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Review

mTOR-Mediated Neuron–Cancer Interactions

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Abstract

The phosphotransferase activity of the protein kinase known as the mechanistic Target of Rapamycin (mTOR) is arguably one of the most studied biochemical events in biomedical sciences because of its importance to human health and evolution. Despite progress being made in understanding the structure, biochemical characteristics, and function of the enzyme, tremendous knowledge gaps remain unfilled. Altered mTOR activity occurs in numerous neurological disorders, including those that present with seizures and neoplasms. Advances in cancer biology have identified that neuron activity is a critical driver of neoplastic growth. Here, we discuss mTOR, examples of neoplasms with altered neuron activity, and the potential utility of using mTOR inhibitors to modulate tumor-associated neurons.

Keywords: mTOR; cancer; neurogenesis; tumor neurons

1. Introduction

The discovery of mTOR and development of mTOR inhibitors can be traced to the discovery of a natural compound from soil bacteria. The story begins with the Medical Expedition to Easter Island (METEI), which was undertaken by a group of Canadian scientists in 1964. The scientists visited Easter Island, also known as Rapa Nui, to investigate the health and environmental challenges of the inhabitants. Among the scientists was the microbiologist Georges Nogrady, who demarcated the island into sixty-four squares and sampled the soil of each square. Upon return, he distributed the soil samples to his colleagues [1]. In 1975, a microbiologist, Claude Vézina, and a biochemist, Surendra (Suren) Nath Sehgal, at Ayerst Research Laboratories in Canada, discovered that the soil samples contained a bacterium called *Streptomyces hygroscopicus*, which produces a compound with antifungal properties. They named the compound rapamycin in honor of Rapa Nui [2]. It was later discovered that this antifungal agent (rapamycin) has immunosuppressive (1977) and anticancer (1984) properties [3,4].

Yeast treated with rapamycin fails to proliferate. Hall and colleagues observed continued proliferation of sporadic colonies in the presence of rapamycin. The yeast had mutations in one of three genes, *FPR1*, *TOR1*, or *TOR2* (Target of Rapamycin) [5]. George Livi and John J. Siekierka identified that the immunophilin FK506 binding protein (FKBP) mediates rapamycin sensitivity in yeast [6,7]. Multiple laboratories subsequently identified a mammalian homolog of TOR which interacts with FKBP12/rapamycin. As a result, this protein was initially given different names, including FKBP–rapamycin-associated protein (FRAP), rapamycin–FKBP12 target 1 (RAFT1), and rapamycin target 1 (RAPT1) [8–11]. The

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term mTOR (mammalian target of rapamycin) was later adopted and is now commonly understood to refer to the mechanistic target of rapamycin.

2. Components of the mTOR Pathway

mTOR catalyzes phosphotransferase reactions as two independent multimeric protein complexes referred to as mTORC1 and mTORC2 based on their components (Figure 1) [12–15].

