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The Pharmacology of mTOR Inhibition

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A flurry of reports indicates that we are entering a new phase in the development of mammalian target of rapamycin (mTOR)–based therapies for oncology. Here, we summarize exciting findings regarding mTOR signaling and the outlook for mTOR inhibitors as tools to study the mTOR pathway and as drugs in the clinic.

Introduction

The mammalian target of rapamycin (mTOR) is a protein kinase at the nexus between oncogenic phosphoinositide 3-kinase (PI3K) signaling and critical downstream pathways that drive tumor growth, and the quest to develop mTOR inhibitors is intense. mTOR exists in two complexes called mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) (Fig. 1). In addition to the mTOR catalytic subunit, mTORC1 contains Raptor, mLST8, and PRAS40; mTORC2 also contains mTOR and mLST8 but is defined by the unique regulatory proteins Rictor, mSIN1, and PROTOR (*1*, *2*). Both mTORC1 and mTORC2 additionally interact with DEPTOR, which inhibits their activities (*3*). The prevailing rationale for mTOR-targeted therapy is based on the premise that Akt, a major PI3K effector, activates the rapamycin-sensitive mTORC1 pathway. However, the unexpected discovery that rapamycin-insensitive mTORC2 phosphorylates Akt on a key activation site indicates that a more intercalary relation between mTOR and PI3K signaling exists. This spurred efforts to develop second-generation mTOR inhibitors targeting the mTOR kinase domain, and prototypes of this class have now been described. Initial studies of these molecules have yielded unexpected results, which have implications for current and future prospects of mTOR-targeted therapy.

First-Generation mTOR Inhibitors: The Rapamycins

The canonical rapamycin-sensitive mTORC1 pathway, best known for its role in controlling cell autonomous growth, responds to diverse extracellular signals that include growth factors and nutrients. Years of research relying heavily on rapamcyin to inhibit mTORC1 led to extensive characterization of the best-known mTORC1 substrates, 4E-BP1 (eukaryotic initiation factor 4E binding protein 1) and S6K1 (ribosomal S6 kinase 1), both of which regulate protein synthesis. The key link between mTORC1 activation and growth factor signaling was the discovery that Akt activates mTORC1 by phosphorylating and inhibiting TSC2, which together with TSC1 composes the tuberous sclerosis complex (TSC) (*4*). TSC negatively controls mTORC1 activity by inhibiting a small guanosine trisphosphatase (GTPase) called Rheb, which directly activates mTORC1. In addition to growth factors, TSC integrates information from oxygen- and energy-sensing pathways into the control of mTORC1 activity. What has been more difficult to decipher is how nutrients modulate mTORC1 signaling. Amino acids in particular activate mTORC1 independently of TSC (*5*). The mechanism requires the Rag GTPases, which, by binding to Raptor, may promote the colocalization of mTORC1 with its activator, Rheb, in response to amino acid sufficiency (*6*, *7*).

Numerous oncogenic mechanisms aberrantly activate PI3K signaling in human cancer. The most direct are activating mutations in the gene *PIK3CA*, which encodes the p110α catalytic subunit of PI3K, or loss of expression of the tumor suppressor *PTEN*, which encodes a lipid and protein phosphatase and which is second only to *p53* in its frequency of deactivation in cancer (*8*). Many tumor-prone syndromes classified as hamartoma syndromes (such as TSC, which is caused by mutations in the *TSC1* or *TSC2* gene) are also associated with elevated mTORC1 activity (*9*). Thus, there is considerable rationale for developing rapamycin for use in oncology, and several rapamycin analogs are in clinical development. Rapamycin shows promise against endometrial cancers, in which *PTEN* is frequently deleted, and mantle cell lymphoma, which is characterized by excessive abundance of cyclin D1 protein (*10*). Moreover, in 2007 the rapamycin analog temsirolimus was approved for treating advanced stage renal cell carcinoma, becoming the first mTORC1 inhibitor to be Food and Drug Administration–approved for oncology (*11*). When effective, rapamycin inhibits tumor cell proliferation and, in some cases, tumor angiogenesis. Unfortunately, rapamycin has not lived up to expectations in the clinic, and clinical outcome with the drug is unpredictable. In general, rapamycin is ineffective as a single agent, and biomarkers predictive of rapamycin sensitivity do not yet exist.

