Tailoring mTOR-based therapy: molecular evidence and clinical challenges

The mTOR signaling pathway integrates inputs from a variety of upstream stimuli to regulate diverse cellular processes including proliferation, growth, survival, motility, autophagy, protein synthesis and metabolism. The mTOR pathway is dysregulated in a number of human pathologies including cancer, diabetes, obesity, autoimmune disorders, neurological disease and aging. Ongoing clinical trials testing mTOR-targeted treatments number in the hundreds and underscore its therapeutic potential. To date mTOR inhibitors are clinically approved to prevent organ rejection, to inhibit restenosis after angioplasty, and to treat several advanced cancers. In this review we discuss the continuously evolving field of mTOR pharmacogenomics, as well as highlight the emerging efforts in identifying diagnostic and prognostic markers, including miRNAs, in order to assess successful therapeutic responses.

**KEYWORDS:** biomarkers, cancer, cardiovascular disease, clinical trials, dual inhibitors, FKBP12, microRNA, mTOR, rapamycin, resistance

The history of mTOR

In the 1960s, the natural macrocyclic lactone rapamycin (C_{41}H_{77}NO_{13}; molecular weight: 914.2), also known as sirolimus, was obtained from the bacterium *Streptomyces hygroscopicus* found in soil samples from Rapa Nui (Easter Island). In the 1970s, rapamycin was used as a potent antifungal agent and shortly afterwards was found to inhibit cell proliferation and possess strong immunosuppressive properties [1,2]. It took 20 years to identify the molecular target of rapamycin and to elucidate its mechanism of action. This was achieved by selection of spontaneous mutations that confer resistance to the growth inhibitory effect of rapamycin in the budding yeast *Saccharomyces cerevisiae*. Three genes were identified. The first was *RBP1*, a homolog of the human peptidyl-prolyl isomerase FKBP12, which was identified using an FK506 binding column in a search for receptors for the immunosuppressant drug with structural homology to rapamycin [3]. Deletion of RBPI in yeast resulted in recessive drug resistance while expression of human FKBP12 restored rapamycin sensitivity [4]. Therefore, rapamycin forms a toxic complex with FKBP12 inhibiting the function of other cellular proteins [4]. The other two genes were *TOR1* and *TOR2*, originally called *DRR1* and *DRR2*, which encode two highly homologous proteins (~280 kDa) [5,6].

Soon after, mTOR was identified [7]. Unlike yeast, higher order eukaryotes have only one TOR gene. mTOR is a large (289 kDa) serine/threonine protein kinase that belongs to the phosphatidylinositol 3’-kinase-related kinase (PIKK) family. At the C-terminus it contains a PIKK domain that exhibits serine and threonine kinase activity but not lipid kinase activity as seen with the other PIKK family members [8]. Another unique characteristic of mTOR, which does not exist in the other members of the PIKK family, is the 11 kDa FKBP12-rapamycin-binding domain (FRB) at the N-terminus of the PIKK domain [9,10].

**Multiprotein complexes of mTOR**

Over the last 30 years mTOR-related research has provided significant insights into its molecular architecture and function. Today, it is clear that mTOR forms two distinct multiprotein complexes: mTORC1 and mTORC2. Both complexes are composed of mTOR, mLST8/GµL, Pras40, Deptor and Tti1/Tel2. Raptor and Pras40 are specific to mTORC1, while Rictor, Protor 1/2 and mSin1 are specific to mTORC2 (Box 1) [11].

In response to growth factors, stress, amino acids and oxygen, mTORC1 regulates numerous pathways including cell growth, autophagy, protein synthesis, cell cycle and metabolism. The best-known mTORC1 substrates are S6K1 and 4E-BP1, both of which are involved in the regulation of protein synthesis. Importantly, S6K1 was shown to form a negative feedback loop by inhibiting expression of the insulin receptor substrate, attenuating the PI3K/Akt pathway (Figure 1) [12,13].
In contrast to mTORC1, little was known about mTORC2 until an important discovery demonstrated that mTORC2 is able to regulate cell proliferation, survival and metabolism by phosphorylating Akt on a key activation site (Ser\textsuperscript{473}) \cite{14, 15}. Notably, Akt activates mTORC1 by phosphorylating and inhibiting the tuberous sclerosis complex, which negatively regulates mTORC1 by inhibiting the small GTPase Rheb that in turn directly activates mTORC1 (Figure 1) \cite{16}.