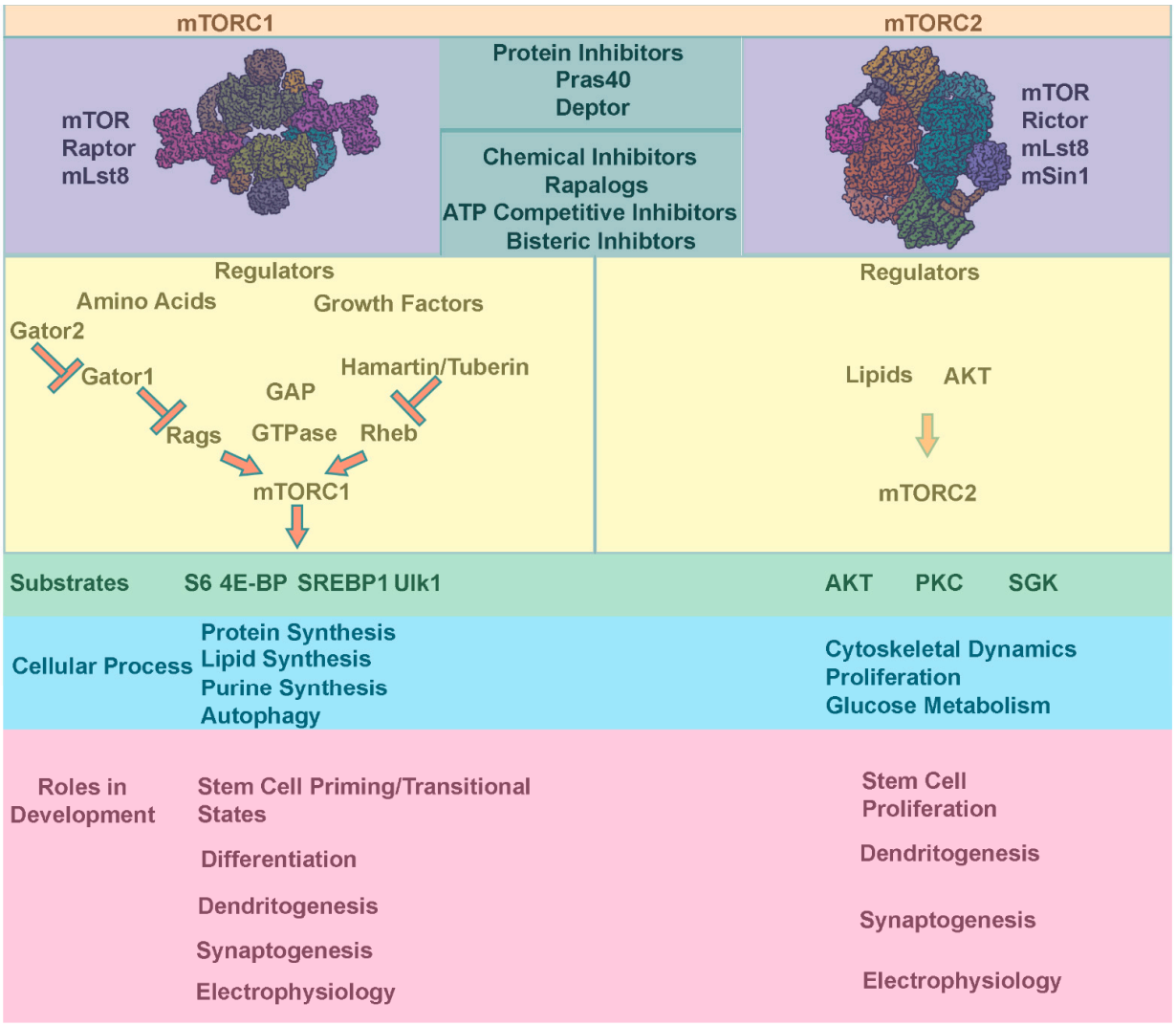


Figure 1. *mTOR Complexes.* The mTOR Complexes (mTORCs) include mTORC1 and mTORC2. mTOR is the catalytic component of both mTORCs. However, mTORC1 also contains mLst8 and Raptor, whereas mTORC2 contains mLst8, mSin1, and Rictor. These components allow for distinct mechanisms of regulation. mTORC1 is largely regulated by amino acid signaling through sensors that control Gator2 or Gator1 complexes. The Gators control the activity of the Rag GTPases, which allow mTORC1 to localize to the lysosome and become activated by the monomeric GTPase Rheb. In contrast, less is known about mTORC2 activity, which appears to include lipids and AKT. Each mTORC has distinct substrates, with mTORC1 phosphorylating numerous proteins and mTORC2 mainly phosphorylating AGC kinases. They also have distinct roles in controlling cellular processes, with mTORC1 regulation of protein synthesis being best documented, whereas mTORC2 regulates cytoskeletal dynamics and proliferation. However, both mTORC1 and mTORC2 play prominent roles in regulating neural stem cells and neuron physiology during brain development. Arrows indicate activation and perpendicular rectangles indicate inhibition.

mTORC1 is activated by the GTPase Rheb [13–16]. Rheb bound to GTP activates mTORC1, but Rheb hydrolysis of GTP to GDP terminates its activation of mTORC1 [17]. The rate of Rheb hydrolysis is controlled by the proteins encoded by *TSC1* and *TSC2*, called hamartin and tuberin, respectively [13–15,18]. They form a GTPase-activating protein (GAP) complex that inhibits mTORC1. A third protein called TBC1D7 and hamartin stabilize tuberin, which is the functional GAP [19]. Active mTORC1 controls translation by phosphorylating eukaryotic initiation factor 4E binding protein (eIF4EBP), which is an inhibitor of eIF4E [20,21]. mTORC1 also phosphorylates and activates p70S6 kinase (p70S6K), phosphorylating the ribosomal S6 subunit (S6) [22,23]. This stimulates translation of anabolic mRNAs involved in processes including ribosome biogenesis [24,25]. mTOR also regulates numerous catabolic cellular processes [26–29].

mTORC1 translocates and colocalizes with Rheb at the lysosome [30–32]. Heterodimeric RAG GTPases (RagA or B bound to RagC or D) at the lysosome activate Rheb-mTORC1 [31]. This is inhibited by a GAP multimeric complex referred to as Gator1 that is formed by Depdc5, Nprl2, and Nprl3 [33]. Gator1 prevents mTORC1 activity. Inactivating mutations in Gator1 components lead to neurological disorders characterized by excessive mTORC1 and epilepsy. A second complex called Gator2 (Mios, WDR24, WDR59, Seh1L, Sec13) inhibits Gator1 [33]. Amino acids that activate mTOR often bind to sensors that activate Gator2, which inhibits Gator1, causing Rags to activate mTORC1 [34–36]. However, mTORC1 activity is also gated by growth factor signaling through a mechanism that includes inactivation of tuberin, for example, by AKT [37–39].

Direct mTORC2 regulation is less well understood but includes regulation by lipids at the membrane. PI3K is a lipid kinase that generates PtdIns(3,4,5)P_3 [40]. PtdIns(3,4,5)P_3 binds to AKT [41]. mTORC2 is inhibited by its binding partner Sin1, but upon binding, PtdIns(3,4,5)P_3 relieves mTORC2 inhibition [42]. This allows mTORC2 (previously hypothesized to be a PDK2) to phosphorylate AKT at serine 473 [43]. Moreover, AKT phosphorylates Sin1 at threonine 86 to stimulate mTORC2 activity [44]. Additional areas of interest include mTORC2 direct binding to and regulation by monomeric GTPases [45].

