PERSPECTIVES

OPINION

mTOR and cancer: insights into a complex relationship

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Abstract | mTOR (mammalian target of rapamycin) has come a long way since its humble beginnings as a kinase of unknown function. As part of the mTORC1 and mTORC2 complexes mTOR has key roles in several pathways that are involved in human cancer, stimulating interest in mTOR inhibitors and placing it on the radar of the pharmaceutical industry. Here, I discuss the rationale for the use of drugs that target mTOR, the unexpectedly complex mechanism of action of existing mTOR inhibitors and the potential benefits of developing drugs that function through different mechanisms. The purpose is not to cover all aspects of mTOR history and signalling, but rather to foster discussion by presenting some occasionally provocative ideas.

In response to growth factors and nutrients mTORC1 (mammalian target of rapamycin complex 1) regulates cell growth by modulating many processes, including protein synthesis, ribosome biogenesis and autophagy (reviewed in REF. 1). mTORC1 is a heterotrimeric protein kinase that consists of the mTOR catalytic subunit and two associated proteins, raptor (regulatory-associated protein of mTOR) and mLST8 (also known as GβL) (BOX 1). The molecular mechanisms that regulate mTORC1 kinase activity are still poorly understood, but it is increasingly clear that many if not most cancer-promoting lesions activate the mTORC1 pathway (FIG. 1). Most dramatically, the TSC1 (tuberous sclerosis 1, also known as harmartin)–TSC2 (also known as tuberin) tumour suppressor complex — the inactivation of which causes the tumour-prone syndrome tuberous sclerosis complex (TSC) and the related disease lymphangioleiomyomatosis (LAM) — has emerged as a key negative regulator of mTORC1 (REFS 2,3). The TSC1–TSC2 heterodimer is a GTPase-activating protein for Rheb (Ras homologue enriched in brain)[4–8], a GTP-binding protein that activates mTORC1, most probably by binding to it[9]. TSC1–TSC2 and Rheb also have important roles in the activation of mTORC1 that occurs when cells lose the PTEN (phosphatase and tensin homologue), NF1 (neurofibromatosis 1), LKB1 (also known as serine–threonine kinase 11) or p53 tumour suppressors[10–15]. In all cases, inactivation of the tumour suppressor triggers a pathway that eventually leads to inhibition of TSC1–TSC2. For example, the loss of PTEN activates Akt (also known as protein kinase B), which then directly phosphorylates and inhibits TSC1–TSC2, whereas the loss of LKB1 suppresses AMPK (AMP-activated protein kinase)[16,17], which normally mediates an activating phosphorylation of TSC1–TSC2 (REF. 18).

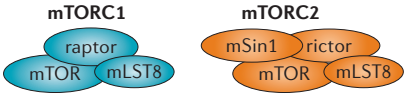
The mTORC1 pathway regulates growth through downstream effectors, such as the regulators of translation 4EBP1 (eukaryotic translation initiation factor 4E binding protein 1) and S6K1 (ribosomal S6 kinase 1) (reviewed in REF. 19). In addition to its role in promoting protein synthesis, S6K1 represses the phosphatidylinositol 3-kinase (PI3K)–Akt pathway by inhibiting IRS1 (insulin receptor substrate 1) and IRS2 expression[20–24]. Therefore, an active mTORC1 pathway can suppress PI3K–Akt signalling, helping to explain the non-aggressive nature of the tumours that are found in TSC[25,26]. The opposite is also true: inhibition of mTORC1 activates PI3K–Akt signalling and, as described below, the activation of PI3K–Akt that is caused by mTORC1 inhibitors might significantly diminish the anti-tumour activity of such molecules.