Perhaps contributing to rapamycin resistance is the existence of a now well-known negative feedback mechanism downstream of mTORC1 that targets the PI3K pathway (*4*). Because of this negative feedback, when mTORC1 is active, the PI3K-Akt pathway is suppressed, whereas if mTORC1 is inhibited, for instance, with rapamycin, PI3K-Akt signaling is enhanced. In cancer cells, losing this feedback inhibition may promote survival and counter the potential therapeutic benefits of inhibiting mTORC1.

Notably, rapamycin is not a rationally designed molecule but rather a naturally occurring compound crafted by evolution to promote the fitness of a soil bacterium called *Streptomyces hygroscopius*. In mammalian cells, rapamycin associates with an intracellular protein called FKBP12, and together they bind mTOR adjacent to its kinase domain in the FKBP12-rapamycin-binding (FRB) domain. Despite the facts that rapamycin does not target the mTOR kinase domain and that we still cannot fully explain how it works, rapamycin was widely assumed to completely inhibit mTORC1 activity. However, three studies challenge this view, providing an alternative possibility for the insensitivity of many cancers to the drug (*12*–*14*).

When phosphorylated by mTORC1, 4E-BP1 dissociates from eIF4E (eukaryotic initiation factor 4E), which promotes assembly of the eIF4F complex and initiation of cap-dependent mRNA translation. S6K1 may facilitate formation of the translation preinitiation complex and unwinding of highly structured mRNAs (*15*, *16*). It is generally believed that rapamycin inhibits the initiation of cap-dependent mRNA

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translation by preventing mTORC1 from phosphorylating 4E-BP1 and S6K1. However, a careful analysis of the long-term effects of rapamycin on cap-dependent translation revealed that rapamycin differentially affects 4E-BP1 and S6K1 phosphorylation depending on the duration of rapamycin exposure and the cell line tested (*12*). Choo *et al*. discovered that, in a subset of cultured cancer and primary cells, 4E-BP1 phosphorylation is initially inhibited by rapamycin but recovers within a few hours despite continued rapamycin exposure and S6K1 hypophosphoryation. This reemerging rapamycin-resistant phosphorylation requires de novo protein synthesis, as well as mTORC1 activity, because it is prevented by cycloheximide (a translation inhibitor) and actinomycin D (a transcription inhibitor) or by knockdown of either mTOR or Raptor, but not by knockdown of Rictor. Reemergent 4E-BP1 phosphorylation does not require PI3K-Akt signaling, ruling out loss of feedback inhibition as the inducing mechanism. These data suggest mTORC1 has rapamycin-resistant activity that may be instigated by synthesis of an unknown regulatory factor (a candidate may be DEPTOR, which binds mTOR and is transcriptionally and posttranslationally regulated by mTOR activity; this is discussed below). Importantly, these findings argue that mTOR catalytic domain inhibitors would likely be more effective at blocking cap-dependent translation.

