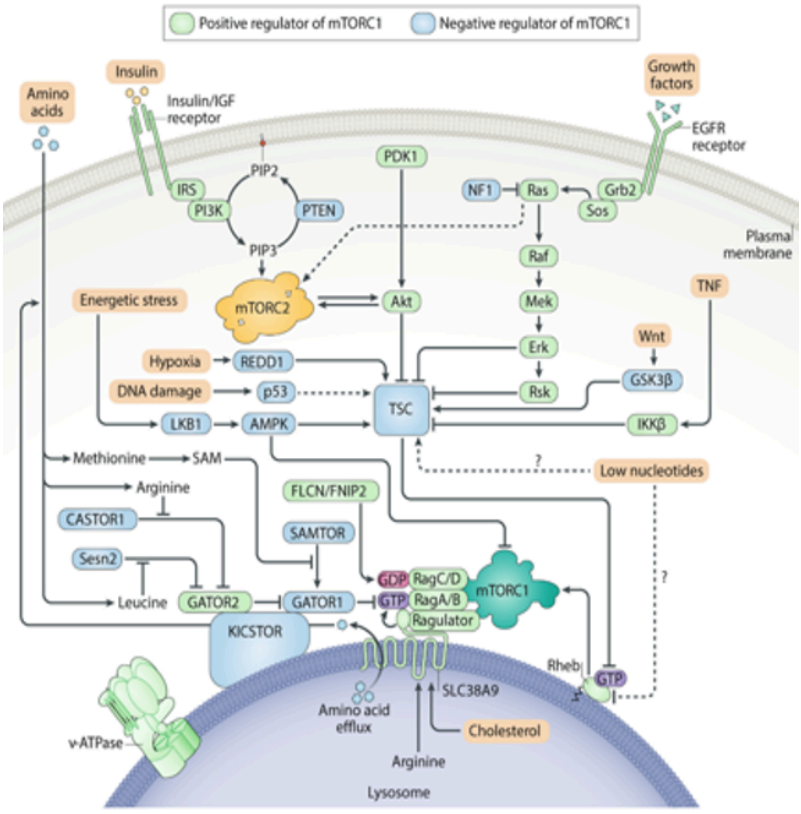
Amino acids, particularly arginine and leucine, are crucial in regulating mTORC1 activation in mammalian cells (Kim et al., 2008). The Rags, a group of obligate heterodimers (RagA-RagB and RagC-RagD), are associated with the lysosomal membrane (Kim et al., 2008; Sancak et al., 2008) through the Ragulator complex (composed of MP1, p14, p18, HBXIP, and C7ORF59) (Sancak et al., 2010) (Figure 2). Upon amino acid stimulation, the Rags are converted to their "on" state, allowing them to bind to Raptor and recruit mTORC1 to the lysosomal surface where Rheb is also located. This creates a conjunction gate that requires both the activation of the Rags and Rheb to trigger mTORC1 signaling. This clarifies the reason why the activation of mTORC1 requires the presence of both amino acids and growth factors (Liu & Sabatini, 2020).

mTORC1 is regulated by both lysosomal and cytosolic amino acids through separate mechanisms. The lysosomal amino acid transporter SLC38A9, part of the Rag-Ragulator-v-ATPase complex, transports arginine from the lysosome to activate mTORC1 (Jung et al., 2015). This mechanism may allow the products of autophagy to reactivate mTORC1 after extended periods of starvation. In addition, cholesterol has been demonstrated to activate mTORC1 through its interaction with SLC38A9 (Rebsamen et al., 2015) (Figure 2). Cytosolic arginine and leucine signal to mTORC1 via a different pathway that involves the GATOR1 and GATOR2 complexes (Bar-Peled et al., 2013). GATOR1 negatively regulates mTORC1 signaling by functioning as a GTPase-activating protein for RagA/B. The KICSTOR complex links GATOR1 to the lysosomal membrane, which is essential for the proper regulation of the mTORC1 pathway by nutrients (Wolfson et al., 2017). GATOR2, in contrast, positively regulates mTORC1 signaling by interacting with GATOR1 at the lysosomal membrane (Lamming & Bar‐Peled, 2018). Sestrin2, a direct leucine sensor upstream of mTORC1, can bind and inhibit GATOR2 in the absence of leucine but dissociates from it when leucine is present (Chantranupong et al., 2014). Furthermore, the affinity of Sestrin2 for leucine plays a crucial role in determining the sensitivity of mTORC1 signaling to leucine in cultured cells. This demonstrates that Sestrin2 acts as the primary leucine sensor for mTORC1 in this context (Saxton et al., 2015). Cytosolic arginine can activate mTORC1 through the GATOR1/2-Rag pathway by directly binding to CASTOR1, an arginine sensor. Similar to Sestrin2, CASTOR1 binds and inhibits GATOR2 in the absence of arginine, but upon binding to arginine, it dissociates and enables the activation of mTORC1 (Chantranupong et al., 2016). Thus,

both leucine and arginine stimulate mTORC1 activity, at least partially, by releasing inhibitors from GATOR2, thereby establishing GATOR2 as a critical node in the signaling of amino acids to mTORC1 (Petit et al., 2013). Importantly, the molecular function of GATOR2, and the mechanisms through which Sestrin2 and CASTOR1 regulate it, remain unknown. Additionally, other mechanisms, such as the Folliculin-FNIP2 complex serving as a GAP (GTPase Accelerating Protein) for RagC/D, which activates mTORC1 in the presence of amino acids, have also been reported (Tsun et al., 2013) (Figure 2). Another study found that the amino acid glutamine, utilized as a nitrogen and energy source by proliferating cells, activates mTORC1 independently of the Rag GTPases through the Arf family of GTPases (Jewell et al., 2015).