mTORC2 also contains mTOR and mLST8 but, instead of raptor, it contains two proteins, rictor (rapamycin-insensitive companion of mTOR) and mSin1 (also known as mitogen-activated-protein-kinase-associated protein 1), that are not part of mTORC1 (BOX 1). This second mTOR-containing complex is less understood than mTORC1 but recent work indicates that it should be considered part of the PI3K–Akt pathway as it directly phosphorylates Akt[27,28] on one of the two sites that are necessary for Akt activation in response to growth-factor signalling (FIG. 1). This finding makes mTORC2 a key part of the pathway that activates Akt and, like PDK1 (3-phosphoinositide-dependent protein kinase 1) and PI3K, a potential drug target for cancers in which there is Akt deregulation. The Akt-activating function of mTORC2 sets up the intriguing situation in which mTOR, as part of two distinct complexes, is potentially both 'upstream' and 'downstream' of itself. mTORC2 has other functions besides activating Akt, such as regulating the cytoskeleton[29,30], but the implications for cancer of these roles are still unknown.

What does rapamycin do to the mTORCs?

mTOR was discovered in the early 1990s in studies into the mechanism of action of rapamycin (also known as sirolimus), which is a macrolide that was originally found as an antifungal agent and was later recognized as having immunosuppressive and anticancer properties. Even today, exactly how rapamycin perturbs mTOR function is not completely understood. The complex of rapamycin with its intracellular receptor FKBP12 binds directly to mTORC1 and, at least *in vitro*, suppresses mTORC1-mediated phosphorylation of the substrates S6K1 and 4EBP1. Rapamycin also weakens the interaction between mTOR and raptor[31], which is a component of mTORC1 that can recruit substrates to the mTOR kinase domain[32–34]. It is not known if mTORC1 has

Box 1 | **The mTORC1 and mTORC2 complexes**



mTOR (mammalian target of rapamycin) is a large protein kinase that nucleates at least two distinct multi-protein complexes — mTORC1 and mTORC2 (REFS 29–32,92,93). The first evidence for the existence of the two complexes came from work in budding yeast, in which two related proteins TOR1p and TOR2p can both participate in complexes that are analogous to those found in mammals[93].

mTORC1 has three components — the mTOR catalytic subunit and two other proteins, raptor (regulatory-associated protein of mTOR) and mLST8 (also known as GβL)[29–32,92,93]. mTOR contains a serine–threonine protein kinase domain near its C terminus and there is no evidence that mTORC1 contains any other enzymatic function besides kinase activity. Raptor and GβL are evolutionarily conserved but their functions are still poorly understood. Raptor might have roles in mTOR assembly, recruiting substrates to mTOR, and in regulating mTOR activity. The strength of the association between mTOR and raptor is regulated by nutrients and other signals that regulate the mTORC1 pathway, but how this translates into regulation of the mTORC1 pathway is unknown. The small GTP-binding protein Rheb (Ras homologue enriched in brain) binds to the mTOR kinase domain and seems to have a key role in activating it.

mTORC2 also contains mTOR and mLST8 but instead of raptor two other proteins, rictor (rapamycin-independent companion of mTOR) and mSin1 (also known as mitogen-activated-protein-kinase-associated protein 1). Both rictor and mSin1 are necessary for the phosphorylation of Akt (also known as protein kinase B) on its C-terminal hydrophobic motif and this function is conserved in *Drosophila*. Compared with raptor and mLST8, rictor, and particularly mSin1, are poorly conserved at the amino-acid-sequence level. Recent work indicates that mTORC2 exists in several distinct forms that are defined by different alternatively spliced isoforms of mSin1. Unlike the raptor–mTOR association, the interaction between mTOR and rictor does not seem to be regulated by upstream signals. However, growth factors do stimulate the mTORC2 kinase activity but the mechanism of regulation is not yet understood. *In vitro*, rictor is required for mTORC2 to be able to phosphorylate Akt.

functions that depend on its kinase activity but are not sensitive to rapamycin, so it is still unclear if a molecule that directly inhibited the mTORC1 kinase domain would have different biological effects to those of rapamycin. Analogues of rapamycin, such as CCI-779 (also known as temsirolimus; Wyeth), RAD001 (also known as everolimus; Novartis) and AP23573 (Ariad Pharmaceuticals), are likely to be the first mTOR-perturbing molecules to be approved for anticancer use in humans (reviewed in REF. 35). These molecules inhibit mTORC1 through the same mechanism of action as rapamycin, but have different pharmacokinetic and solubility properties that increase their desirability for clinical use.