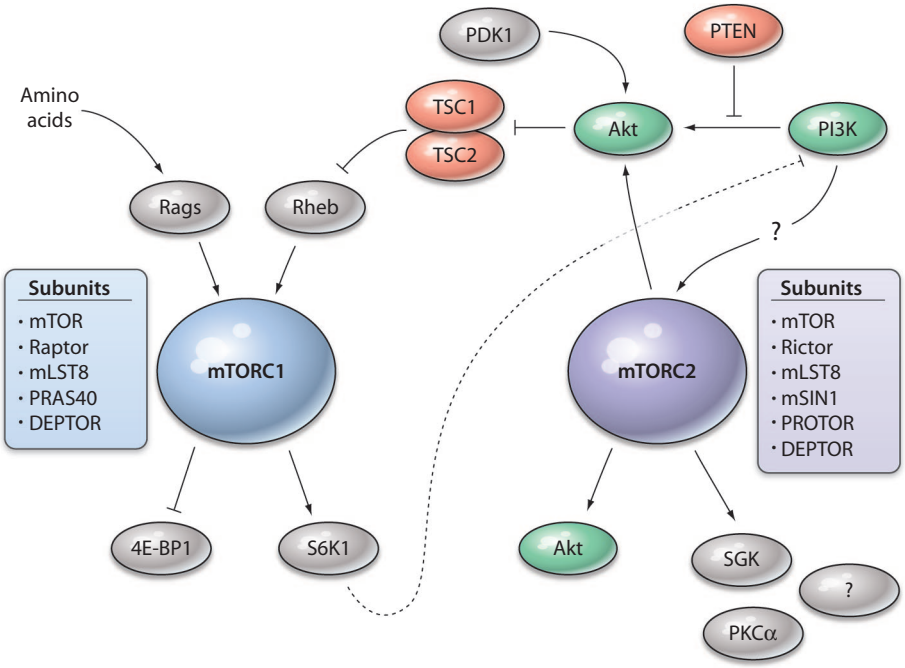

Fig. 1. The basics of mTOR signaling in cancer. The mTOR protein kinase is the catalytic core subunit of two multiprotein complexes, mTORC1 and mTORC2. mTORC1 additionally contains a positive regulatory subunit called Raptor (which also functions as a scaffold for recruiting substrates), two negative regulators, PRAS40 and DEPTOR, and a protein of unknown function called mLST8. mTORC2 also contains mLST8 and the negative regulator DEPTOR as well as two unique positive regulatory subunits, Rictor and mSIN1, and a protein on unknown function called PROTOR. The first direct connection between mTORC1 and signaling pathways aberrantly active in cancer was the discovery that the PI3K-Akt pathway activates mTORC1 by deactivating the TSC1-TSC2 complex. Amino acids regulate mTORC1 activity independently of TSC1-TSC2 by a mechanism involving the Rag GTPases. When active, mTORC1 suppresses PI3K activity by way of a strong negative feedback loop that is at least in part mediated by S6K1. Inhibiting mTORC1 deactivates this inhibitory feedback loop and potentiates PI3K signaling, resulting in increased phosphorylation of Akt at both the PDK1 and the mTORC2 phosphorylation sites. The mechanism by which mTORC2 activity is regulated in response to PI3K signaling is currently unclear. Proteins colored red are tumor suppressors; those colored green are oncogenes. PKCα, protein kinase C α.

Second-Generation mTOR Inhibitors: Targeting the Catalytic Site

Speculating that mTOR kinase inhibitors might have broad application because they would target mTORC1 and mTORC2, our group developed Torin1 while Feldman *et al*. contemporaneously developed PP242 and PP30 (Table 1) (*13*, *14*). By binding the catalytic site, these adenosine triphosphate (ATP)–competitive inhibitors potently inhibit the kinase activity of mTOR in vitro and in cells exhibiting median inhibitory concentration (IC_{50}) values in the low nanomolar range toward mTORC1 and mTORC2 as determined by S6K1 phosphorylation at T389 and Akt phosphorylation at S473, respectively (residue numbering in accordance with human proteins). Kinases with structurally related catalytic sites are inhibited only at much higher concentrations, indicating specificity toward mTOR. The fact that these inhibitors block Akt^{S473} and $S6K^{T389}$ phosphorylation at similar concentrations strengthens the argument that mTOR is the major kinase that phosphorylates the hydrophobic motif site of Akt, which had been controversial.