C. Energy, Oxygen, and DNA Damage

mTORC1 signaling is susceptible to both intracellular and environmental stress that hinder growth, including low ATP levels, hypoxia, DNA damage, and reduced nucleotide availability (Hoxhaj et al., 2017). These stressors activate the TSC complex protein, leading to a suppression of mTORC1 signaling (Inoki et al., 2003). AMPK, a stress-responsive metabolic regulator, can activate the TSC complex and inhibit mTORC1 in response to a decrease in cellular energy levels caused by glucose deprivation (Gwinn et al., 2008). Additionally, hypoxia can partially inhibit mTORC1 through both AMPK activation and the induction of REDD1, which also activates the TSC complex. Finally, the DNA damage response pathway inhibits mTORC1 by inducing p53 transcription factor target genes, which increase TSC expression (Efeyan et al., 2012).



Adapted from Liu & Sabatini, 2020.

FIGURE 2. mTORC1 activation is dependent on the availability of amino acids, insulin/growth factors, ATP, and oxygen, which all converge on the TSC complex that regulates the small GTPase Rheb. When all requirements are satisfied, mTORC1 translocates to the lysosome and is activated by GTP-bound Rheb. On the other hand, mTORC2 is mainly regulated by growth factors and may be recruited to the plasma membrane by mSIN1.

Upstream Regulators of mTORC2

The insulin/PI3K signaling pathway activates mTORC2. PIP3 recruits mTORC2 and Akt to the plasma membrane (Yin et al., 2016), where they undergo reciprocal phosphorylations that modulate their localization and activation (Ebner et al., 2017) (Figure 2). mSin1 can directly catalyze mTORC2 kinase activity at the plasma membrane, connecting mTORC2 to oncogenic Ras and emphasizing its role in driving cancer cell survival and proliferation (Kovalski et al., 2019). AMPK can also activate mTORC2 during energetic stress, suggesting a potential role in mediating

cellular adaptation to low oxygen or nutrient conditions in tumor environments in vivo (Kazyken et al., 2019).

mTORC1 can regulate mTORC2 through a negative feedback loop between mTORC1 and PI3K–Akt signaling. Additionally, mTORC1 can activate Grb10, a negative regulator of the insulin/IGF-1 receptor signaling upstream of Akt and mTORC2. S6K1 suppresses mTORC2 activation by phosphorylation-dependent degradation of IRS1. This negative feedback loop may explain some of the paradoxical metabolic effects associated with long-term rapamycin treatment (Hsu et al., 2011; (Yu et al., 2011).

Downstream of mTORC1

mTORC1 regulates the balance between anabolism and catabolism. Key substrates and cellular processes downstream of mTORC1 contribute to cell growth and proliferation by boosting protein, lipid, and nucleotide synthesis, while suppressing autophagy in response to environmental stimuli.

A. Protein Synthesis

mTORC1 primarily promotes protein synthesis by phosphorylating the eukaryotic initiation factor 4E-binding proteins (4E-BPs) and p70S6 kinase 1(S6K1) (Figure 3B).

The unphosphorylated form of 4EBP binds to and sequesters eIF4E (Brunn et al., 1997; Gingras et al., 1999), a crucial component of the cap-binding complex, eIF4F, thereby inhibiting translation initiation. mTORC1's phosphorylation of 4EBP at multiple sites causes its dissociation from eIF4E, enabling 5' cap-dependent mRNA translation to occur. Global ribosome footprinting analyses have shown that while acute mTOR inhibition modestly suppresses overall mRNA translation, it has a profound impact on mRNAs containing pyrimidine-rich 5' TOP or "TOP-like" motifs, which encompasses most genes involved in protein synthesis (Hsieh et al., 2012; Thoreen et al., 2012).

The activation of S6K1 by mTORC1 leads to the promotion of mRNA translation initiation through several mechanisms. Upon phosphorylation at its hydrophobic motif site, Thr389, by mTORC1, S6K1 becomes active and triggers the activation of eIF4B, a positive regulator of the 5' cap binding eIF4F (Holz et al., 2005) complex. This results in the degradation of PDCD4, an inhibitor of eIF4A (Dorrello et al., 2006), and an increase in the translation efficiency of spliced mRNAs through its

interaction with SKAR, a component of exon-junction complexes (Ma et al., 2008).

Additionally, S6K1 and mTORC1 directly stimulate the production of ribosomal RNA (rRNA) by increasing the activity of RNA polymerase I and III through the phosphorylation of regulatory factors, such as upstream binding factor (UBF) (Hannan et al., 2003), transcription initiation factor 1A (TIF-1A) (Mayer, 2004), and MAF1 (Michels et al., 2010; Shor et al., 2010).

B. Lipid Synthesis

The mTORC1 signaling pathway can activate SREBP (sterol-responsive element binding protein), which controls the expression of metabolic genes involved in fatty acid and cholesterol biosynthesis (Porstmann et al., 2008) (Figure 3A). This activation can occur through the phosphorylation of S6K (Düvel et al., 2010) or Lipin1 (Peterson et al., 2011). SREBP, as a transcription factor, is responsible for regulating genes necessary for the formation and expansion of new membranes in growing cells.