In contrast to mTORC1, FKBP12–rapamycin cannot bind directly to mTORC2 (REFS 29,30), suggesting that the effects of rapamycin on cellular signalling are due to inhibition of mTORC1. A potentially important wrinkle in this seemingly closed story has recently emerged[36]. It turns out that prolonged treatment with rapamycin — clearly a situation that is relevant to its use in patients — perturbs mTORC2 assembly and, in about 20% of cancer cell lines, the drop in intact mTORC2 levels is sufficient to strongly inhibit Akt signalling (FIG. 2). The binding of FKBP12–rapamycin to mTOR seems to block the subsequent binding of the mTORC2-specific components rictor[36] and mSin1 (REF. 37) but it is unknown why in certain cell types rapamycin only partially inhibits mTORC2 assembly. No absolute correlation exists between the tissue of origin of a cell line and the sensitivity of mTORC2 formation to rapamycin, although many cell lines with this property are derived from the haematological system. Recent work provides the first evidence that mTORC2 function can be rapamycin-sensitive in patients. In more than 50% of patients with acute myeloid leukaemia, rapamycin or an analogue inhibited Akt phosphorylation in primary leukaemic cells and the inhibition correlated with the loss of intact mTORC2 (M. Konopleva, personal communication).

So, rapamycin and its analogues are universal inhibitors of mTORC1 and S6K1, and cell-type specific inhibitors of mTORC2 and Akt. As the inhibition of mTORC2 by rapamycin is time and dose dependent[36,38], Akt activity in tumours will vary with the length of rapamycin treatment and the dosing regimen (FIG. 2). It is important to keep in mind that, because inhibition of mTORC1 and mTORC2 will not always occur at the same time, markers of mTORC1 inhibition, such as loss of phosphorylated S6, will not necessarily reflect mTORC2 activity. As discussed below, the capacity to sometimes inhibit mTORC2 might help explain why the cellular effects of rapamycin vary among cancer cell lines. Moreover, in a tumour this inhibition might have the beneficial effect of preventing the activation of Akt, through inhibition of S6K1 (FIG. 1), that rapamycin would otherwise cause.

Anticancer uses for mTOR inhibitors

Rapamycin and its analogues can inhibit several processes that are relevant to the anti-tumour properties that these molecules exert in pre-clinical cancer models, including cell proliferation, cell survival and angiogenesis (reviewed in REF. 35). Exactly how mTORC1 inhibition mediates all these varied effects is not well worked out and the potential for rapamycin to inhibit mTORC2 and Akt provides additional mechanisms to consider. A case in point is the effects of rapamycin on apoptosis, which vary depending on which cell line is tested. There are many reports of rapamycin promoting pro-apoptotic stimuli[39–44] but there are also reports of it promoting cell survival[45]. As rapamycin universally inhibits the mTORC1 pathway, its effects on apoptosis might correlate with its varying effects on Akt, a well-known regulator of cell survival. In cells in which the drug inhibits mTORC2 and Akt it might promote apoptosis, as has been shown[36]. On the other hand, when the drug does not inhibit mTORC2, so that mTORC1 inhibition leads to Akt activation, the drug might protect against apoptosis. As induction of apoptosis rather than cytostasis is increasingly considered a prerequisite for an effective anticancer agent, it will be crucial to understand when rapamycin has such effects and where it does not, and to learn how to trigger apoptosis with additional therapies.

Despite the substantial pre-clinical data indicating that rapamycin and its analogues have anti-tumour effects and that mTOR participates in many cancer-related pathways, these molecules have not shown universal anti-tumour activity in early clinical trials. Response rates vary among cancer types from a low of less than 10% in patients with glioblastomas[46,47] or advanced renal-cell cancer[48] to a high of around 40% in patients with mantle-cell lymphoma (MCL; an aggressive non-Hodgkin lymphoma with a poor prognosis)[49]. Many in the community have found these results disappointing, but until we understand why rapamycin analogues do have significant anti-tumour effects in certain patients it is too early to draw a conclusion on the utility of inhibiting mTOR in cancer treatment. Clearly, we require more information on which combination of

molecular lesions is likely to make a tumour susceptible to mTOR inhibition.