Interestingly, both Torin1 and PP242 inhibit the proliferation of primary cells to a greater extent than does rapamycin. For example, wild-type mouse embryo fibroblasts (MEFs) treated with rapamycin continue to proliferate at a reduced rate, whereas Torin1 or PP242 completely inhibits the proliferation of wild-type MEFs and causes a G1/S cell cycle arrest (*13*, *14*). It was assumed that the greater efficacy observed with Torin1 is a result of inhibiting mTORC2 in addition to mTORC1. However, MEFs genetically deficient for mTORC2 activity unexpectedly show the same response; mTORC2-deficient MEFs show reduced proliferation in the presence of rapamycin, whereas they arrest in G1/S when treated with Torin1. This finding suggests that the greater efficacy observed with Torin1 is a result of more-complete mTORC1 inhibition and not a consequence of inhibiting both mTORC1 and mTORC2. This also supports the hypothesis that mTORC1 has rapamycin-resistant activity and that, consistently and compared to rapamycin, both Torin1 and PP242 are superior inhibitors of 4E-BP1 phosphorylation and cap-dependent mRNA translation (*13*, *14*). Torin1-treated cells also exhibit decreased abundance of cyclin D1 and D3 protein and increased phosphorylation of the cyclin-dependent kinase inhibitor $p27^{Kip1}$ (*13*). Considering these observations and the historical reliance on rapamycin to inhibit mTORC1, it is likely that some mTORC1-dependent functions have been missed because they are insensi-

Table 1. mTOR inhibitors. The rapamycin category includes rapamycin (sirolimus) and its analogs: temsirolimus (CCI-779), everoliums (RAD001), and deforolimus (AP23573). PI3K indicates the p110α isoform. PI-103 and XL765 also inhibit DNA-PK (IC_{50} of 2 nM for PI-103; IC_{50} of 150 nM for XL765).

Drug	Structure	Binding site	Mechanism of action	mTORC1 (IC_{50})	mTORC2 (IC_{50})	PI3K (IC_{50})	References
Rapamycins	Macrolide ester	mTOR FRB domain (adjacent to kinase domain)	Functions when bound to the immunophilin FKBP12 Partial mTORC1 inhibitor Cell-type specific mTORC2 inhibitor	<10 nM	—	—	Reviewed in (*10*)
Torin1	Pyridinonequinoline	mTOR ATP-binding pocket	mTOR kinase inhibitor	<10 nM	<10 nM	1.8 M	(*13*)
PP242	Pyrazolopyrimidines	mTOR ATP-binding pocket	mTOR kinase inhibitor	<10 nM	<10 nM	1.96 M	(*14*)
PP30	Pyrazolopyrimidines	mTOR ATP-binding pocket	mTOR kinase inhibitor	<100 nM	<100 nM	3.0 M	(*14*)
NVP-BEZ235	Imidazoquinazoline	mTOR/PI3K ATP-binding pocket	Dual kinase inhibitor of mTOR and PI3K	<10 nM	<10 nM	<10 nM	(*23*)
PI-103	Tricyclic pyridofuropyrimidine	mTOR/PI3K ATP-binding pocket	Dual kinase inhibitor of mTOR and PI3K	20 nM	83 nM	8 nM	(*36*)
XL765	Not available	mTOR/PI3K ATP-binding pocket	Dual kinase inhibitor of mTOR and PI3K	157 nM*	157 nM*	39 nM	Reviewed in (*22*)

*Based on immunoprecipitation kinase assays.

tive to the drug. In fact, Torin1 potently activates autophagy, which is thought to be inhibited by mTORC1 activity but has been difficult to prove because rapamycin has variable and modest effects on autophagy in mammalian cells (*13*). We anticipate that research using the mTOR ATP-competitive inhibitors will fill many gaps in our knowledge of mTORC1 function.