Dysregulation of the mTOR pathway has been linked to several pathological conditions, including cancer, diabetes, obesity, autoimmune disorders, neurological disease and aging, making it an attractive target for the development of new pharmacological treatments \cite{11, 17, 18}.

**Rapamycin: mechanism of action & first applications**

Upon entering the cell, rapamycin binds to FKBP12, which then interacts with the FRB domain of mTORC1 inhibiting its serine/threonine kinase activity and preventing the translation of specific cell cycle mRNAs required for G1 to S phase transition, ultimately leading to growth arrest \cite{19, 20}. By contrast, the rapamycin–FKBP12 complex cannot interact with the FRB domain of mTORC2, and therefore cannot inhibit it acutely. In some cases, chronic treatment with rapamycin has been shown to block the mTORC2 assembly, thereby inhibiting its activity \cite{21}.

In 1999, rapamycin was approved by the US FDA as an immune suppressor agent to prevent organ rejection in renal transplant patients. Shortly thereafter, a number of studies demonstrated that rapamycin was also a potent inhibitor of vascular smooth muscle proliferation and migration \cite{19, 22–24}. These findings led to the development of the rapamycin-eluting stent used to treat atherosclerotic blockages in coronary arteries, which was approved by the FDA in 2003 to prevent in-stent restenosis. The antiproliferative properties of rapamycin were also tested in a broad range of malignancies and numerous clinical trials have been conducted.

**First-generation inhibitors of mTOR**

After the discovery of rapamycin and the elucidation of its mechanism of action, other macrolide ester derivatives (also known as ‘rapalogs’) that share the same mechanisms of action have been synthesized both to improve pharmacokinetic properties and to ensure patent protection (Figure 2). These include everolimus (RAD001) marketed by Novartis; temsirolimus (CCI-779) developed by Wyeth Pharmaceuticals; and deforolimus or ridaforolimus (AP23573) codeveloped by Merck and ARIAD Pharmaceuticals.

**Everolimus (RAD001)**

Everolimus is an oral rapamycin analog (half-life: 30 h). It was approved by the FDA for the treatment of patients with advanced kidney cancer \cite{25}; for the treatment of subependymal giant cell astrocytoma, alone or associated with tuberous sclerosis complex \cite{26–28}; for progressive neuroendocrine tumors of pancreatic origin in patients with tumors not surgically removable; and for advanced hormone receptor-positive, HER2-negative breast cancer in combination with exemestane, after failure of treatment with anastrozole or letrozole \cite{29}.

Recently, the addition of everolimus to trastuzumab and vinorelbine was shown to extend progression-free survival in women with HER2-positive advanced breast cancer, compared with treatment with placebo plus trastuzumab and vinorelbine, in the Phase III BOLERO-3 trial. The study enrolled women whose disease was resistant to prior trastuzumab treatment (Data presented at American Society of Clinical Oncology [ASCO] Meeting, June 2013 \cite{30}). Everolimus is also used for the prevention of organ rejection after renal or heart transplants and in drug eluting coronary stents (Xience). The drug is being tested as a therapy for prostate, colorectal and non-small-cell lung cancers as either a single agent or in combination with additional therapies.

**Temsirolimus (CCI-779)**

Temsirolimus is a water-soluble ester derivative of rapamycin available in oral and intravenous...
formulations (half-life: 13–22 h). In 2007, it was approved by the FDA for the treatment of advanced-stage renal cell carcinoma [31]. It represents the first mTOR inhibitor approved for cancer therapy. Temsirolimus was also approved in Europe for the treatment of mantle cell lymphoma [32]. Temsirolimus is currently being tested either alone or in combination therapy in tumor types such as melanoma, myeloma, and renal and gynecological cancers.

Deforolimus or ridaforolimus (AP23573)
Ridaforolimus is an oral rapamycin analog (half-life: 56–74 h) that selectively targets mTOR and has been shown to possess potent antitumor activity both in cell lines and in xenograft tumor models. It is currently being evaluated (Phase III) in non-small-cell lung cancer, glioblastoma, soft tissue and bone sarcoma, prostate, endometrial, and pancreatic cancer, metastatic breast cancer and relapsed hematological tumors. It has thus far shown good tolerability with dose-limiting stomatitis in both single and combination treatments. In November 2012, Merck officially withdrew its application for a marketing authorization for deforolimus concerning the maintenance treatment of patients with metastatic soft tissue sarcoma or bone sarcoma previously treated with chemotherapy owing to inconclusive benefit–risk balance evaluations.