C. Nucleotide Synthesis

mTORC1 activation phosphorylates ATF-4, inducing MTHFD2 expression, a crucial component of the tetrahydrofolate cycle that provides one-carbon units for purine synthesis (Ben-Sahra et al., 2016) (Figure 3A). S6K1 phosphorylates and activates CAD, a critical component of the pyrimidine synthesis pathway (Ben-Sahra et al., 2013; Robitaille et al., 2013). These pathways are essential for synthesizing nucleotides required for DNA replication and ribosome synthesis, necessary for new cell formation, through which mTORC1 acts.

D. Glucose Metabolism

mTORC1 promotes a transition from oxidative phosphorylation to glycolysis, incorporating nutrients into new biomass. It also stimulates the oppression of HIF1alpha, leading to greater production of glycolytic enzymes such as PFK (Mor et al., 2011) (Figure 3A). SREBP activation results in increased oxidative PPP activity, producing NADPH and other metabolites necessary for cell growth and proliferation.

E. Inhibiting Autophagy

mTORC1 regulates autophagy through its influence on the ULK1-ATG13-FIP200 protein complex (Dikic & Elazar, 2018; Hosokawa et al., 2009). Under nutrient-rich conditions, mTORC1 phosphorylates ULK1, preventing activation by AMPK, a critical initiator of autophagy (Kim et al., 2011) (Figure 3C). By phosphorylating UVRAG (Kim et al.,

2015), mTORC1 impedes autophagosome maturation and conversion of endosomes into lysosomes, controlling both early and late stages of autophagy. mTORC1 also regulates autophagy by phosphorylating and preventing nuclear translocation of TFEB (Settembre et al., 2012; Martina et al., 2012), driving expression of genes necessary for lysosomal biogenesis and autophagy machinery operation (Figure 3C).

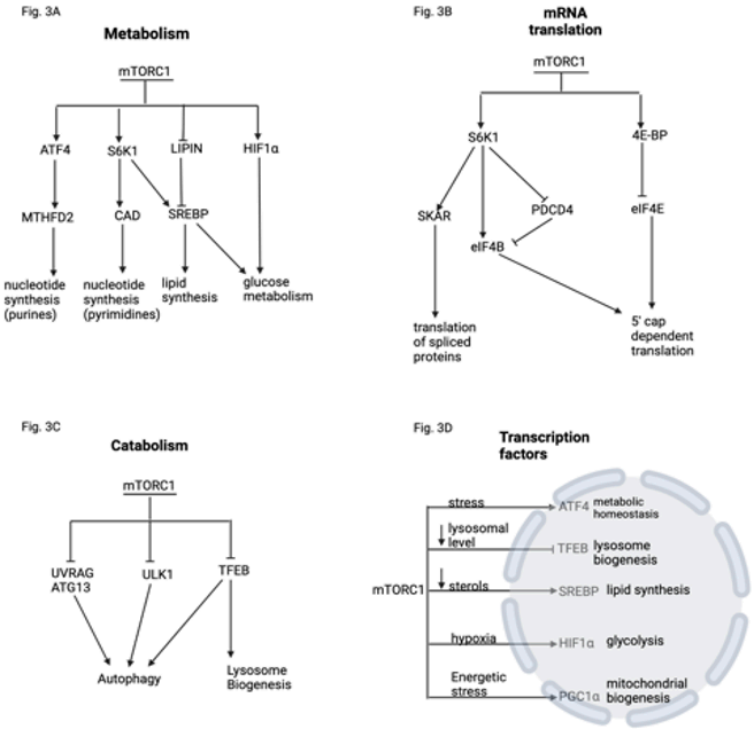


FIGURE 3A, 3B, 3C. The major pathways downstream of mTORC1 signaling in metabolism, mRNA translation, and catabolism respectively.
FIGURE 3D. mTORC1 controls the activity of several transcription factors that can also be independently regulated by cell stress.

Downstream of mTORC2

mTORC2's primary substrate is PKCα (Larsson, 2006), a protein kinase that regulates cytoskeleton and cancer cell mobility and metastasis (Morrison Joly et al., 2017; Jacinto et al., 2004) (Figure 4). mTORC2 also plays a crucial role in phosphorylating and activating Akt, a mediator of insulin/PI3K signaling that promotes cell survival, growth, and proliferation by inhibiting key substrates, including FoxO1/3a transcription factors, GSK3β, and TSC2 (Sarbassov, 2005; Webb & Brunet, 2014; Guertin et al., 2006) (Figure 4). Additionally, mTORC2

activates SGK1 (García-Martínez & Alessi, 2008), another AGC-kinase that regulates ion transport and cell survival.