As discussed below, good scientific reasons are emerging as to why rapamycin might benefit particular tumour types, and the hope is that with the proper insights this drug or other mTOR inhibitors might be used for patient benefit.

TSC. A strong scientific rationale exists for the use of rapamycin and its analogues in the treatment of TSC. Rapamycin suppresses the molecular consequences of TSC1–TSC2 loss on the mTORC1 pathway and, in cultured cells and model organisms, the drug also reverses the increase in cell size that is a hallmark of the disease (reviewed in REF. 35). In a recent clinical trial rapamycin reduced the sizes of the astrocytomas that are frequently seen in patients with TSC[50], providing the first human data that supports the widely held expectation that rapamycin will be a useful drug for TSC. Because mTORC1 is at least two molecules downstream of the TSC1–TSC2 complex it is unlikely that rapamycin will reverse all TSC-associated phenotypes. It is known that TSC1–TSC2 has targets besides Rheb[51,52] and it is likely that Rheb has targets in addition to mTORC1 (REFS 53–57), potentially allowing TSC1–TSC2 loss to cause many mTORC1-independent sequelae. There is already evidence that this is the case as rapamycin cannot reverse the dendritic-spine elongation that is seen in neurons that lack TSC2 (REF. 58), or the resistance of TSC2-null fibroblasts to hypoxia-induced apoptosis[59]. The role of mTORC1-independent pathways in disease pathogenesis remains to be determined but will surely be a topic of great interest if not all clinical features of TSC prove sensitive to mTORC1 inhibitors.