Clinical challenges
Rapalogs are generally well-tolerated and do not lead to changes in blood pressure, liver function or renal toxicity, although fatigue, rash, hematological abnormalities and gastrointestinal disturbances are quite common. In addition, hypercholesterolemia and hypertriglyceridemia have also been reported; therefore, the monitoring of blood lipid levels is recommended [33].

The mTOR-targeted therapies are currently being evaluated in 1444 clinical trials (clinicaltrials.gov [101]) as single agent or in combination therapies. In preclinical studies performed in vitro and in vivo they have shown significant antiproliferative activity against a broad panel of tumors, with encouraging safety profiles and clinical benefit responses, achieving disease stabilization and/or tumor regression owing to inhibition of tumor cell proliferation. Notably, inhibition of the mTOR pathway also exerts antiangiogenic effects, mainly attributable to the fact that mTOR controls the production of HIF1α, which in turn mediates the expression of several angiogenic genes [34]. However, despite the proven efficacy of rapalogs against a number of tumors, their anticancer activity is quite unpredictable [35].

The negative feedback loop that exists downstream of mTORC1 clearly contributes to the

Figure 1. mTOR signaling pathways.
GF: Growth factor; GFR: Growth factor receptor; TSC: Tuberous sclerosis complex.
observed resistance to rapalogs. Since active mTORC1 suppresses the PI3K/Akt pathway, mTORC1 inhibition by rapalogs abolishes the negative feedback loop, resulting in hyperactivation of the PI3K/Akt signaling and leading to increased cell survival (Figure 1) [36]. Notably, rapamycin-insensitive functions of mTORC1 were recently revealed, challenging the dogma that rapamycin completely inhibits mTORC1 activity [37,38]. Alternative survival pathways and crosstalk with other signaling pathways including MEK/ERK could also limit the efficacy of rapalogs [39]. In human cancers, inhibition of mTORC1 leads to MAPK pathway activation through a PI3K-dependent feedback loop [40]. Indeed, the combination of temsirolimus with the MAPK inhibitor, SL327, significantly reduced brain metastases in vivo, while treatment with temsirolimus alone yielded no significant effect [41].

Figure 2. Molecular structures of rapamycin and the first generation of mTOR inhibitors (rapalogs).

- **Second-generation inhibitors of mTOR**
  New drugs, referred to as mTOR kinase domain inhibitors, are being developed to inhibit the ATP binding site of both mTORC1 and mTORC2. These drugs are small molecules that bind competitively and reversibly to the mTOR–ATP binding pocket, blocking the enzymatic activity of the kinase. Numerous mTORC1 and mTORC2 inhibitors are under preclinical evaluation and in Phase I/II clinical trials for various cancers (Table 1). Although mTOR kinase inhibitors target both complexes, preclinical and early clinical data showed hyperactivation of the PI3K/Akt signaling caused by decreased mTORC1 activity, which superseded the effects of inhibition of mTORC2.

Since the catalytic domain of mTOR and the p110α subunit of PI3K are highly homologous, some second-generation compounds have dual
activity against both PI3K and mTOR [42]. The main advantage of such dual inhibitors is the simultaneous inhibition of PI3K–Akt–mTOR signaling and reduction of the hyperactivation of PI3K that typically results in mTORC1 inhibition. Numerous dual PI3K/mTOR inhibitors have already entered Phase I and II clinical trials for a variety of cancer types, either alone or in combination with other chemotherapies (Table 1). Early clinical results suggest that these dual PI3K/mTOR inhibitors are more efficacious than rapalogs, but also demonstrate increased toxicity. This was especially evident in the digestive tract with adverse effects including diarrhea, nausea and vomiting. Hyperglycemia has also been reported.

Molecular biomarkers for mTOR-targeted therapy

Our knowledge of the mTOR pathway has increased dramatically in recent years, yet many gaps still exist in our understanding of the molecular mechanisms involved in the response of cancer cells to such inhibitors. Therefore, there is an urgent need for efficient biomarkers not only to predict who will benefit from mTOR-targeted therapies, but also for patients to avoid developing unnecessary toxicities. In recent years, determinants of rapalog sensitivity and resistance have begun to emerge [43]. Several preclinical and clinical models showed that cancer cells where the mTOR pathway is hyperactive owing to PTEN deficiency [44], Akt phosphorylation [45] or PI3K mutations [39] are particularly sensitive to mTOR inhibitors. Tumor cells that have functional apoptotic pathways, overexpress cyclin D1 [32,46], or have greatly increased angiogenic signaling [47] are more sensitive to rapamycin. Overexpression of antiapoptotic proteins such as Bcl2 may also serve as viable predictors of resistance to mTOR inhibitors [48]. Recently, we showed that rapamycin treatment was effective primarily in tumors that exhibit rapamycin-sensitive dephosphorylation of Akt and consequently decreased expression of the oncogene Skp2 [49]. However, these and many others candidate biomarkers still need to be validated in the clinical setting.