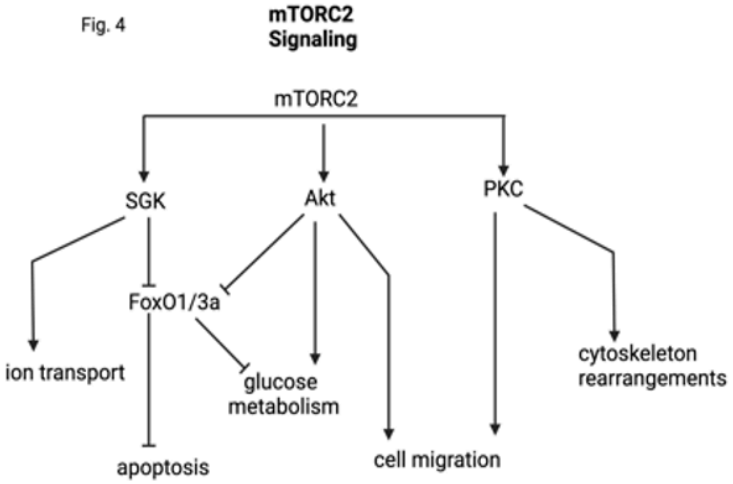


FIGURE 4. The major pathways downstream of mTORC2 signaling.

MUTATIONS IN THE mTOR SIGNALING PATHWAY CAUSING ONCOGENESIS AND METASTASIS

The mTOR pathway is frequently activated abnormally in cancer cells, allowing the cells to bypass metabolic checkpoints that normally limit their growth in low-nutrient environments. Mutations in genes encoding components of the PI3K-AKT-mTOR and Ras-MAPK signaling pathways are commonly observed in cancer, and a few mutations have been identified in the gene encoding the mTOR kinase itself (Grabiner et al., 2014; Sato et al., 2010). These mutations tend to occur in six distinct regions of the C-terminal half of mTOR. They are prevalent in multiple types of cancer, with a particularly high frequency in kidney cancer (Chiarini et al., 2015).

As previously mentioned, mutations in the key nodes of the PI3K/AKT/mTOR signaling pathway are frequently observed in cancers and contribute to angiogenesis and metastasis. Any alterations in receptor tyrosine kinases (RTKs), upstream of PI3K, can result in increased pathway activity. In non-small cell lung cancer (NSCLC), epidermal growth factor receptor (EGFR) activation of PI3K is a major contributor (Owusu-Brackett et al., 2018). In glioblastomas, gene amplification and overexpression of EGFR are commonly observed. HER2 (human epidermal growth factor receptor 2), a member of the EGFR family, is also amplified and overexpressed in invasive breast and gastric cancers. The

PIK3CA gene, which encodes the p110α catalytic subunit of PI3K, is frequently mutated in various human cancer types, including breast, endometrial, colorectal, and ovarian tumors (Owusu-Brackett et al., 2018).

The PI3K/AKT/mTOR signaling pathway promotes angiogenesis through the overexpression of proangiogenic factors, the suppression of antiangiogenic factors, and the induction of factors that support the stability of developing blood vessels. By tilting the balance toward proangiogenic factors, angiogenesis is facilitated. This signaling pathway increases the expression of HIF-1α through the induction of NOS and inhibition of GSK-3β and FOXO, which results in the activation of transcriptional VEGF (vascular endothelial growth factor) (Owusu-Brackett et al., 2018; Jiang & Liu, 2008) (Figure 5A). Additionally, AKT inhibits the endogenous angiogenic inhibitor TSP-1 (Owusu-Brackett et al., 2018; Jiang & Liu, 2008).

The activation of the PI3K pathway contributes to tumor metastasis by triggering the production of matrix metalloproteinases and urokinase-type plasminogen activators, which degrade the extracellular matrix (ECM) (Owusu-Brackett et al., 2018; Jiang & Liu, 2008). Furthermore, the PI3K pathway enhances the production of chemokines such as C-X-C motif ligand 1 (CXCL-1), cyclooxygenase-2(COX-2), and interleukin-8 (CXCL-8), while promoting epithelial-mesenchymal transition (EMT) through NF-kB and repressing E-cadherin, all of which facilitate the cell mobility necessary for tumor metastasis (Owusu-Brackett et al., 2018; Jiang & Liu, 2008). (Figure 5B).

PTEN is a tumor suppressor gene that regulates the PI3K signaling pathway and is one of the most commonly mutated genes in human cancers. The loss or mutation of PTEN has been identified in both hereditary and sporadic cancers, including glioblastoma and endometrial sarcoma. Amplification and activation of somatic mutations in the PH domain (E17K) of AKT1 have also been reported in various cancers, such as breast, colorectal, pancreatic, and ovarian (Owusu-Brackett et al., 2018; Yuan & Cantley, 2008).

Cell cycle progression is regulated by the mTORC1 pathway, which activates S6K1 and inhibits 4E-BP1, leading to the translation of essential mRNA for progression into the S phase of the cell cycle (Owusu-Brackett et al., 2018; Magnuson et al., 2011). Moreover, the transition to the S phase is facilitated by the inhibition of negative regulators of cell cycle progression, such as p27 and p21 (Owusu-Brackett et al., 2018; Magnuson et al., 2011). Additionally, mTORC1 also promotes cell cycle progression by suppressing pro-apoptotic factors, such as forkhead box O3 (FOXO3),

mouse double minute 2 homolog (MDM2), and BAD (Owusu-Brackett et al., 2018; Magnuson et al., 2011).

Ras proteins, encoded by HRAS, KRAS, and NRAS genes, are proto-oncogenes due to their frequent mutation in human cancers. In pancreatic cancers, K-Ras mutations are present in 90% of tumors, while N-Ras mutations are more common in hematopoietic tumors (Prior et al., 2012). mTORC1 activation by growth signals and LKB1 mutations can phosphorylate RNF168, decreasing H2A ubiquitination after DNA damage and potentially promoting tumor formation (Zou et al., 2020).