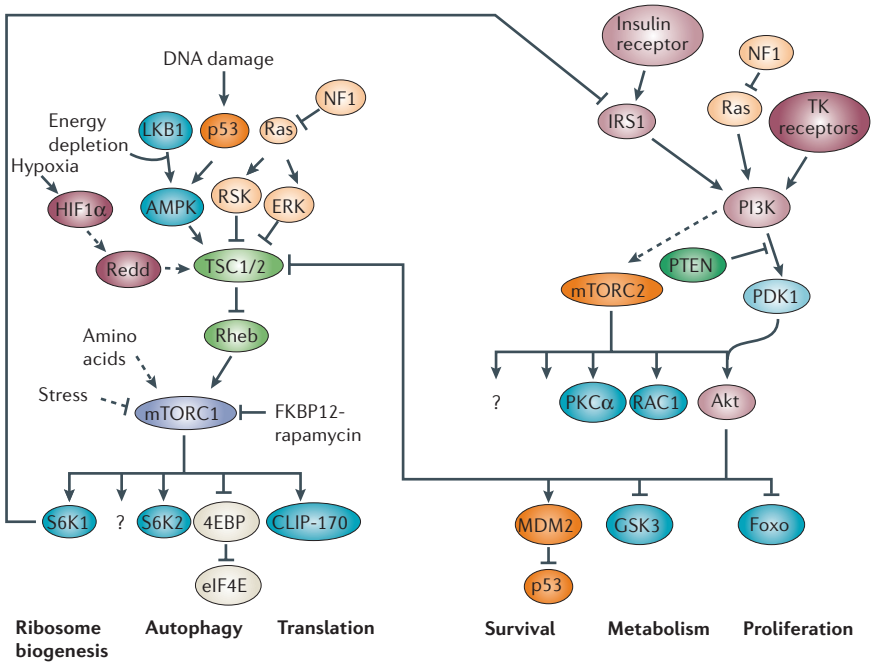


Figure 1 | **Circuitry of the mTORC1 and mTORC2 pathways and their relationships to the PI3K pathway.** The main points of contact between the mTORC1 (mammalian target of rapamycin complex 1) and PI3K (phosphatidylinositol 3-kinase)–Akt (also known as protein kinase B) pathways are emphasized. A main function of the mTORC1 pathway is to regulate the accumulation of cell mass by activating mRNA translation and ribosome biogenesis and by inhibiting autophagy. mTORC1 directly phosphorylates and activates S6K1 (ribosomal S6 kinase 1), which is an important regulator of cell size. Phosphorylation of S6K1 by PDPK1 (3-phosphoinositide-dependent protein kinase 1) is also important for its activation, but for clarity this connection is not shown. S6K1 inhibits IRS1 (insulin receptor substrate 1) by directly phosphorylating it, a connection that in the mTOR field is frequently called 'the feedback loop' and is responsible for the inhibition of Akt that is caused by high mTORC1 activity. By phosphorylating the 4EBP (eukaryotic translation initiation factor 4E binding protein) family of proteins mTORC1 represses their capacity to inhibit the mRNA cap-binding protein eIF4E (eukaryotic initiation factor 4E). Less is known about how mTORC1 activates S6K2 and CLIP-170 (cytoplasmic linker protein 170, also known as restin) and it is likely that many direct substrates of mTORC1 remain to be discovered. The TSC1 (tuberous sclerosis 1)–TSC2 heterodimer is a key negative regulator of mTORC1 that functions by suppressing Rheb (Ras homologue enriched in brain), a small GTP-binding protein that activates mTORC1. Mammals contain two Rhebs, RHEB1 and RHEB2, which can both activate mTORC1 signalling. Insulin and other growth factors, energy status and DNA damage signal to TSC1–TSC2 by regulating kinases that directly phosphorylate TSC2. Hypoxia induces the expression of REDD1 (regulated in development and DNA-damage responses 1) and REDD2, which activate TSC1–TSC2 through an unknown mechanism. It is unknown how osmotic and heat-shock stress, as well as amino acids, signal to mTORC1 and it might be that mechanisms apart from the Redds are involved in the regulation of mTORC1 by hypoxia. mTORC2 directly phosphorylates Akt on the hydrophobic site in the C-terminal tail, which together with the PDK1-mediated phosphorylation of the activation loop is necessary for full Akt activation. How mTORC2 is regulated is unknown but its activity does respond to growth factors; this is mediated through tyrosine kinase (TK) receptors. mTORC2 can be considered upstream of mTORC1 because by activating Akt it leads to the inhibition of TSC1–TSC2, which causes the activation of Rheb and mTORC1. AMPK, AMP-activated protein kinase; ERK, extracellular signal-regulated kinase; FKBP12, intracellular receptor for rapamycin; Foxo, Forkhead box; GSK3, glycogen synthase kinase 3;HIF1α, hypoxia-induced factor 1α; LKB1, serine–threonine kinase 11; MDM2, mouse double minute 2; NF1, neurofibromatosis 1; PKCα, protein kinase Cα; PTEN, phosphatase and tensin homologue; RAC1, Ras-related C3 Botulinum toxin substrate 1; RSK, ribosomal protein S6 kinase.

Tumours with activated PI3K–Akt signalling. Data from cancer cell lines *in vitro* and from xenografts indicate that a strong correlation exists between the antiproliferative effects of the rapamycin analogues and the loss of PTEN[60,61]. Although this correlation is not perfect, work in mouse models bolsters the idea that rapamycin might be particularly effective against tumours with an activated PI3K–Akt pathway. Rapamycin or an analogue blocked both prostate intraepithelial neoplasia[62] and the lymphoproliferative disease[63] that is caused by expression of an activated allele of Akt. These findings indicate that tumorigenesis that is driven by a hyperactive PI3K–Akt pathway requires the activation of mTORC1 by Akt. Unfortunately, the situation is not as straightforward in patients because rapamycin analogues have not shown good anti-tumour activity against tumours that are known to have high Akt activity, such as glioblastomas[46,47] and breast cancers[64].