3. mTORC1 and the Nervous System

mTORC1 regulates several steps of nervous system development. Mutations in upstream regulators of mTORC1 do not appear to directly affect proliferation. Quiescent mouse inhibitory neural stem cells (NSCs) of the postnatal V-SVZ turn mTORC1 on as they transition to an active phase of cell division [46]. This is likely due to growth factors such as EGF and FGF, which cause AKT to turn off tuberin, thereby leading to mTORC1 activation [39,47–50]. mTORC1 is also active in neuroprogenitor cells, including transit-amplifying cells, which produce early neuroblasts [46,50]. mTORC1 stimulates translation in these cells but then pauses as differentiation proceeds [51]. Loss of control of mTORC1 in postnatal V-SVZ NSCs caused by the removal of *TSC1* or *TSC2* does not appear to induce proliferation. For example, loss of *TSC1* from quiescent NSCs leads to more dividing progenitors but not more stem cells [46]. This is consistent with the findings that mTORC1 induces symmetric division and differentiation of slow-cycling NSCs into proliferative daughter cells [46]. Rheb knockdown prevents NSC differentiation, resulting in reduced expansion of neuron lineages and aborted neuron production [46]. Loss of *Tsc1* from NSCs and from transit amplifying cells results in growths along the ventricles [52,53]. Loss of *Tsc2* from lateral V-SVZ NSCs that produce glia causes transcription and translation of the incorrect mRNAs and altered stem cell transitional states, leading to astrocytes that can have stem cell properties and cause hamartomas in mice [54]. One reason that mTORC1 is turned down during these complex events may be to allow the translation of only select mRNAs and to uncouple stem cell transcript abundance from translation [51].

Similar findings have been observed in the embryonic mouse brain. Embryonic loss of *Tsc1/2* genes causes abnormal cortical development. This is evident when upper-layer excitatory cortical neurons are being produced [55]. Loss of *TSC* genes reduces the number of radial glia (NSCs) but increases the ratio of intermediate progenitors, which yields more upper-layer neurons, a disorganized cerebral cortex, and macrocephaly [56,57]. The neurons produced by *Tsc1* or *Tsc2* null NSCs are cytomegalic, have increased dendrite complexity, and have abnormal electrical activity. While mutations in each mTORC1 regulator may cause slightly different changes, the general effects are highly conserved [58,59]. There may be functional consequences the further upstream from mTOR that mutations occur, for example, with phosphatase and tensin homolog (PTEN). In fact, activating mutations in mTOR itself can occur, and these mutations are predicted to affect both mTORC1 and mTORC2 [60]. Since mTORC2 signaling is implicated in AKT activation, as occurs with PTEN inactivating mutations, there may be additional effects on cell proliferation or differentiation [61–65].

mTOR has critical roles in regulating electrophysiological characteristics. Numerous ion channels are changed in distinct neuron subtypes when mTOR is activated. This important topic has been reviewed by experts elsewhere [66,67]. Among the first findings relating mTOR to neuron electrophysiology was that neuron activity and rapamycin repress the translation of the dendrite-localized voltage-dependent potassium channel Kv1.1 [68]. mTOR acts as a voltage sensor that resets dendrite polarity following synaptic excitation by controlling Kv1.1, Kv1.2, and Kvb2 expression [69]. Such potassium channel subunits have also been linked to upstream interaction with the Slc7a5 amino acid transporter, which controls mTORC1 activity, dendrite growth, and neuron survival [70–72]. The removal of mTORC1 regulators also alters numerous ion channels. For example, the removal of *Nprl2* (GATOR1) increases the voltage-dependent sodium channel SCN1a [73]. In TSC, mutant neurons repress CaV1.2/α2δ2 [74]. Another example is that HCN4 channels are increased in TSC and this drives seizure activity in a focal cortical dysplasia model [75]. mTOR also regulates chloride transporters, which affects whether GABAa receptor activation leads to hyperpolarization or depolarization [76]. These results highlight the necessity of tightly controlling mTOR pathway activity during development [77]. As a result of this wide-spanning significance, mTOR dysregulation is thought to play a crucial role in the initiation and progression of numerous neurological disorders.

4. An mTORopathy Leads to Benign Tumor Growth

Neurological disorders for which mTOR activity is altered are called mTORopathies. Tuberous Sclerosis Complex (TSC) is the prototypical mTORopathy based on the relationship of *TSC1/2* to Rheb and mTORC1 [78]. TSC patients are born with a mutation in one of the copies of *TSC1* or *TSC2*. It is proposed that a subset of cells acquire a mutation in the other functional copy of the *TSC1* or *TSC2* gene during development [78]. This is called loss of heterozygosity (LOH). LOH that occurs in NSCs is proposed to cause abnormal brain development in TSC. Approximately 85% of TSC patients have small growths along the ventricular system called subependymal nodules (SENs). In a smaller percentage of cases (~15–25%), patients will develop larger subependymal giant cell astrocytomas (SEGAs) (Figure 2) [79,80]. The term astrocytoma appears slightly misleading, as SEGAs grow slowly [81]. They appear as benign grade I neoplasms. Their fetal appearance as SENs and early childhood presentation as SEGAs further support their benign nature [82,83]. SEGAs can be calcified and exhibit immune cell infiltration and prominent vascularization. SEGAs have variable levels of reactive astrocytes and may express NSC markers. However, Buccoliero and colleagues report that SEGAs have a significant neuronal composition comprising synaptic markers and appear reminiscent of focal cortical dysplasias or cortical tubers [84].