Several components involved in transmitting nutrient signals to the mTORC1 complex have been linked to cancer progression. For example, mutations in all three subunits of the GATOR1 complex are occasionally found in glioblastoma (Saxton, 2018), while RagC - a component of the Rag GTPase complex that senses amino acids - has recently been discovered to have high mutation frequency (around 18%) in follicular lymphoma (Ying et al., 2016). Furthermore, mutations in the FLCN gene - which encodes folliculin - are the underlying cause of the Birt-Hogg-Dube hereditary cancer syndrome (Schmidt & Linehan, 2018). This condition presents symptoms like those of Tuberous Sclerosis Complex disease.

Mutations in the upstream protein kinases that trigger activation of AMPK, such as LKB1 (liver kinase B1), CaMKK (calcium/calmodulin-dependent protein kinase), and TAK1 (transforming growth factor β (TGF-β)-activated kinase), can fail to activate AMPK and therefore lead to unchecked cell proliferation (Owusu-Brackett et al., 2018).

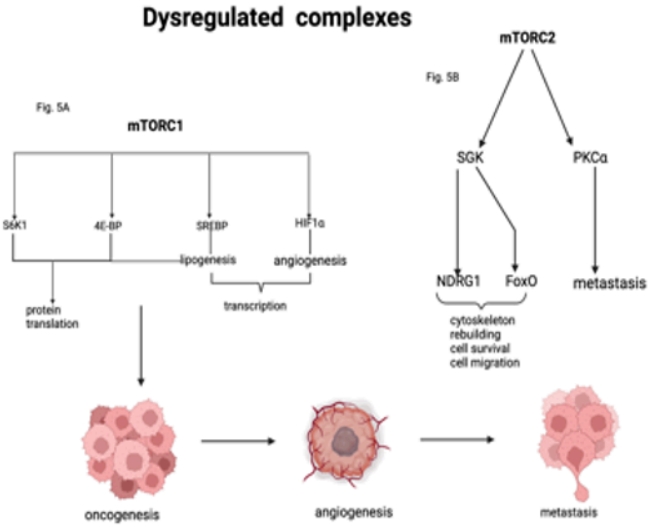


FIGURE 5A, 5B. mTORC1 and mTORC2 have been implicated in cancer progression by promoting biosynthesis and enhancing cell proliferation and survival. Additionally, emerging evidence suggests that mTORC2 contributes to metastatic transformations.

PARADOXICAL EFFECTS AND NON-CANONICAL ROLES OF mTOR

While mutations in the mTOR complexes play a critical role in promoting oncogenesis and metastasis, they do not fully explain the complexity of mTOR's function in cancer biology. Beyond its canonical roles in regulating cell growth and metabolism, mTOR exhibits paradoxical effects and non-canonical roles that are crucial for understanding its broader impact in cancer progression and therapy. These roles, often counterintuitive, highlight the need for a more nuanced approach in targeting mTOR for therapeutic purposes. Below, we explore these complex aspects of mTOR biology that challenge the traditional view of its function and open new avenues for research and treatment.

PARADOXICAL EFFECTS OF mTOR INHIBITION

A. Contrasting Effects on Immune Responses

mTOR plays a complex role in immune modulation, and its inhibition frequently produces paradoxical immune outcomes. For instance, mTOR inhibition via rapamycin attenuates airway inflammation when administered during the induction phase of asthma but exacerbates inflammation during established disease states. These opposing effects mirror the activation levels of mTOR signaling and the sensitivity of immune cells during various phases. This highlights the need for careful timing and context-specific approaches in therapeutic applications (Zhang et al., 2017).

B. Feedback Activation of Survival Pathways

In some systems, mTOR inhibition triggers compensatory activation of survival pathways like the PI3K/AKT and MEK/ERK axes. The suppression of mTOR relieves negative feedback, paradoxically increasing PI3K/AKT signaling, which can counteract the anti-cancer benefits of mTOR inhibition and lead to therapeutic resistance. This paradox complicates the development of effective mTOR inhibitors for cancer therapies (Rodrik-Outmezguine et al., 2011).

C. Cell-Specific Contexts

Paradoxical effects are also evident in cell-specific contexts. For instance, mTOR inhibition can reduce cancer cell proliferation in some systems while impairing the function and viability of normal cells, such as β-cells in the pancreas. Inhibition of mTOR in cancer can suppress tumor growth but may exacerbate certain aspects of normal aging due to its roles in metabolic and cellular health (Rumala et al., 2020).

NON-CANONICAL ROLES OF mTOR

A. Nuclear Functions and Beyond

Emerging research has identified previously unrecognized roles for mTOR in nuclear functions. For instance, mTOR influences gene transcription and chromatin modifications, independently of its protein synthesis activity in the cytoplasm. These functions include selective increases in certain histone methylation marks (e.g., H3K27me3), which affect gene expression dynamics but are independent of the canonical kinase pathways downstream of mTOR complexes (Torres & Holz, 2020).

B. Lysosome-Dependent and Non-Lysosome-Dependent Activities

Non-canonical mTOR signaling has been observed to operate at non-lysosomal locations, regulating processes that do not fit within its classical growth and metabolic roles. For example, mTORC1 can phosphorylate substrates at spatial domains distinct from the lysosome, including functions at other organelle interfaces. This hints at broader regulatory networks modulated by mTOR beyond traditional signaling paradigms (Fernandes et al., 2023).

