The immunosuppressive drug rapamycin played a key role in the functional characterization of mammalian target of rapamycin (mTOR), an unusual protein kinase that coordinates growth factor and nutrient availability with cell growth and proliferation. Several rapamycin-related compounds are now in various stages of clinical development as anticancer agents. This article highlights recent advances in our understanding of the mTOR signaling pathway and the implications of these findings for the clinical application of mTOR inhibitors in cancer patients.

**Background**

The clinical development of mammalian target of rapamycin (mTOR) inhibitors highlights the pivotal contributions of natural products to cancer therapy as well as the power of chemical genetics as a tool for the elucidation of intracellular signaling pathways (1–3). The archetypal mTOR inhibitor is the macrolide ester rapamycin, which was first isolated from the bacterium *Streptomyces hygroscopicus* by researchers at Wyeth (4). Rapamycin was initially characterized as a potent antifungal and immunosuppressive agent and was later shown to exert powerful antiproliferative effects on a wide range of eukaryotic cells, including human tumor cells. These studies provoked considerable interest in the clinical development of rapamycin and related compounds ("rapalogs") in areas such as transplantation and cancer. However, the mechanism of action of rapamycin remained a mystery until the mid-1990s, when several laboratories converged on the same target protein, now universally termed as target of rapamycin (TOR).

The pathway to TOR biology opened with studies in the budding yeast *Saccharomyces cerevisiae*, a genetically tractable model system that was sensitive to the growth-inhibitory effects of rapamycin. The generation of a series of rapamycin-resistant yeast mutants led to the discovery that the expression of a conserved cytoplasmic immunophilin receptor, termed FK506-binding protein-12 (FKBP12), was required for high-potency cell growth inhibition by rapamycin. In addition, specific mutations in either of two novel and highly related genes, termed Tor1 and Tor2, conferred resistance to rapamycin (5). As their names indicate, the products of the two Tor genes were the presumptive targets of rapamycin in budding yeast (reviewed in refs. 6, 7). Whereas the two Tor genes were highly homologous, they were not functionally redundant. Yeast cells lacking the Tor1 protein were slow growing but viable, whereas loss of Tor2 was lethal to these cells. These seminal findings in yeast portended a level of complexity in the TOR signaling pathway that we are only beginning to appreciate today.

The yeast studies described above laid the groundwork for an important set of biochemical studies done in mammalian cells and tissues. Based on the assumption that rapamycin must first bind to FKBP12 to generate the proximate growth-inhibitory complex, several laboratories used a FKBP12 rapamycin affinity matrix as the definitive step in the biochemical purification of a high molecular mass protein, now known as mTOR (8–10). In recent years, the mTOR signaling field has grown explosively, as has the clinical development of mTOR inhibitors. Three rapamycin-related mTOR inhibitors [i.e., Torisel (temsirolimus, CCI-779; Wyeth), everolimus (RAD001; Novartis), and AP23573 (Ariad)] are now showing significant activity against a variety of cancers, including mantle cell lymphoma, sarcoma, and renal cancer (11). This review will focus on several key pathway-related issues that could hold the key to stratifying responder and nonresponder patient populations in the oncology clinic. The take-home message is clear: whereas experiments with "simple" yeast and mammalian cell model systems were crucial first steps, clinical studies in human patients have much to teach us about mTOR biology and mTOR inhibitor–based cancer therapy. 

**TOR structure and signaling complexes.** The TOR proteins are members of the phosphoinositide 3-kinase–related kinase (PIKK) family, whose members (ATM, ATR, DNA-PK, hSMG1, mTOR, and TRAPP in mammalian cells) transmit signals related to cell growth, proliferative, and stress responses (12). Like the other PIKKs, mTOR is a very large protein (~300 kDa) bearing a COOH-terminal catalytic domain with significant homology to the lipid kinase phosphatidylinositol 3-kinase (PI3K). However, in spite of the sequence homology to lipid kinases, mTOR and the remaining PIKKs function exclusively as protein serine-threonine kinases. The PIKKs, including mTOR, also express a very extended NH2-terminal region consisting of large numbers of HEAT repeat subunits (12, 13). These HEAT repeats likely serve as sites for the recruitment of regulatory proteins and/or substrates to the PIKKs. In the case of mTOR, such protein-protein interactions apparently parse the intracellular pool of mTOR molecules into multiple, functionally distinct complexes (14, 15).
The clinically active rapalogs inhibit mTOR kinase activity through an unconventional mechanism that is most aptly characterized as allosteric. Structural studies have shown that the FKBP12-rapamycin complex binds to mTOR through the FRB domain, an ~110-amino-acid sequence that lies just upstream of the canonical catalytic domain (16, 17). Among the PIKK family members, the FRB domain is found only in the TOR proteins, which explains the exquisite specificity of the rapalogs for mTOR in mammalian cells. The selectivity of these compounds for mTOR is truly remarkable: the drug directly attacks only one subpopulation of mTOR proteins residing in multiprotein complex, termed mTORC1. At least one additional complex, mTORC2, holds mTOR in a form that cannot be recognized or inhibited by FKBP12-rapamycin (18, 19).