An interesting hypothesis is emerging as to why this might be. As described earlier, by inhibiting mTORC1 rapamycin and its analogues are expected to strongly activate Akt, a prediction that has now been observed in many cancer cell lines *in vitro*[65,66] and in tumours in patients[66]. Inhibition of PI3K signalling blocks rapamycin-mediated activation of Akt in cancer cells[65–67], suggesting a possible strategy for boosting the anti-tumour efficacy of mTORC1 inhibitors[65–67]. Consistent with this idea, the combination of

rapamycin and an inhibitor of IGF1R (insulin-like growth factor 1 receptor) prevents Akt activation in various human cancer lines and has a greater antiproliferative effect than rapamycin alone[66]. Similar antiproliferative effects occur in multiple glioma cell lines that have been treated with PI-103 (REF. 67), which is a molecule that inhibits the kinase activity of both mTOR and PI3K p110α (the isoform of the PI3K catalytic subunit that activates Akt in response to insulin[68,69]). Even though PI-103 inhibits mTORC1, mTORC2 and PI3K p110α it has anti-tumour activity in mice without overt toxicity[67].

In cancer cells in which rapamycin inhibits both mTORC1 and mTORC2, the drug inhibits Akt instead of activating it[36]. This phenomenon seems to occur in only a minority of cancer lines[36] and perhaps many of the tumours that do respond to rapamycin monotherapy have drug-sensitive mTORC2 activity and depend on PI3K–Akt signalling. To test this hypothesis it will be necessary to develop biomarkers that predict in which tumours rapamycin will inhibit Akt and to understand the molecular mechanisms that confer this phenotype. Because rapamycin-mediated inhibition of mTORC1 activates the PI3K–Akt pathway, the relative strength of this activation versus the degree of Akt suppression that is caused by inhibition of mTORC2 assembly might set the ultimate levels of Akt activity in a rapamycin-treated cell. Of course, it is probable that the insensitivity of certain tumours to rapamycin does not depend on the inherent sensitivity of mTORC2 assembly to the drug. Rather, as yet unidentified mutations in tumour cells might determine how important mTORC1 signalling is to the proliferation and survival of a particular cancer cell.