C. Translation Machinery and Stress Responses

mTOR suppression can trigger alternative modes of translation independent of its canonical role in promoting ribosome biogenesis. Quiescent cancer cells, for instance, adapt to mTOR inhibition by modifying their proteome to evade therapeutic interventions, thereby sustaining survival through non-canonical translational mechanisms. This dynamic proteome remodeling underscores the versatility of mTOR in cellular adaptation under stress (Clohessy et al., 2012).

These controversial aspects of mTOR biology present both challenges and opportunities in therapeutic design:

1. Therapeutic Challenges

Paradoxical and context-dependent effects of mTOR inhibitors necessitate the use of predictive biomarkers and combination strategies to enhance therapeutic precision while minimizing toxicities (Perl, 2015).

2. Opportunities in Non-Canonical Pathways

Targeting non-canonical roles of mTOR could present novel therapeutic avenues against cancer and other diseases, especially those rooted in translational control and cellular metabolism (Ilagan & Manning, 2016).

Overall, a deeper understanding of the paradoxical and non-canonical roles of mTOR has the potential to transform its application from a one-size-fits-all approach to a nuanced, context-specific strategy.

mTOR PATHWAY TARGETED DRUG THERAPY

mTOR's pivotal role in oncogenic signaling has made it a prime therapeutic target, leading to the development of successive generations of inhibitors. From first-generation Rapalogs to advanced dual PI3K/mTOR inhibitors, these drugs have transformed treatment paradigms for certain malignancies, such as renal cell carcinoma and hormone receptor-positive breast cancer. However, challenges such as incomplete pathway inhibition, feedback activation, and resistance mechanisms have limited their broader efficacy.

Fig. 6A

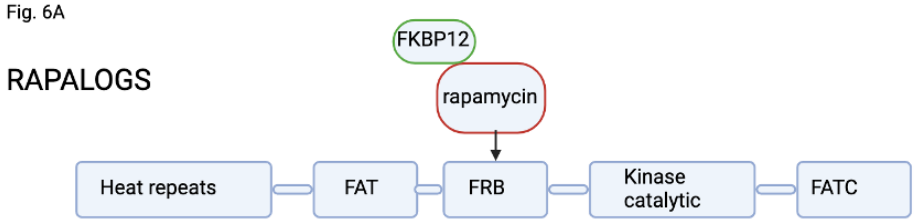


FIGURE 6A. Rapalogs, such as rapamycin, bind together with FKBP12 to the FRB domain of mTOR and block some functions of mTORC1.

THE FIRST GENERATION OF RAPAMYCIN DERIVATIVES (FIGURE 6A)

A. Drugs

Drugs referred to as "Rapalogs," saw the approval of Temsirolimus by Pfizer for the treatment of advanced renal cell carcinoma in 2007, followed by Everolimus by Novartis in 2009 (Coppin, 2010).

B. Mechanism of Action

Temsirolimus and Everolimus selectively inhibit mTORC1; however, this inhibition does not suppress the negative feedback loop that leads to the phosphorylation and activation of AKT. This incomplete suppression reduces their overall effectiveness in treating cancer (Feldman & Shokat, 2010).

C. Mechanism of Action

The clinical impact of rapalogs, while significant, has been limited. Temsirolimus improved median overall survival in renal cell carcinoma from 7.3 months to 10.9 months compared to interferon therapy (Hadoux et al., 2010).

Everolimus, when combined with exemestane, improved progression-free survival from 4.1 to 10.6 months in endocrine-resistant metastatic breast cancer (Riccardi et al., 2018).

D. Limitations

Rapalogs are limited by their inability to inhibit mTORC2, which mediates pro-survival Akt activation that can undermine therapeutic efficacy. This incomplete pathway blockade offers only partial inhibition of cancerous progression. Moreover, their cytostatic nature—inhibiting tumor growth rather than causing cell death—was often insufficient in diseases with aggressive features or compensatory signaling pathways (Yang et al., 2015).

E. Potential Biomarkers for Patient Stratification

Potential biomarkers include TSC1/2 mutations and high baseline mTOR pathway expression. High levels of pAKT and pS6, as well as p-mTOR and p-S6RP expression, may also be predictive (Alves et al., 2015).

Fig. 6B

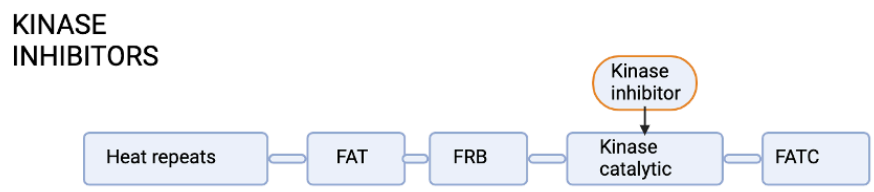


FIGURE 6B. Kinase inhibitors of mTOR bind to the kinase domain of mTOR and block both mTORC1 and mTORC2.

SECOND GENERATION mTOR INHIBITORS (FIGURE 6B)

To overcome the limitations of the first-generation Rapalogs, second-generation ATP-competitive mTOR kinase inhibitors were developed.

A. Drugs

Torin-1, Torin-2, AZD8055, Torkinib (PP242), PP30, Sapanisertib (also known as MLN0128, INK-128, or TAK-128), and OSI-027 (ASP4786).

B. Mechanism of Action

These inhibitors function as ATP analogs and compete with ATP for binding to the kinase domain of mTOR (Figure 6B).