Returning to yeast for a moment, the essential nature of the TOR2 gene product is now explained by its exclusive role as a component of the homologous TORC2 complex in this organism (7, 20). Interestingly, either TOR1 or TOR2 functions in the rapamycin-sensitive TORC1 complexes in yeast. Why yeast evolved with two TOR proteins in parallel with two TORC complexes whereas metazoan organisms rely on a single TOR protein to serve in two or more such complexes (21) remains a mystery. In summary, whereas the rapalogs are highly specific inhibitors of mTOR, the existence of multiple mTOR complexes with widely different sensitivities to these drugs has important therapeutic ramifications in the oncology setting. Preclinical evidence that rapamycin exerts selective rather than global effects on mTORC1-associated signaling functions further complicates efforts to identify those patients who are most likely to respond to mTOR inhibitors, either as monotherapy or in combination (22).

The segregation of mTOR into at least two different complexes allows this protein kinase to respond to coordinate a plethora of upstream signals, ranging from nutrients to growth factor receptor stimulation, with an increasingly broad range of downstream responses (Fig. 1). The defining element in the mTORC1 complex is the regulatory subunit Raptor (23). The mTORC1 complex carries out many of the primordial signaling functions of mTOR, chiefly those related to coordination of cell mass accumulation with the supply of amino acids and energetic precursors for protein synthesis. As such, it is not surprising that the two most well-characterized mTORC1 substrates, 4E-BP1 and S6 kinase 1 (S6K1), are components of the translational control machinery (24, 25). Phosphorylation of these two proteins by mTOR promotes cap-dependent translation and ribosome biogenesis, respectively. Inhibition of mTORC1 function by rapamycin results in only modest decreases in protein synthesis and cell size in most mammalian cell types (3, 26). Nonetheless, it has been proposed that impaired cell mass accumulation contributes to the protracted G1 delay imposed by rapamycin on cycling cells (7). In contrast to mTORC1, the mTORC2 complex lacks Raptor and contains instead a distinct regulatory subunit termed Rictor (18, 19). A recent report identified the protein serine-threonine kinase AKT as a key substrate for mTORC2-associated mTOR (27). AKT is a central effector of cell growth, survival, and bioenergetic signaling by mitogen-activated class IA PI3Ks (28). Phosphorylation of human AKT at Ser473 by mTORC2 is required for full

Fig. 1. Integration of the mTOR pathway into the mitogenic signaling network. The mTORC1 and mTORC2 complexes are highlighted in green, and upstream regulators and downstream targets of each complex are depicted in blue boxes. Clinical compounds that inhibit various targets in the pathways other than mTOR are highlighted in orange, and drugs that inhibit the mTORC1 complex are highlighted in red. The negative feedback loop from S6K to IRS1 is shown on the left. CII PI3K, class III PI3K; RTK, receptor tyrosine kinase; RasFTI, Ras farnesyltransferase inhibitor. See text for additional details on this signaling cascade.
activation of this protein kinase by mitogenic signals. It now seems that the mTORC2 complex functions as an upstream activator of AKT, which, as will be discussed below, delivers a stimulatory signal to mTORC1. These types of regulatory loops have not only made life more difficult for basic cell biologists, but, as will be seen below, also complicated clinical efforts to define those patients most likely to respond to the antitumor activities of the rapalogs.