Single-nuclei RNA sequencing of SEGAs identified that when compared to tissue from the caudate nucleus, there were many similarities in the cellular composition [85]. While endothelial cells and perivascular macrophages were increased in SEGAs, and some changes to oligo-lineage cells were noted, GABAergic neurons are a predominant cell type. Indeed, many SEGA neurons had signatures of hyperexcitability, as noted by the upregulation of immediate early genes. While it remains to be seen what role neurons may have in SEGAs, mouse models also appear to share some features, including the presence of neurons [54]. Thus, NSCs that lose TSC genes may have altered development, leading to the production of abnormal neurons that have high mTORC1 activity. TSC mutant neurons might drive SEGA growth. However, this remains to be tested.

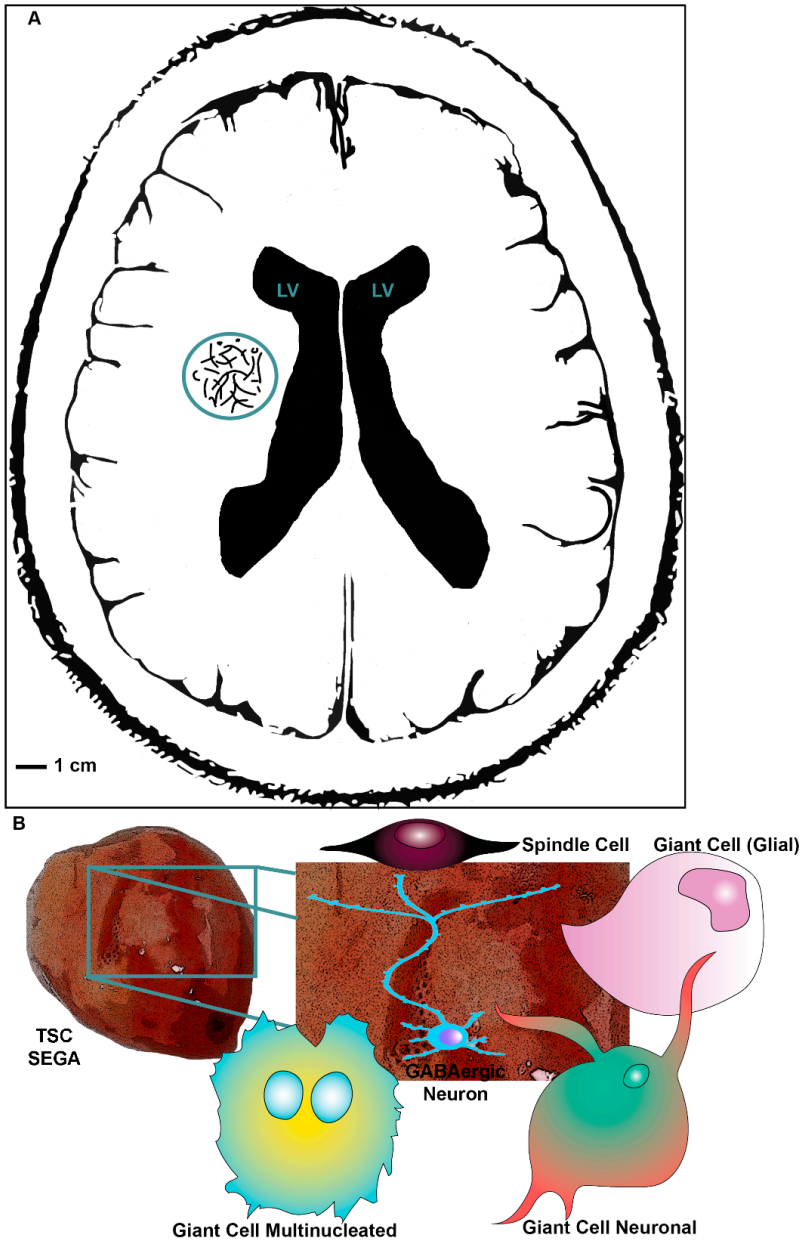


Figure 2. *Cellular Composition of SEGAs.* (**A**) Schematic diagram of Tuberous Sclerosis Complex subependymal giant cell astrocytoma arising in the parenchyma near the lateral ventricles (LV) and within the striatum. (**B**) A schematic of an SEGA and cell-type composition based on prior histopathology, electron microscopy, and immunohistochemistry, incorporating new findings based on single-nuclei RNA sequencing demonstrating the presence of multiple GABAergic inhibitory neuron subtypes.

5. Precedence for Neuronal Regulation of Brain Tumors

Here, we provide the term tumor-associated neurons as an all-encompassing idea to consider the possible roles that neurons have in tumor growth. The classification, therefore, does not distinguish between the several possibilities, which may include the following: 1. neurons that are not mutated but which innervate tumors, 2. neurons that are normal but are aberrantly produced at the wrong time and in the wrong place by tumor cells, 3. neurons that are aberrantly produced by non-tumor cells caused by the release of factors from tumor cells, and 4. mutant neurons that have abnormal properties that may cause the proliferation of other cells, including mutated or non-mutated cells. Therefore, we have selected only a handful of seminal studies that explore how tumor-associated neuron activity may drive cancer growth and briefly identify relationships with mTOR, if any.

In 2015, Venkatesh et al. demonstrated that the activity of normal neurons can drive the growth of patient-derived glioblastoma cells [86]. Glioblastoma cells were transplanted into the cortex of mice that expressed channel rhodopsin in neurons. Light stimulation of the cortical neurons drove neuronal activity and glioblastoma proliferation [86]. Stimulation of the mouse neurons enhanced release of the protein neuroligin (NLGN3), which activated mTORC1 and AKT. NLGN3 also caused feedforward production of NLGN3 by the glioblastoma cells.