**miRNAs & mTOR**

miRNAs are small ncRNAs (22 nucleotides) that regulate gene expression at the post-transcriptional level by either translational repression or mRNA cleavage [50]. miRNAs play an essential role in tumorigenesis, and it has recently been shown that circulating miRNAs can be measured in the serum and are emerging as a novel class of biomarkers for both diagnostic and prognostic assessments, giving rise to the field of miRNA pharmacogenomics [51,52].

Recently, various studies showed that miRNAs affect the mTOR pathway by targeting upstream regulators including IGF-R, PI3K, PTEN and Akt. Here we will focus on the functional role of miRNAs in the cellular response to mTOR inhibitors and the reciprocal regulation of mTOR

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and miRNAs (Figure 3). We demonstrated that rapamycin-resistant myogenic cells, developed by prolonged rapamycin treatment, displayed an extensive reprogramming of the miRNA transcriptome, characterized by upregulation of the oncogenic miR-17–92 and related clusters and downregulation of tumor suppressor miRNAs, such as miR-143, miR-29 and miR-22. Conversely, rapamycin-sensitive cells exhibited an increase in tumor suppressor miRNAs. Intriguingly, inhibition of members of the miR-17–92 cluster or delivery of tumor suppressor miRNAs restored sensitivity to rapamycin [53,54]. In support of our findings, rapamycin was shown to increase expression of miR-143 in human glioma cells [55]. Additionally, everolimus increased miR-143 expression in a time-dependent manner in human pancreatic cancer cells [56]. Endothelial cells treated with rapamycin showed increased levels of miR-21, mediating the antiproliferative and antimigration effect of rapamycin [57]. Moreover, mTOR was shown to control MyoD-dependent transcription of miR-1 in differentiating myoblasts and in mouse regenerating skeletal muscle [58]. Another report demonstrated that mTOR, by negatively controlling miR-125b biogenesis, regulates the production of IGF-II, a master switch governing the initiation of skeletal myogenesis [59].

On the other hand, several miRNAs, including miR-7a and miR-99a, were shown to directly target different components of the mTOR pathway [60–63]. Inhibition of miR-7a activated mTOR signaling and promoted adult β-cell replication in primary islets, which was reversed by rapamycin treatment [63]. In oral squamous cell carcinoma and renal cell carcinoma, miR-99a was shown to directly modulate mTOR signaling pathways [64,62]. miR-99a downregulation was also associated with mTOR upregulation in various human lung cancer cells/tissues [64]. Interestingly, downregulation of miR-99a has been detected in different human cancers in which tumor growth was mediated by the upregulation of the tyrosine kinase c-Src [64]. Re-expression of miR-99a suppressed tumor growth of c-Src-transformed cells, and this effect was restored by mTOR overexpression. Downregulation of miR-99a was also observed in EGF- and Ras-transformed cells, and was suppressed by inhibiting the MAPK pathway [64]. Additionally, in colorectal cancer, miR-144 downregulation led to poor prognosis via activation of the mTOR signaling pathway [65]. In oral squamous cell carcinoma, miR-218 targeted Rictor lead to an inhibition of Akt phosphorylation at Ser [67] [66]. miR-100 was shown to repress mTOR signaling in endothelial and vascular smooth muscle cells, displaying an antiangiogenic function. Whereas miR-100 inhibition increased mTOR levels in endothelial cells, overexpression of miR-100 reduced mTOR expression and consequently attenuated cellular proliferation [67]. In clear-cell ovarian carcinoma cell lines, mTOR was repressed by miR-100 at the mRNA and protein levels, and decreased phosphorylation of 4EBP1 and p70 S6 kinase were also observed [68]. Human cytomegalovirus infection altered the expression of miR-100 and miR-101 to target components of the mTOR pathway, resulting in an improved ability to replicate [69]. In childhood adrenocortical tumors, miR-99a and miR-100 coordinately regulated the expression of mTOR, Raptor, and IGF via binding sites in their 3′-UTR regions [70]. In esophageal squamous cell carcinoma, wherein decreases in miR-99a and miR-100 are correlated with worse overall survival, miR-99a and miR-100 suppressed the expression of mTOR by directly binding to its 3′-UTR [71]. miR-101 was also shown to target mTOR in anaplastic large-cell lymphoma [72]. In a different study, miR-199a-3p, which is known to be downregulated in several human malignancies and in hepatocellular carcinoma, was also shown to target mTOR. The inhibition of miR-199a-3p in hepatocellular carcinoma cells led to G(1)-phase cell cycle arrest [73].