Integration of mitogenic and bioenergetic signals through the mTOR pathway. The molecular mechanisms whereby environmental conditions regulate mTORC1 function are now partially understood. The PI3K-AKT axis is centrally involved in the delivery of growth factor–derived stimulatory signals to the mTORC1 complex (Fig. 1). The proximate target for AKT in this pathway is the tuberous sclerosis 2 (TSC2) protein, which functions in a heterodimeric complex with TSC1. Inactivating mutations in either TSC1 or TSC2 in humans give rise to tuberous sclerosis, a debilitating syndrome characterized by benign tissue overgrowths and increased cancer susceptibility (29). The TSC1/2 complex expresses GTPase-activating protein activity toward the Ras-related GTPase Rheb, and this activity is inhibited by AKT-dependent phosphorylation of TSC2. When active, TSC1/2 converts the GTP-bound form of Rheb to its inactive, GDP-bound state. When TSC1/2 activity is suppressed, GTP-bound Rheb stimulates mTORC1 signaling through a poorly understood mechanism that may involve a direct interaction between Rheb and mTORC1 (30). The positioning of mTOR as a downstream target in the PI3K-AKT pathway provides a clear link to oncogenesis. Dereguated signaling through the PI3K pathway is a feature of most, if not all, types of cancer cells (31). Perhaps the most widely heralded alteration leading to hyperactivation of the PI3K pathway involves loss of PTEN gene function through mutation or epigenetic modification. The PTEN phosphatase dephosphorylates the class IA PI3K metabolite phosphatidylinositol-3,4,5-trisphosphate, thereby inactivating this critical second messenger (32). Conversely, loss of PTEN function during oncogenesis favors accumulation of phosphatidylinositol-3,4,5-trisphosphate, leading to deregulated signaling through the PI3K-AKT-TSC1/2-mTORC1 pathway.

In addition to traditional mitogenic stimuli, TSC1/2 responds to a variety of metabolic signals, including supplies of amino acids, glucose, and oxygen (14, 15, 29). Unfortunately, the details of the pathways leading from amino acid, glucose, and oxygen availability to mTOR are far less well understood than the class IA PI3K–dependent pathway described above. Recent studies suggest that yet another PI3K, in this case a class III isoform, delivers signals that connect amino acid availability to activation of mTOR (33–35). Class III PI3K converts phosphatidylinositol to a distinct second messenger, phosphatidylinositol 3-phosphate. This metabolite controls protein trafficking events in mammalian cells; however, the mechanism through which the accumulation of phosphatidylinositol 3-phosphate conveys suppressive signals to TSC1/2 (and in turn activating signals to mTORC1) remains largely unknown. Bioenergetic signals are relayed to TSC1/2 through the AMP-activated protein kinase, which is activated by an increase in the AMP/ATP ratio, an indicator of limiting cellular energy supply (36). Hypoxia also suppresses mTORC1 function in a TSC1/2-dependent fashion, although this bioenergetic stress acts through a distinct mechanism involving the hypoxia-inducible factor-1 (HIF-1). Activation of the HIF-1 transcription factor at low oxygen tensions induces expression of the REDD1 gene, which encodes a protein that stimulates the Rheb GTPase–activating protein activity of TSC1/2 via an unknown mechanism (37, 38). In summary, the TSC1/2 complex lies at the crossroads of both the mitogenic and the bioenergetic signals that impinge on the mTORC1 complex. Much less is known about the upstream events leading to mTORC2 activation, although it seems that TSC1/2 is not involved and that this second mTOR complex is responsive to a signal(s) emanating from growth factor receptors (15).

Clinical-Translational Advances

Unanticipated effects of rapalogs on the mTOR signaling pathway. Until recently, we held a rather simplistic view of the mTOR pathway, which led to a fairly logical set of predictions about the use of rapalogs as anticancer agents. These drugs were viewed as highly targeted inhibitors of mTORC1 function and were expected to leave both mTORC2 activity and the activity of other signaling proteins relatively intact. Unfortunately, life and, in particular, signal transduction are rarely so simple. First, several investigators uncovered a negative feedback loop wherein the mTORC1-activated kinase S6K1 phosphorylates and destabilizes the IRS1 and IRS2 proteins in insulin/insulin-like growth factor–responsive cells (see ref. 15 for review). In these cell types, inhibition of S6K1 activity by rapalogs disrupts this feedback loop, leading to increased IRS1/2 expression and enhanced insulin/insulin-like growth factor–dependent AKT activation. In cancer patients, the obvious concern is that the increase in AKT activity induced by rapalog exposure could promote escape from the antitumor activity of the mTOR inhibitor and perhaps more global resistance to chemotherapy (39, 40). The extent to which disruption of the S6K1-IRS1 negative feedback mechanism actually limits the therapeutic activities of the rapalogs in cancer patients remains to be determined.