C. Clinical Outcome

Sapanisertib demonstrated higher efficacy in a broader spectrum of malignancies, including glioblastoma and endometrial carcinoma. Studies in vitro also highlighted its ability to inhibit cell proliferation more effectively than first-generation inhibitors. However, the clinical advancements of these inhibitors have been tempered by their toxicity profiles (Zhang et al., 2021).

D. Limitations

While these second-generation mTOR inhibitors initially suppress Akt signaling by inhibiting mTORC2, the negative feedback on insulin/PI3K signaling eventually overcomes this blockade, and Akt becomes reactivated after long-term treatment (Rodrik-Outmezguine et al., 2011).

The clinical advancements of these inhibitors have been tempered by their toxicity profiles. Patients often reported dose-limiting toxicities such as hyperglycemia and gastrointestinal distress (Ali et al., 2022).

E. Potential Biomarkers for Patient Stratification

Sustained mTORC1 signaling has been identified as a predictive biomarker for the EGFR antibody nimotuzumab in glioblastoma (Ronellenfitsch et al., 2018).

Fig. 6C

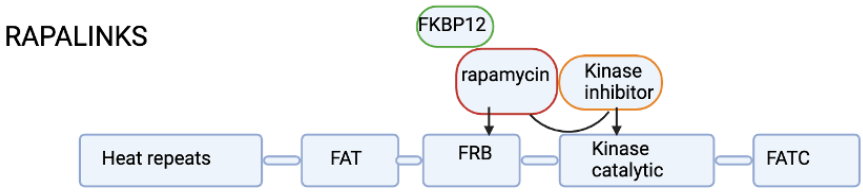


FIGURE 6C. Rapalinks are composed of rapamycin cross-linked to a kinase inhibitor of mTOR.

THIRD GENERATION mTOR INHIBITORS (FIGURE 6C)

Third-generation mTOR inhibitors, known as "Rapa-link" drugs, have been developed to address the limitations of first- and second-generation mTOR inhibitors.

A. Drugs

Third-generation mTOR inhibitors include RapaLink-1. RapaLink-1 combines Rapamycin with MLN0128 using an inert chemical linker (Selleckchem, 2015).

B. Mechanism of Action

These drugs consist of a combination of rapamycin and an mTOR kinase inhibitor, and they can potentially overcome the drug resistance of cancer cells with mutations in the mTOR FRB/kinase domain (Figure 6C). This includes mutations that confer resistance to first-generation rapalogs and second-generation mTOR-KIs (Xie et al., 2016).

C. Clinical Outcome

Promising results were observed in preclinical trials showing that RapaLink effectively inhibited mTORC1 and mTORC2 in Akt-driven malignancies resistant to early-generation inhibitors, particularly glioblastoma. Additionally, third-generation inhibitors have shown prolonged therapeutic relevance, demonstrated by the elimination of chemotherapeutic resistance in experimental mice models after nine months of treatment. However, clinical data on the broader efficacy of third-generation drugs remains limited, necessitating further trials (Fan et al., 2015).

D. Limitations

Tissue toxicity remains a concern with third-generation mTOR inhibitors. The highly complex regulatory mechanism network of mTOR proposes huge challenges to the development of clinically efficient mTOR inhibitors (Qiu et al., 2021).

E. Potential Biomarkers for Patient Stratification

Identification of biomarkers for the activation of the mTOR pathway facilitates patient stratification to determine the highest expression. Elevated pAKT levels are associated with response to Rapalink-1. KRAS,

BRAF, and TSC mutations are known resistance markers for mTOR inhibitors, including Rapalinks. PIK3CA mutations are associated with sensitivity to mTOR inhibitors, including Rapalinks (Hua et al., 2019).

DUAL pI3K/mTOR INHIBITORS

A. Drugs

Examples include Dactolisib, Apitolisib, Voxtalisib, Paxalisib, Bimiralisib, and Gedatolisib. One of the most promising compounds from this class of inhibitors is NVP-BEZ235, a derivative of the imidazoquinoline developed by Novartis (Xie et al., 2016; Maira et al., 2008).

B. Mechanism of Action

These inhibitors target both PI3K and mTOR, two important signaling pathways that drive cancer cell growth.

C. Clinical Outcome

Clinical trials have shown promising results with this drug, and its efficacy can be increased when combined with inhibitors against other pro-mitogenic pathways, such as MEK/ERK inhibitors (Liu et al., 2024). Dactolisib inhibited phosphorylation of key downstream targets such as Akt, S6K, and 4E-BP1, inducing apoptosis in colorectal cancer cells in xenografts (Wu et al., 2022). Voxtalisib exhibited significant efficacy across diverse cancers like glioblastoma, leukemia, and ovarian cancer, with its mechanism profoundly affecting PI3K/mTOR-dependent survival pathways (Wu et al., 2022).

D. Limitations

PI3K inhibitors in the central nervous system may cause mood alterations such as anxiety or irritability. They may also fail to fully suppress tumors with alterations downstream of PI3K but upstream of mTOR. A phase I study of BEZ235 was terminated early due to toxicity and a lack of clinical efficacy (Pongas & Fojo, 2016).

E. Potential Biomarkers for Patient Stratification

Triple-negative breast cancer cells with activated PI3K/Akt signaling due to PIK3CA mutations or PTEN loss were more sensitive to PI3K/mTOR inhibitors (O'Regan, 2023).