Glioblastomas (GBMs) are aggressive primary malignant neoplasms of the brain arising from uncontrolled glial cell proliferation [87]. A 2025 study by Sun et al. highlighted how neurons control GBMs [88]. Using a herpes simplex virus (HSV) anterograde transmonosynaptic tracing approach in mice using transplanted GBM organoids (GBOs) that predominantly express the NSC markers Nestin and Sox2, the authors found that GBM cells express a wide range of receptors [88]. These organoids rapidly formed synapses with sectioned human cortical organoids. Transplanted GBM organoids also formed synapses across multiple neuron types found throughout the brain but appeared to preferentially form synapses with and receive input from glutamatergic and cholinergic neurons. *In vitro* treatment with acetylcholine or cholinergic activation using *in vivo* expressed channel rhodopsins in cholinergic neurons caused increased calcium oscillations in GBOs. Acetylcholine also induced long-term changes in calcium oscillation and transcriptional reprograming of GBOs related to cell motility, conferring increased tumor migration that could subsequently be inhibited by knockdown of the cholinergic receptor muscarinic 3 (CHRM3).

Glioma is also associated with the development of seizures. PDGFA^{+}/p53$^{-/-}$ glioma cells injected into Thy1-GCaMP6f mice allowed for the monitoring of calcium transients and neuronal activity [89]. The glioma cells induced neuron hyperexcitability 25–30 days later. Eventually, the glioma cells caused the progressive development of spontaneous epileptiform activity. It appeared that loss of putative parvalbumin inhibitory interneuron synapses and decreased firing rates were correlated with increased activity of the Thy1 excitatory neurons. Seizure activity in these mice could be rescued by treatment with the mTOR inhibitor, AZD8055. Interestingly, mTORC1 activity and calcium transients were reduced in the neurons of Thy1-GCaMP6f mice following AZD8055 treatment. Nevertheless, whether mTORC1 was the only target and whether excitatory neurons were uniquely affected was unclear. Building from this work, PDGFA^{+}/p53$^{-/-}$/mCherry-Luciferase^{+} glioma cells were injected into transgenic mice engineered to express Rpl22^{HA} in excitatory neurons [90]. Immunoprecipitation of HA-tagged ribosomes was then performed. There was significant enrichment of mTOR-regulated TOP mRNA transcripts from excitatory neurons. This could be rescued by treating mice with an mTOR inhibitor AZD8055. The glioma cells also modified the expression of numerous cytoskeletal and synaptic transcripts

which were associated with the loss of inhibitory synapses onto excitatory neurons. Indeed, the number of dendritic spines on excitatory neurons was reduced in glioma-bearing mice. Glioma cells invaded the whisker barrel cortex of the somatosensory cortex. Whisker stimulation generated an increase in single-neuron calcium oscillations and calcium oscillations in glioma cells and enhanced glioma cell proliferation. Treatment with AZD8055 reduced total calcium oscillations and oscillations between intervals of whisker stimulation in the infiltrating glioma cells. This study provides evidence that gliomas alter neuronal connections and respond to these altered neural circuits. Moreover, it implicates elevated mTOR activity in the maladaptive changes that occur in glioma.

The role of GABAergic input into brain cancers has also been examined, but in relation to diffuse midline glioma (DMG) cells [91]. DMGs are frequently caused by mutations in histone H3 (H3K27M). These DMGs are enriched in transcripts encoding GABAergic receptor subunits and GABAergic postsynaptic proteins. GFP-tagged $GABA_A$-expressing diffuse midline glioma (DMG) cells transplanted into the hippocampus of mice generate functional GABAergic synapses. Contrary to its traditional role as an inhibitory neurotransmitter in mature adult neurons (via hyperpolarization), GABA depolarizes and induces DMG proliferation. Importantly, the authors demonstrate that optogenetic stimulation of GABAergic neurons in the hippocampus drives DMG proliferation.

Additional work has revealed how neurons affect gliomas in neurofibromatosis patients. Patients that have neurofibromatosis have one mutant NF1 allele and one wild-type allele. The wild-type allele undergoes LOH in a subset of cells. Approximately 15 percent of patients that have NF1 mutations develop low-grade optic pathway gliomas (OPGs). OPGs sporadically occur in mice that undergo NF1 LOH [92]. Switching these mice from a dark environment to one with light causes them to develop OPGs more frequently [92]. Optogenetic stimulation of retinal ganglion neurons increases the release of NLGN3 and BDNF in these mice [92]. NF1 mouse retinal ganglion neurons shed more NLGN3. NLGN3 release stimulates NF1 null progenitors and drives OPGs to form [92]. The removal of NLGN3 partially rescues OPG formation [92].

NF1 mutant neurons also release midkine to T cells [93]. This causes T cells to produce more CCL4, a chemokine that induces microglial production of CCL5 [93]. Importantly, CCL5 supports tumor cell survival and proliferation in glioma [94,95]. Midkine expression is elevated in NF1-mutant optic pathway glioma (OPG) and pilocytic astrocytoma. NF1 mutant neurons also have increased action potential firing rates [96]. NF1 mutant neurons have reduced hyperpolarization-activated cyclic nucleotide-gated (HCN) channel activity. Loss of NF1 drives mTOR activity and mTOR inhibition rescues tumorigenesis; however, the extent that mTOR in neurons is involved remains to be determined [97–99].