A second unforeseen consequence of rapalog exposure is an indirect inhibitory effect on the assembly of the mTORC2 complex (15). One model suggests that the FKBP12-rapalog complex binds tightly to mTORC1-associated mTOR, effectively eliminating this population of mTOR molecules from the system. As the cell attempts to compensate via assembly of additional mTORC1 complexes, less mTOR is available for mTORC2. The net effect is that prolonged rapalog exposure in a susceptible cell type will lead not only to loss of mTORC1 function but also to inhibition of mTORC2-dependent AKT activation. This phenomenon has been observed in ~20% of tumor lines and, in principle, could magnify the antitumor effect of rapalog treatment by delivering two hits to the PI3K-AKT-mTOR pathway. It is tempting to propose that tumor cells in which both mTORC1 and mTORC2 functions are disrupted by rapalogs will show greater sensitivity to these agents in the clinical setting.

Impact of rapalog pharmacology on optimal dose selection. Historically, traditional cytotoxic anticancer agents have been administered at doses near the maximal tolerated dose, as determined in phase I clinical trials. With the entry of molecularly targeted agents into the clinic, this practice has been challenged, and an alternative dosing strategy, based on biomarker-based measurements of target inhibition, has gained credibility. The rationale is that target-based dosing might spare patients the adverse side effects associated with potential
off-target actions of the drugs at supra-pharmacologic dosages. The rapalogs seem to fit this concept perfectly, in that they are extremely potent and specific inhibitors of their common target protein, mTOR. However, the decision between target- and maximum tolerated dose–based dosing of the rapalogs is not so clear-cut, due once again to the complexity of the mTOR signaling pathway. Several factors contribute to the uncertainty about the optimal dosing strategy for mTOR inhibitors. First, the major downstream effectors of mTORC1 with respect to tumor growth are not well understood, and recent preclinical findings suggest that these downstream effectors exhibit variable sensitivities to rapalog-mediated mTORC1 inhibition. For example, phosphorylation of the canonical mTORC1 substrate S6K1 is highly sensitive to inhibition by the rapalogs, even in cells that are completely refractory to the antiproliferative activity of these drugs (41). In contrast, the expression of an amino acid transporter on the cell surface was far more resistant to mTORC1 inhibition by rapamycin (22). In this setting, dose selection based on changes in S6K1 phosphorylation is likely to result in insufficient inhibition of other mTOR1-dependent responses in the clinical setting.

A second complication stems from recent findings that complex formation with FKBP12 is not obligate for inhibition of mTOR by rapalogs. In the absence of FKBP12, rapamycin inhibits mTOR function at micromolar concentrations (i.e., with ~ 100- to 1,000-fold lower potency than in the presence of the immunophillin; ref. 42). Although the in vivo pharmacologic implications of this discovery remain unclear, it should be noted that these are highly hydrophobic drugs that are prone to accumulate in lipid-rich microcompartments, such as cell membranes. The possibility that rapalogs accumulate to levels sufficient to inhibit mTOR activity in an FKBP12-independent fashion cannot be ignored. If this alternative and direct mechanism of action is important for overall antitumor activity, higher doses of the rapalogs might be needed to achieve a therapeutically effective level of mTOR inhibition.

Perhaps most importantly, we now know that persistent exposure to rapalogs indirectly inhibits mTORC2 assembly and functions in certain cancer cell types (15). A plausible but unproven idea is that dual suppression of mTORC1 and mTORC2 is causally related to tumor responsiveness to rapalogs. The preclinical data suggest once again that higher levels of drug exposure over longer time periods are needed to affect mTORC2 function in human cancer cells (43, 44). Collectively, these recent insights may explain long-standing observations that the dose of rapamycin needed to inhibit tumor growth is often several orders of magnitude higher than the dose required for suppression of T-cell–mediated organ allograft rejection (45, 46). Whereas the full immunosuppressive effect of rapamycin or its derivatives is achieved at doses well below the maximum tolerated dose, a strong argument can be made for maximum tolerated dose–based dosing in the oncology clinic. Although toxicity is obviously a greater risk at higher dosage levels, this strategy seems a reasonable trade-off for capturing the maximal number of cancer patients whose tumors are susceptible to mTOR inhibition, whatever the mechanism.