FORWARD-LOOKING PERSPECTIVES ON CANCER THERAPIES WITH mTOR & RELATED APPROACHES

The evolving landscape of oncology is shifting toward integrative strategies that extend beyond conventional mTOR inhibition. Novel approaches, including combination therapies with mTOR inhibitors, mTOR-independent metabolic interventions, and immunotherapy synergies, are emerging as promising avenues to enhance treatment efficacy. These strategies aim to address drug resistance, exploit metabolic vulnerabilities in cancer cells, and fine-tune immune responses, ultimately improving patient outcomes.

COMBINATION THERAPIES WITH mTOR INHIBITORS

Combination therapies seek to enhance the impact of mTOR inhibitors by targeting multiple pathways simultaneously or compensating for mTOR inhibition-related resistance.

A. Targeting Alternative Pathways

One approach is combining mTOR inhibitors with drugs that block pathways activated as resistance mechanisms. For instance, inhibiting MNK genes or c-Myc activity with BET inhibitors complements mTOR inhibition, particularly in cases of acute myeloid leukemia (AML), as it impairs alternative proliferative pathways used by cancer cells (Kosciuczuk et al., 2016).

B. Epigenetic Combinations

Combining mTOR inhibitors with epigenetic drugs like entinostat, which inhibit histone deacetylases (HDAC), has shown synergistic effects in preclinical cancer models. These approaches enhance apoptosis and cell cycle arrest (Biermann et al., 2022).

C. Oncogenic Pathway Interactions

Cross-talk between the mTOR pathway and others, such as MAPK and VEGF pathways, has led to combinations of mTOR inhibitors with MEK inhibitors or anti-angiogenic agents, which demonstrate improved anti-tumor effects by blocking tumor growth and microenvironmental support (Wang et al., 2012).

mTOR-INDEPENDENT METABOLIC INTERVENTIONS

In parallel with mTOR-targeting approaches, non-mTOR metabolic interventions aim to leverage metabolic vulnerabilities of cancer cells to impair their growth and proliferation.

A. Glycolysis Inhibitors

These drugs disrupt the glycolytic pathways' hyperactivity in many cancers, reducing the energy supply critical for tumor cell survival. By targeting glycolysis, treatments address the metabolic reliance of rapidly dividing cells (Ganapathy-Kanniappan & Geschwind, 2013).

B. Glutaminase Inhibitors

Targeting glutaminolysis, another metabolic pathway crucial for cancer proliferation, has shown promise in preclinical studies. This approach disrupts the cancer cells' ability to balance redox reactions and synthesize key biomolecules (Choi et al., 2023).

C. Novel Metabolomic Targets

Therapies focusing on oxidative phosphorylation and other metabolic processes offer a promising avenue for cancers resistant to standard treatments, especially when integrated with immunotherapy or targeted therapies (Sica et al., 2019).

IMMUNOTHERAPY SYNERGIES WITH mTOR INHIBITORS

The combination of mTOR inhibitors with immunotherapy represents a forward-looking methodology that could revolutionize treatment paradigms by improving anti-tumor immune responses.

A. Enhancing Immune Checkpoint Blockade

mTOR inhibitors potentiate the effects of immune checkpoint inhibitors such as anti-PD-1/PD-L1 therapies by modulating the tumor immune microenvironment, promoting T cell infiltration, and reducing immune suppression (Wu et al., 2020).

B. Memory T Cell Generation

mTOR inhibitors, such as rapamycin, have been shown to expand memory CD8+ T cells, enhancing long-term immunological memory and potentially prolonging response durations in cancer patients (Sowell & Marzo, 2015).

C. Specific Synergies

Preclinical studies demonstrate that combining mTOR inhibitors with cancer vaccines or heat shock protein-based therapies strengthens cytotoxic T cell responses. This creates a more robust and sustained anti-tumor effect (Sowell & Marzo, 2015).

TRANSLATIONAL AND FUTURE DIRECTIONS

Harnessing the interplay between mTOR-dependent and independent pathways, as well as integrating immuno-metabolic modulation, presents a compelling opportunity for more effective cancer treatments. Ongoing clinical trials and translational research are essential to refining these strategies, including the identification of predictive biomarkers, optimization of dosing regimens, and mitigation of therapy-associated toxicities (Wang et al., 2022). These advancements will drive the development of personalized and durable cancer therapies, shaping the future of oncological treatment.

CONCLUSION

The discovery of the mTOR pathway initially sparked immense excitement in the scientific community as a promising target for cancer therapy, given its central role in regulating cell growth, metabolism, and survival. Early successes with Rapalogs in specific cancers offered hope, but the complexity of mTOR signaling soon revealed significant challenges. Its paradoxical behaviors, such as feedback activation of AKT and pro-survival autophagy, along with non-canonical roles in nuclear signaling and compensatory pathway activation, limited the efficacy of early inhibitors. Despite these setbacks, innovative approaches have emerged to overcome these hurdles. Biomarker-driven patient stratification and dual PI3K/mTOR inhibitors now aim to refine therapeutic precision. Additionally, combination therapies, such as mTOR-independent metabolic interventions and immunotherapy synergies are unlocking new potential by targeting complementary vulnerabilities. As we move beyond the initial disappointments, these advancements mark a turning point in mTOR-targeted therapy, transforming its complexity from a challenge into an opportunity for personalized and durable cancer treatments.

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