Obviously, there is considerable work to do before the clinical potential of these inhibitors is realized. One major caveat is inferred from the study of DEPTOR and concerns the strong negative feedback loop that is disabled upon mTORC1 inhibition. DEPTOR binds directly to mTOR near the FRB domain and is associated with both mTORC1 and mTORC2 (*3*). The abundance of DEPTOR is negatively regulated at the transcriptional and posttranslational levels by a complicated mechanism involving both mTOR complexes (*3*). DEPTOR functions as an mTOR inhibitor because its depletion activates both complexes in vitro and in cells (*3*). Paradoxically, exogenous overexpression of DEPTOR, which could be considered analogous to treating cells with an mTOR kinase inhibitor, inhibits mTORC1-dependent $S6K^{T389}$ phosphorylation but activates both phosphoinositide-dependent kinase 1 (PDK1)–dependent Akt^{T308} and mTORC2-dependent Akt^{S473} phosphorylation (*3*). This may be explained by the fact that DEPTOR-dependent inhibition of mTOR partially inhibits mTORC1 and relieves the strong negative feedback loop, which overrides the partial inhibitory effect of DEPTOR overexpression on mTORC2.

To test whether these same effects are observed with an mTOR kinase inhibitor, Peterson et al. performed an analogous experiment with Torin1 (*3*). At a low dose of 50 nM, Torin1 inhibits both mTORC1 and mTORC2 after acute exposure. However, Akt^{S473} phosphorylation recovers by 48 hours despite $S6K1^{T389}$ remaining dephosphorylated. Under these conditions, PDK1-dependent phosphorylation of Akt at the T^{308} site is also enhanced. In response to PI3K pathway activation, PDK1 is recruited along with Akt to the membrane, which facilitates Akt phosphorylation by PDK1. Thus, T^{308} phosphorylation is an indirect measure of PI3K activity. The increase in Akt^{T308} phosphorylation implies augmentation of the PI3K pathway, as would be expected with loss of the feedback loop. One interpretation of these findings is that 50 nM Torin1 (like DEPTOR overexpression) is not sufficient to inhibit all mTORC2 complexes, and although it is not understood how mTORC2 activity toward Akt is regulated, the eventual increase in S^{473} phosphorylation suggests that uninhibited mTORC2 is activated by PI3K signaling. Consistent with this hypothesis, a higher dose of Torin1 (250 nM) more completely inhibits mTORC2 and blocks Akt^{S473} phosphoryation after 48 hours, whereas phosphorylation of Akt^{T308} is still greatly boosted. Collectively, these experiments suggest that, even though mTOR kinase inhibitors target both complexes, if inhibition is incomplete, enhanced PI3K signaling provoked by decreasing mTORC1 activity could override the effects of inhibiting mTORC2. The consequence of losing feedback inhibition of PI3K signaling clearly needs to be scrutinized.

Another consideration is that there may be functions of Akt that do not require mTORC2-dependent Akt^{S473} phosphorylation. For example, in MEFs knocking out *Rictor*, *mLST8*, or *mSIN1*, which encode essential mTORC2 regulatory proteins, ablates Akt^{S473} phosphorylation but only par-

tially impairs Akt activity toward some downstream substrates (*17*–*19*). Consistent with in vitro assays showing that Akt phosphorylated only at the PDK1-dependent T^{308} site is partially active, Akt retains T^{308} phosphorylation in these mTORC2-deficient MEFs. Feldman *et al*. also find that, in contrast to direct Akt inhibitors, PP242 only partially impairs Akt activity toward some of its substrates. However, the mTORC2 substrate serum- and glucocorticoid-induced kinase (SGK) is completely inhibited by PP242 (*14*, *20*). The extent to which SGK is involved in cancer remains to be seen, but this emphasizes the important point that mTORC2 substrates other than Akt should also be considered as important downstream targets affected by mTOR inhibitors.