**Molecular determinants of therapeutic responsiveness to mTOR inhibitors.** Despite the substantial progress toward a detailed understanding of the mTOR pathway, we still have much to learn about the rationale design of mTOR inhibitor–based therapies in cancer patients. A well-publicized concept is that alterations (e.g., loss of PTEN function) leading to deregulated PI3K signaling will predict sensitivity to mTOR inhibitors in the clinic (47–50). In practice, however, certain tumor types, such as melanoma and glioblastoma, in which loss of PTEN function is a frequent event, failed to show significant responses to single-agent treatment with Torisel in phase II studies (51–53). A possible explanation is that concomitant activation of the Ras-mitogen-activated protein kinase pathway in these tumor types overrides the drug sensitivity that would normally be conferred by activation of the PI3K pathway alone. Supporting evidence for this hypothesis comes from the finding that combined treatment with rapamycin and the c/B-Raf kinase inhibitor Nexavar(sorafenib) causes synergistic growth inhibition of melanoma cell lines in vitro (50). In addition, we have found that introduction of an oncogenic Ha-Ras mutant into human prostate epithelial cells results in increased resistance to the growth-inhibitory effect of rapamycin.1 Thus, one route to overcome resistance to mTOR inhibitors might be to combine these drugs with Ras pathway inhibitors, such as mitogen-activated protein kinase/extracellular signal–regulated kinase or Raf kinase inhibitors.

In contrast to the negative results obtained in glioblastoma and melanoma patients, clinical studies in endometrial cancer patients strengthen the idea that aberrant PI3K signaling can, under certain circumstances, correlate with mTOR inhibitor sensitivity. Endometrial carcinomas show a high frequency of PTEN loss, and a recent phase II study indicated a remarkable 26% objective response rate for patients with this disease (54). In the small number (n = 9) of patients evaluated for PTEN status, responses were observed in both PTEN-normal and PTEN-deficient patients. The occurrence of responses in patients with normal PTEN status may reflect the fact that PI3K pathway hyperactivity can be achieved by other mechanisms, which would obviate the need for loss of PTEN function. Interestingly, PTEN loss is an early event in endometrial cancer development that manifests even in precancerous, hyperplastic lesions (55). In summary, the clinical results to date suggest that patient selection on the basis of PTEN status will not provide equivalent enrichment of mTOR inhibitor–responsive patients across all tumor types. The natural history of the tumor, as well as the genetic background of the tumor cells at the time of treatment, likely plays determinant roles in tumor sensitivity or resistance to mTOR inhibitor–based therapies.

To date, one successful phase III clinical trial with the mTOR inhibitor Torisel has been reported in patients with advanced renal cell carcinoma (56). The overall survival of these patients was increased by nearly 50% (~ 3 months) relative to the control population, which received standard of care therapy (IFN-α). Nearly 80% of renal clear cell carcinomas are characterized by loss of function of the tumor suppressor gene von Hippel-Lindau (VHL). This alteration promotes the abnormal activation of the heterodimeric HIF-1 transcription factor through stabilization of the HIF-1α and HIF-2α subunits (57). These proteins individually pair with the constitutively expressed HIF-1β subunit to form the active transcription factor, which mediates expression of a broad range of potentially pro-oncogenic proteins, including glycolytic enzymes and proangiogenic cytokines (58, 59). Given that mTOR inhibitors

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1 Unpublished observations.
suppress steady-state levels of HIF-1α (60, 61), inhibition of HIF-1α-mediated transactivation may contribute to the activity of Torisel in renal clear cell carcinomas. In support of this model, a recent report showed that VHL loss confers heightened sensitivity to a mTOR inhibitor in renal cancer cells (62). Once again, however, VHL expression status is not the whole story, as responses to Torisel were also observed in VHL-positive renal cancers. Other factors may come into play here. For example, mutated or amplified c-Met receptor tyrosine kinase expression is found in renal papillary and clear cell carcinomas, respectively, and mitogenic signaling through this receptor is inhibited by rapamycin (63). A separate mutation in the metabolic enzyme fumarate dehydratase is observed in certain non-clear-cell renal cancers and seems to promote tumorigenesis by inducing abnormal accumulation of HIF-1α (64). Inhibition of HIF-1α expression by mTOR (60, 61) might reverse the pseudohypoxic phenotype observed in this subset of renal cancers.