**Future perspective**

Our knowledge about the mTOR pathways has seen extraordinary advances over the past 30 years. The ever-expanding appreciation of
miRNAs have been recently identified as new regulators of the mTOR-signaling pathway. The first targets of rapamycin (Tor1, Tor2 and FKBP12) were identified in Saccharomyces cerevisiae. Along with the isolation of rapamycin, much has been learned about the molecular mechanisms through which rapamycin exerts its effects. The second-generation inhibitors of mTOR are comprised of new compounds able to inhibit the ATP-binding site of mTORC1 and mTORC2. The mTOR pathway has been linked to several disorders including cancer, diabetes, obesity, autoimmune disorders, neurological disease and aging. miRNAs play a functional role in the response to mTOR inhibitors. They regulate mTOR pathways will provide the framework for their development as diagnostic and prognostic biomarkers as well as for the design of novel therapeutic tools in the clinic.

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No writing assistance was utilized in the production of this manuscript.

Executive summary

History of mTOR
- Rapamycin is a bacterial product (Streptomyces hygroscopicus) found in soil samples from Rapa Nui (Easter Island).
- The first targets of rapamycin (Tor1, Tor2 and FKBP12) were identified in Saccharomyces cerevisiae.
- Eukaryotes have only one TOR gene, which is called mTOR.

Multiprotein complexes of mTOR
- mTOR forms two distinct multiprotein complexes: mTORC1 and mTORC2.
- The mTOR pathway has been linked to several disorders including cancer, diabetes, obesity, autoimmune disorders, neurological disease and aging.

Inhibitors of mTOR
- Rapamycin (sirolimus) is a natural compound that has been approved in the clinical scenario as an immunosuppressant in kidney-transplanted patients and as an antiproliferative agent to prevent in-stent restenosis after angioplasty.
- The first-generation inhibitors of mTOR are analogs of rapamycin, also known as rapalogs, and include temsirolimus, everolimus and deforolimus.
- The second-generation inhibitors of mTOR are comprised of new compounds able to inhibit the ATP-binding site of mTORC1 and mTORC2, or PI3K and both mTORC1 and mTORC2.

Molecular biomarkers in mTOR-targeted therapy
- Numerous gaps still exist in our understanding of the molecular mechanisms underlying the response to mTOR inhibitors.
- There is an urgent need for efficient biomarkers not only to predict who will benefit from mTOR-based therapy but also to avoid the development of unnecessary toxicity.

miRNAs & mTOR
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- miRNAs play a functional role in the response to mTOR inhibitors.

References
Papers of special note have been highlighted as:
* of interest
** of considerable interest
* Along with [1], this is one of the first original reports of the isolation of rapamycin.
2 Vezina C, Kudelski A, Sehgal SN. Rapamycin (AY-22,989), a new antifungal antibiotic. II. Taxonomy of the producing streptomycete and isolation of the active principle. J. Antibiot. (Tokyo) 28(10), 721–726 (1975). Along with [1], this is one of the first original reports of the isolation of rapamycin.
**Seminal paper reporting the identification of mTOR in eukaryotes.**


**Authoritative paper showing for the first time that mTORC2 is able to activate Akt.**


**Important study showing in vitro the relevance of rapamycin in the inhibition of vascular smooth muscle cell proliferation.**


**Important study showing in vitro the importance of rapamycin in the inhibition of restenosis after angioplasty.**


**Important clinical study demonstrating that the rapalog temsirolimus is able to improve overall survival among patients with metastatic renal-cell carcinoma.**


**Future Oncol.**

1524 Pharmacogenomics (2013) 14(12) future science group
Noteworthy paper reporting the relevance of the mTORC1–MAPK feedback loop in human cancer.

*Original report identifying miRNAs as new downstream components of the mTOR signaling pathway.*


Tailoring mTOR-based therapy: molecular evidence & clinical challenges
Excellent paper showing that the simultaneous targeting of mTORC1 and mTORC2 may represent an effective antilymphoma strategy.


Website