An anomaly that is yet to be explained is that acute exposure to mTOR kinase inhibitors in wild-type MEFs reduces phosphorylation of Akt at both S^{473} and at the PDK1-dependent T^{308} site, which is reminiscent of what is observed in cultured cancer cells after acute Rictor knockdown or in *PTEN*-deficient prostate epithelial cells also deleted for *Rictor* (*3*, *14*, *19*, *21*). However, neither Torin1 nor PP242 affect T^{308} phosphorylation in MEFs that lack S^{473} phosphorylation because they are null for the essential mTORC2 subunit-encoding genes *Rictor*, *mLST8*, or *mSIN1* (*13*, *14*). A simple model to explain this peculiarity is that mTORC2-deficient MEFs, having been devoid of mTORC2 activity since their origin, experience chronic mTORC2 inhibition and consequently invoke a compensatory mechanism that stabilizes T^{308} phosphorylation to maintain a sufficient amount of Akt activity. Cells may not be capable of rapidly establishing this mechanism when challenged with acute mTORC2 inhibition. It will be important to determine whether a compensatory mechanism exists in cancer cells that experience prolonged exposure to mTOR kinase inhibitors.

A class of inhibitors related to the mTOR kinase inhibitors is the mTOR and PI3K dual-specificity inhibitors (Table 1). These molecules, which include PI-103, XL765, and NVP-BEZ235, simultaneously target the mTOR and PI3K ATP binding sites and subsequently block mTORC1, mTORC2, and PI3K activity (and in some cases DNA-PK) at similar concentrations (*22*). Because they are less selective, they cannot be used to delineate mTOR-specific activities in cells, but by targeting at least three key enzymatic activities in the PI3K pathway, they may have unique advantages. For example, the concern of releasing PI3K from feedback inhibition may be less problematic with these types of inhibitors because both mTOR and the target of the negative feedback, PI3K, are suppressed. Studies of NVP-BEZ235 indicate that it exhibits greater antiproliferative effects compared with that of rapamycin against a panel of cancer cells and, in animal models, can cause tumor vascular reduction (*23*–*25*). In two mouse models of lung cancer, one driven by oncogenic *PIK3CA* (p110α-H1047R), the other by oncogenic *Kras*, NVP-BEZ235 was effective against PI3K-driven tumors as a single agent but was only effective against the KRas-driven tumors when combined with a mitogen-activated protein kinase kinase (MEK) inhibitor (*26*). Thus, careful consideration regarding the molecular pathology of the particular cancer will be an important factor in the development of these inhibitors.

Although the first-generation mTORC1 inhibitor rapamycin does not target the kinase domain, in a subset of cancer cells rapamycin additionally inhibits mTORC2, thus functioning as a dual mTORC1 and mTORC2 inhibitor in a cell-type specific manner (*27*). Mechanistically it appears that, upon prolonged exposure to the drug, FKBP12-rapamcyin binds free mTOR and that this prevents the assembly of new mTORC2 complexes, which in some cells decreases mTORC2 activity below the threshold required for efficient Akt^{S473} phosphorylation (*27*, *28*). It is possible that this phenomenon is more widespread but masked in many cell types by losing the feedback inhibition of PI3K, which may activate any remaining intact mTORC2 complexes. Notably, free rapamycin (not bound to FKBP12) can also bind and inhibit both complexes, but only at much higher concentrations (*29*). Interestingly, rapamycin potently inhibits the proliferation of the protozoan parasite *Trypanosoma brucei*, and this is completely dependent on TbTORC2 inhibition because TbTORC1 is insensitive to rapamycin (*30*). In this unique situation, rapamycin also blocks TbTORC2 assembly. Although the cell-type specificity of this phenomenon is puzzling, it could be important for determining the clinical effectiveness of rapamycin against cancer cells.

Future-Generation mTOR Inhibitors

The development of mTOR catalytic inhibitors marks the beginning of an exciting new phase in mTOR-based therapies. With the converging development of genetic models of mTOR in cancer, it may now be possible to predict the effectiveness of mTOR inhibitors. Using a mouse model of prostate cancer dependent on conditional deletion of *PTEN*, Nardella *et al*. find that deleting *PTEN* and *mTOR* simultaneously in the prostate epithelium suppresses tumor initiation, whereas conditional *mTOR* deletion alone in the prostate epithelium has no effect on normal prostate function (*31*). In the same model, the rapamycin analog RAD001 only mildly suppresses tumorigenesis, arguing that mTOR catalytic inhibitors will be more effective than rapamycin, although the authors also suggest that inhibiting both mTOR complexes may be the key. Studies to determine the efficacy of mTOR kinase inhibitors in tumor models are currently under way.