A different underlying set of genotypic alterations may contribute to the sensitivity of mantle cell lymphoma (a B-cell-derived neoplasm) to mTOR inhibitors. In a recent clinical trial, mantle cell lymphoma patients treated with Torisel showed a remarkable 40% objective response rate (65). Mantle cell lymphoma is characterized by a chromosomal t:11-14 translocation, which results in marked overexpression of cyclin D1. Preclinical studies in both yeast and mammalian model systems revealed that D-type cyclin expression was strongly dependent on TOR function and provided a strong rationale for the use of mTOR inhibitors in mantle cell lymphoma (66, 67). However, the link to cyclin D1 is far from certain, in that recent studies implicate mechanisms other than a reduction in cyclin D1 expression in the antiproliferative effects of the rapalogs in mantle cell lymphoma cells (68). This example further underscores the need to understand which spectrum of mTOR-dependent signaling events are the real drivers for the growth of different types of cancer cells. In the case of mantle cell lymphoma, deregulated cyclin D1 activity may be one such driver, but other consequences of mTOR signaling may be equally pivotal in this particular disease.

Rational design of mTOR inhibitor–based combination therapies. An extensive body of preclinical in vitro and in vivo data suggest that the rapalogs will act mainly as cytostatic agents in cancer patients. Hence, the expectation is that these drugs will be used mainly in combination therapy, particularly in carcinomas and other solid tumors. Many of the molecularly targeted drugs now entering the clinic are paired with conventional cytotoxic agents based on standard of care guidelines rather than a strong scientific rationale. However, as mTOR inhibitors become more established in the clinic, a number of possibilities exist for partnering of mTOR inhibitors with other signaling pathway inhibitors to achieve maximal antitumor effects. The prevalence of Ras pathway alterations, together with supportive preclinical data (50), provides a strong rationale for combining mTOR inhibitors with agents that inhibit Ras pathway components, such as the Raf kinase or the mitogen-activated protein kinase/extracellular signal-regulated kinase kinase kinase (69). Ironically, the farnesyltransferase inhibitors, which were originally developed to disable oncogenic Ras signaling in tumor cells, may combine effectively with mTOR inhibitors due to an unanticipated effect on the Rheb GTPase, now known as a key activator of mTORC1 signaling (3, 70). Rheb is strongly dependent on farnesylation for membrane recruitment and activity, suggesting that a farnesyltransferase inhibitor plus a mTOR inhibitor might deliver two reinforcing hits to the mTOR signaling pathway. A similar “two-hit” concept could also come into play with agents that target upstream components of the mTOR signaling pathway. For example, inhibitors of the epidermal growth factor receptor family may synergize with mTOR inhibitors, particularly in tumors that exhibit hyperactivation of PI3K, due, for example, to expression and activation of the epidermal growth factor receptor family member HER3 (71). Similarly, the existence of the negative feedback loop from mTORC1-S6K1 to IRS1 in certain cancer cell types provides a rationale for combination therapies with rapalogs and either insulin-like growth factor receptor antagonists or PI3K inhibitors now in development by several pharmaceutical companies. Finally, we know that mTOR inhibitors affect the tumor microenvironment as well as the tumor itself (72, 73). Combinations with multitargeted kinase inhibitors, such as Nexavar (Bayer) or Sutent (Pfizer), or with the vascular endothelial growth factor–targeting antibody Avastin (Genentech) therefore merit serious consideration. The above list of potential combinations with mTOR inhibitors is by no means comprehensive, and it is likely that these compounds will be tested, either scientifically or empirically, with a broad array of established drugs or new agents currently in development.

Conclusions

The mTOR signaling pathway has been studied intensively for more than 10 years. These research efforts have been facilitated greatly by the availability of the highly potent and selective mTOR inhibitor rapamycin. Although some important conceptual gaps remain to be filled, the mTOR pathway is now understood at a level of molecular detail that rivals that of any other signaling cascade in mammalian cells. The exceedingly rapid rate of knowledge accumulation in this area stands as a tribute to the combined powers of chemical biology, yeast and Drosophila genetics, and biochemical and genetic studies in mammalian cells. Nonetheless, the challenges associated with the transition of the rapalogs from the laboratory bench to the oncology clinics have underscored the fact that we still have much to learn about the intricacies of the mTOR pathway itself, as well as the integration of this pathway into the network of signaling cascades that underpin the cancer phenotype, in all its heterogeneity, in human patients. As frequently the case, human disease is a humbling teacher, but the lessons learned will lead to better cancer treatments as well as novel insights into the roles of mTOR in cancer biology—if we are observant students.

References


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