6. mTOR Inhibitors

A potential therapeutic approach to treating CNS neoplasms is the use of mTOR inhibitors. mTOR inhibitors work by targeting and suppressing hyperactive mTOR, thereby restoring cellular homeostasis.

There are three distinct generations of mTOR inhibitors (Figure 3). The first-generation inhibitors include rapamycin (sirolimus) and its derivatives, known as rapalogs (e.g., everolimus, temsirolimus, and ridaforolimus). In mammalian cells, rapamycin binds to FKBP12, forming a drug–protein complex that associates with the FKBP12–rapamycin-binding (FRB) domain of mTOR. This interaction induces steric hindrance, thereby acting as a physical barrier that restricts access of certain substrates to the catalytic site to prevent their phosphorylation [100]. Rapamycin primarily inhibits mTORC1 because of the complex's exposed FRB domain. Rapamycin inhibits mTORC1 phosphorylation of p70 ribosomal S6 kinase (p70S6K). However, rapamycin is inefficient at blocking mTORC1 phosphorylation

of eukaryotic translation initiation factor 4E-binding protein (4E-BP). In mTORC2, the FRB domain is masked by the Rictor subunit. Therefore, the rapamycin–FKBP12 complex is unable to bind to and interact with mTORC2. However, prolonged rapamycin exposure can inhibit mTORC2 activity by preventing the assembly of new mTORC2 complexes [101].

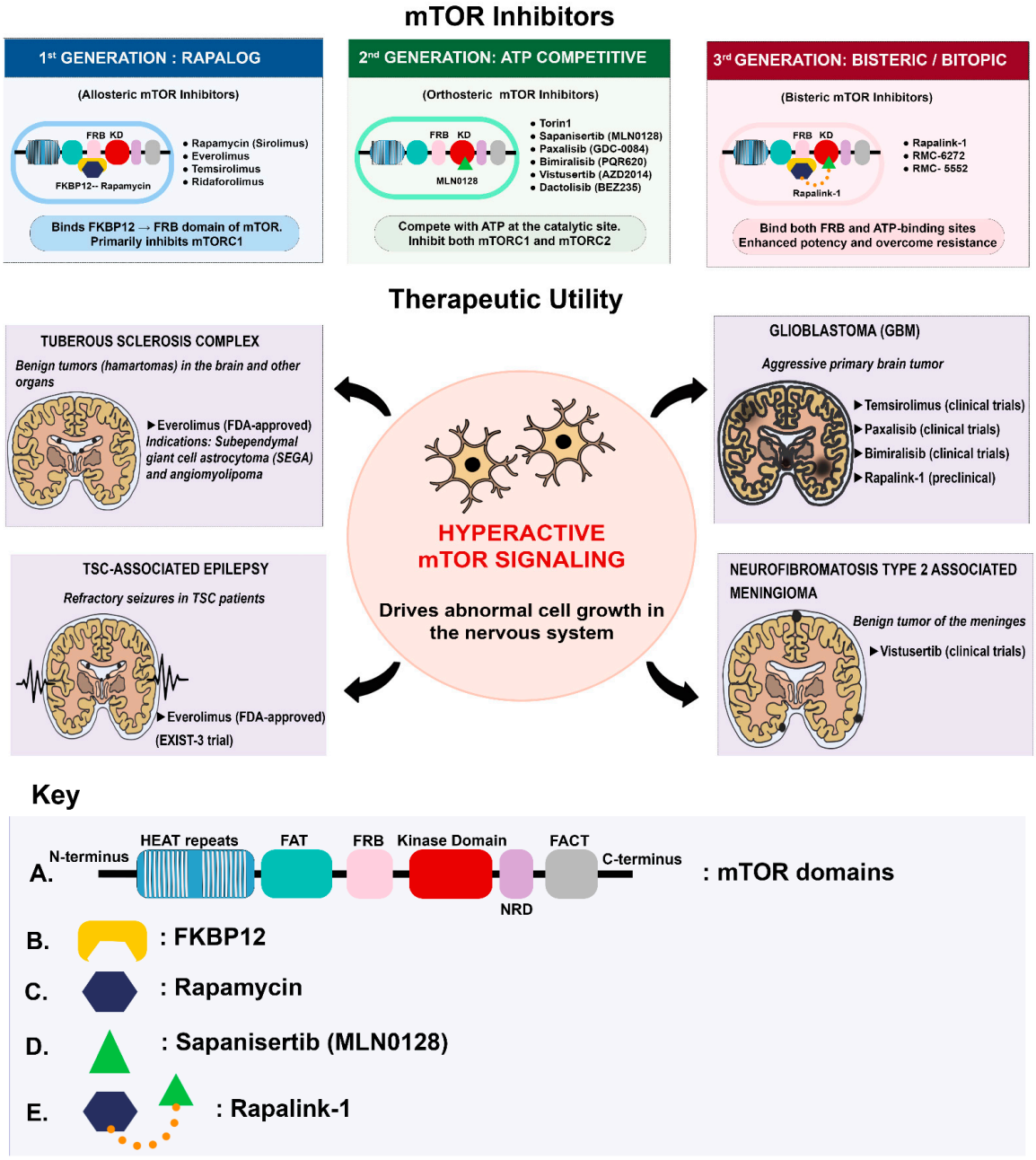


Figure 3. *mTOR inhibitors: evolution and therapeutic utility in neurological disorders.* Schematic diagram illustrating the mechanisms of action of the three generations of mTOR inhibitors and their current or emerging therapeutic applications in neurological disorders. The blue panel illustrates how the prototypical first-generation mTOR inhibitor rapamycin forms a complex with FKBP12, which binds to the FRB domain of mTOR and primarily inhibits mTORC1 (allosteric inhibition). The green panel illustrates how the exemplary second-generation mTOR inhibitor sapanisertib (MLN0128) binds directly to the mTOR kinase domain and inhibits both mTORC1 and mTORC2 (orthosteric inhibition). The red panel illustrates how Rapalink-1, a third-generation mTOR inhibitor, binds to both the FRB and kinase domains of mTOR through its rapamycin and MLN0128 moieties, respectively (bisteric inhibition). The purple panels illustrate exemplary neurological diseases for which various mTOR inhibitors have been clinically or preclinically investigated.