But is there rationale for developing mTOR complex–specific inhibitors? Using a mouse model of prostate cancer, we addressed this question for mTORC2. By deleting *Rictor*, an essential regulatory component of mTORC2, in combination with *PTEN* specifically in the murine prostate epithelium, we found that mTORC2 alone is required for tumor initiation (*32*). As is the case with mTOR, the deletion of *Rictor* has no overt deleterious effects on normal prostate morphology or function but is required for transformation induced by *PTEN* loss. Thus, mTORC2-specific inhibitors may have clinical value in treating certain cancers with elevated PI3K activity.

A theoretical mTORC2 inhibitor might have distinct advantages. Importantly, mTORC2 activity is not essential in normal prostate epithelial cells but is required for transformation induced by aberrant activation of the PI3K pathway. Although these criteria are ideal for a small-molecule target, the extent to which mTORC2 is required in other cell types needs to be investigated. It is possible, perhaps likely, that the therapeutic window of an mTORC2 inhibitor would be broader than that of an mTOR kinase inhibitor. For example, muscle-specific deletion of the gene encoding the mTORC1 regulatory subunit Raptor causes muscle dystrophy, whereas deleting the gene for the mTORC2-specific component Rictor in muscle has only minor consequences (*33*, *34*). Perhaps equally as important is that targeting mTORC2 would not directly tamper with the feedback loop downstream of mTORC1. This may turn out to be the decisive factor in the clinical application of

mTOR inhibitors. Going forward, it will be important to determine whether more clinically relevant advanced stages of cancer, as opposed to initiation (*31*, *32*), are similarly susceptible to mTOR inhibition.

With the realization that rapamycin is an incomplete mTORC1 inhibitor and a cell-type–specific inhibitor of mTORC2, we suggest that the full potential (or pitfalls) for mTORC1 inhibitors has yet to be realized. There is strong rationale for such a drug because mutations in *TSC1* or *TSC2*, as well as mutations in genes that encode upstream regulators of their activity, form the molecular basis for numerous growth diseases. The fact that postmitotic prostate epithelial cells are unaffected by *mTOR* deletion suggests that mTORC1 inhibitors might have an acceptable therapeutic window. However, with any molecule that perturbs mTORC1 the consequences of disrupting the feedback loop must be considered. Interestingly, curcumin, a polyphenol natural product of the plant *Curcuma longa*, inhibits phosphorylation of mTORC1 substrates in cells at concentrations that do not inhibit mTORC2-dependent phosphorylation of Akt (*35*). Curcumin's mechanism of action is enigmatic but may involve destabilizing the mTOR-Raptor interaction. Curcumin shows promise against various oncogenic activities and is currently in early clinical trials as an anticancer agent.

Conclusion

Although rapamycin has been an invaluable research tool for elucidating mTOR biology, investigations into its mechanism of action are uncovering many surprises that likely explain its modest clinical performance. We anticipate that second-generation mTOR inhibitors, such as Torin1, PP242, and PP30, will be more effective. However, the founding members of this class are in their early days of evaluation, and considerable research and development is required before their therapeutic potential is realized. Integrating data from pharmacological studies with mouse genetics will be critical in determining the potential efficacy of mTOR inhibitors. Genetic studies provide clear rationale for developing molecules that specifically target mTORC2. One could imagine a complex-specific inhibitor that can dissociate one of the unique mTORC2 (or mTORC1) regulatory subunits or perhaps block localization of the complex to an intracellular site required for its activation or interaction with its substrates. However, a major roadblock, at least to rationally developing complex-specific inhibitors, is our lack of knowledge concerning the structure and assembly of the mTORCs. With a growing appreciation of mTOR's central role in cancer, especially those addicted to PI3K activity, we are optimistic that second- and future-generation mTOR inhibitors will broadly affect the treatment of various cancers plaguing our society.

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