Rapalogs are derivatives of rapamycin that share the same mechanism of action but have been developed to enhance efficacy and clinical utility. Everolimus (RAD001) is the hydroxyethyl ether derivative developed by Novartis (Switzerland), which is administered orally [102,103]. In 2006, Franz and colleagues reported the regression of TSC-associated SEGAs following treatment with rapamycin [104]. Rapamycin was approved in 2012 by the Food and Drug Administration (FDA) for the treatment of SEGA associated with TSC in the pediatric population [105]. Rapamycin has since been used in post-transplant immunotherapy and in the treatment of neuroendocrine tumors [103]. Temsirolimus (CC1-779) is the ester derivative of rapamycin developed by Wyeth-Ayerst/Pfizer; it is given both intravenously and orally and has been approved for treating advanced renal carcinoma [106]. Deforolimus/ridaforolimus (AP22573) is a dimethyl phosphonate derivative of rapamycin, which is considered an investigational drug in the management of advanced solid tumors like sarcoma and breast cancer. However, it has not been approved for any clinical indications [107]. Zotarolimus is a tetrazole-containing derivative of rapamycin developed by Abbott and Medtronic, which was designed for coating coronary stents [103,108]. These synthetic modifications confer several pharmacological advantages, such as improved water solubility and enhanced oral bioavailability.

Rapalogs have been used to treat several neurological disorders. The most prominent clinical utility of these drugs is in the management of TSC, wherein mTORC1 is hyperactive. Everolimus is FDA-approved for the treatment of SEGAs and as an adjuvant therapy for refractory seizures in this population [107,109]. In the phase III clinical trial EXIST-3, everolimus (blood concentration: 9–15 ng/mL) significantly reduced seizure frequency in patients with refractory focal-onset epilepsy [110].

Rapamycin and its analogs, everolimus and temsirolimus, have been investigated as a therapy for PTEN-deficient glioblastoma. Unfortunately, these treatments are limited by incomplete mTORC1 inhibition and the loss of negative feedback regulation, particularly when administered at chronic doses. This leads to compensatory activation of upstream signaling pathways such as PI3K/AKT via the S6K1-IRS1 feedback loop, thereby promoting the survival of tumor cells [111]. Additionally, chronic rapamycin treatment can select for cells with mutations in the FRB region of mTOR (e.g., S2035F, F2108L, A2034V), which disrupt the FKBP12–rapamycin interaction and render drugs ineffective [112,113]. These limitations have driven the development of second-generation mTOR inhibitors.

Unlike the first-generation inhibitors that act allosterically, the second-generation inhibitors bind directly to the kinase site or the catalytic domain of mTOR, in an ATP-competitive manner; hence, they are called ATP-competitive inhibitors or orthosteric inhibitors. These drugs effectively inhibit both mTORC1 and mTORC2 [112]. They achieve superior inhibition of the phosphorylation of many substrates when compared to rapalogs. Second-generation inhibitors completely inhibit mTORC1 phosphorylation of 4EBP and mTORC2 phosphorylation of AKT at Ser473, which are rapamycin-insensitive.

The second-generation inhibitors are broadly categorized into two groups based on their selectivity. The first group to be discovered was the dual PI3K/mTOR inhibitors, exemplified by LY294002, PI 013, dactolisib (NVP-BEZ235), paxalisib (GDC-0084), bimiralisib (PQR309), etc. [108,114]. They were originally designed to target PI3K but were later shown to inhibit mTOR due to structural similarities between the two kinases. Because PI3K functions upstream of mTOR, it is often difficult to attribute specific drug effects, such as the inhibition of AKT signaling, to either kinase. This limitation led to the development of a second group, known as selective mTOR kinase inhibitors, which include torin-1, torin-2, AZD8055, torkinib (PP242), PP30, sapanisertib (MLN0128 or INK-128), and OSI-027 (ASP4786) [115,116].

Second-generation inhibitors have been investigated for their efficacy in treating neurological conditions both in the preclinical and clinical settings. A prominent clinical application of second-generation inhibitors is in the treatment of glioblastoma, a highly aggressive brain cancer. Dual PI3K/mTOR inhibitors, such as paxalisib (GDC-0084) and bimiralisib (PQR309), are brain-permeant drugs that have been investigated in newly diagnosed and progressive glioblastoma, respectively [114]. Vistusertib (AZD2014) has also been investigated in a clinical trial involving patients with neurofibromatosis type 2 (NF2) and progressive or symptomatic meningiomas [117]. Additionally, these agents are being studied as a therapeutic regimen for mTORopathies characterized by cortical malformations and intractable seizures. Notably, an experimental brain-permeant ATP-competitive inhibitor, a thiazolopyrimidine derivative, has demonstrated efficacy in mouse models of Tuberous Sclerosis Complex [118].

Despite their efficacy in suppressing mTOR, the clinical translatability of second-generation inhibitors is slowed by several hurdles. One major limitation is metabolic side effects, particularly hyperglycemia and insulin resistance, which arise from the inhibition of mTOR, which plays a critical role in hepatic glucose metabolism [108,119]. Additionally, cancer cells harboring activating mutations within the kinase domain (e.g., M2327I) exhibit resistance to AZD8055, a classical selective mTOR kinase inhibitor [113]. These observations suggest that mutations within the kinase domain can render such inhibitors ineffective. These downsides have inspired the development of the third-generation mTOR inhibitors.

The third-generation mTOR inhibitors, exemplified by Rapalink-1, represent the most recent therapeutic frontier for inhibiting hyperactive mTOR. They were designed to overcome the challenge of incomplete inhibition and acquired drug resistance seen in earlier mTOR inhibitors [102,108,111–113]. These inhibitors are referred to as bisteric or bitopic because they link a rapalog moiety with a kinase inhibitor (second-generation mTOR inhibitor) to simultaneously target the allosteric (FRB domain) and orthosteric (ATP-binding) sites of mTORC1 [112].

Third-generation mTOR inhibitors include bisteric compounds such as those in the Rapalink and RMC series. Shokat et al. developed Rapalink-1, the most widely investigated prototype [112]. It was designed to have a rapamycin moiety linked to MLN0128 via a 39-heavy-atom PEG-rich linker, allowing it to bind both the FRB and catalytic sites simultaneously. Although Rapalink-1 is approximately four-fold more selective for mTORC1 than for mTORC2, recent advances have focused on tuning the affinity of the inhibitor moieties to achieve greater mTORC1 selectivity while sparing mTORC2 [120]. mTORC1-selective bisteric inhibitors include experimental compounds of the RMC series developed by Revolution Medicines Incorporated. RMC 5552 is the first of its kind to make it through a Phase 1 clinical trial for solid tumors (NCT04774952) [121]. RMC 5552 features eight ethylene glycol units connecting a rapamycin moiety and a rigid MLN0128 moiety. This compound demonstrates approximately 40-fold selectivity for mTORC1 over mTORC2. RMC-6272 is another member of this series and differs from RMC-5552 in its active-site inhibitor component, incorporating XL388 instead of MLN0128. RMC-6272 exhibits approximately 27-fold selectivity for mTORC1 over mTORC2 [122].

Another major innovation in third-generation mTOR inhibitors involves a dual-agent system in which the brain-permeant Rapalink-1 is paired with a brain-impermeant blocker, Rapablock, to minimize peripheral side effects [123]. Brain-impermeant Rapablock occupies FKBP12 in peripheral tissues such as the liver and muscles, thereby preventing Rapalink-1 from accumulating and causing toxicity in them. The utility of their contrasting brain permeability lies in enabling Rapalink-1 to accumulate within the brain and potently inhibit mTOR signaling in central nervous system disorders such as glioblastoma. Although this strategy provides greater anatomical selectivity, achieving cell-type selectivity within

the brain remains an important challenge. The mechanism by which bisteric inhibitors interact with mTOR remains incompletely characterized. Future research should, therefore, consider structural studies to refine models that optimize target selectivity.

The brain's cellular heterogeneity complicates the interpretation of pharmacological mTOR inhibition. mTOR inhibitors may inhibit mTOR in diverse cells, including non-neoplastic neurons, neoplastic cells, and other cell types within and around the tumor microenvironment. As such, the cellular target responsible for the therapeutic effect of these drugs often remains unresolved. Determining which cells contribute to neuron–tumor interactions through mTOR signaling could help guide the development of more targeted therapies. Existing mTOR inhibitors may provide a foundation for developing such targeted approaches. Modifying their pharmacological properties or delivery strategies could also enable preferential inhibition of mTOR signaling in the disease-driving cell type.

7. Limitations

This review has several limitations. Much of the evidence supporting neuronal control of tumors and the tumor microenvironment comes from preclinical investigations using model systems such as xenografts, organoids, and engineered mouse models, which do not fully recapitulate the complexity and progression of human disease. Further studies in human tissues and patients will be important for establishing the translational significance of these findings. As discussed above, the cellular targets responsible for the therapeutic effects of mTOR inhibitors also remain incompletely resolved. Furthermore, the narrative design of this review introduces the possibility of literature selection bias because neither a predefined systematic search strategy nor formal inclusion and exclusion criteria were used. Studies were identified through PubMed searches and the authors' familiarity with literature. Therefore, this may not encompass all relevant studies. Nevertheless, this review provides a framework for identifying knowledge gaps and guiding future mechanistic studies of neuronal control of tumor growth.

8. Conclusions

In conclusion, mTOR regulates nervous system development and neuronal physiology, and its dysregulation contributes to mTORopathies and neoplastic processes in the brain. Accumulating evidence supports that the initiation and progression of some neoplastic processes are associated with neuronal activity. Neurons may promote tumor growth by secreting paracrine factors and establishing circuitry and synaptic interactions with tumors, thereby altering the tumor microenvironment in ways that favor tumor progression. mTOR signaling represents a potential mechanistic link between neuronal activity and tumor progression. Identifying and selectively targeting mTOR signaling in disease-driving cell types may, therefore, provide new opportunities for therapeutic intervention.

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