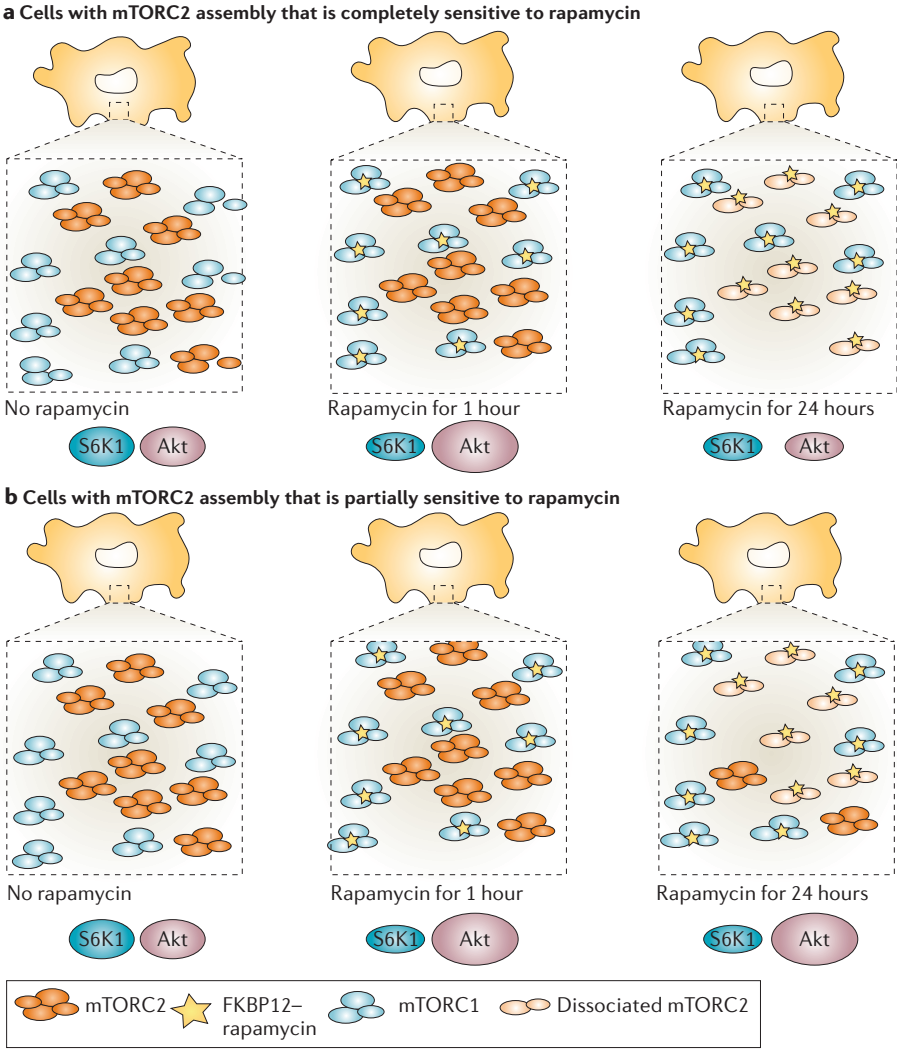


Figure 2 | **Two models to explain the varying effects of long-term rapamycin treatment on Akt activity. a** | In this scenario, the assembly of mTORC2 (mammalian target of rapamycin complex 2) is completely sensitive to rapamycin treatment — 24 hours after rapamycin addition no intact mTORC2 remains in the cell. Therefore, Akt (also known as protein kinase B) phosphorylation does not occur and its activity drops. After 1 hour of rapamycin treatment the drug inhibits only mTORC1. This eliminates the inhibitory signal that is normally mediated by S6K1 (ribosomal S6 kinase 1) to IRS1 (insulin receptor substrate 1), which suppresses the activity of the PI3K (phosphatidylinositol 3-kinase)–Akt pathway. Therefore, Akt activity increases with short rapamycin treatment times but is inhibited by prolonged treatment. **b** | In this scenario, Akt activity also increases after 1 hour of treatment but mTORC2 assembly is not completely sensitive to rapamycin, so some mTORC2 remains intact even with prolonged treatment and Akt activity remains at increased (shown) or at baseline (not shown) levels. Only about 20% of cancer cell lines seem to have mTORC2 assembly that is completely sensitive to rapamycin. The size of the icons that represent S6K1 and Akt depicts their activity at different times after rapamycin treatment. FKBP12, intracellular receptor for rapamycin.

Tumours with VEGF-driven angiogenesis or VHL loss. As mentioned earlier, rapamycin suppresses angiogenesis[70], indicating that mTOR inhibition might be useful in tumours in which this is an important component of the pathogenesis. A striking example is the regression caused by rapamycin of Kaposi sarcoma[71,72], a tumour in which VEGF (vascular endothelial growth factor)-driven angiogenesis is a prominent feature (reviewed in REF. 73). Recent work indicates that rapamycin inhibits activated Akt signalling in endothelial cells and suppresses the angiogenesis that is promoted by the expression *in vivo* of constitutively active Akt[74]. It is feasible that the anti-angiogenic effect of rapamycin is the combined result of both mTORC1 and mTORC2 inhibition. By inhibiting the mTORC1-dependent translation and activity of HIF1α (hypoxia-induced factor 1α)[75–77], rapamycin decreases VEGF production by cancer cells. In endothelial cells the drug also inhibits VEGF-driven proliferation[70] and promotes apoptosis[78]. Given the important role of Akt in these processes (reviewed in REF. 79), it is not unreasonable to hypothesize that the known capacity of rapamycin to inhibit Akt in endothelial cells[36] might be important for its anti-angiogenic properties. In support of this idea, rapamycin suppresses angiogenesis in mice at high concentrations but not at the low concentrations that are sufficient to inhibit mTORC1 (REF. 70). Lastly, it is interesting to note that in Kaposi sarcoma Akt hyperactivation in endothelial cells is essential for tumorigenesis[80].

The HIF1α transcription factor stimulates VEGF production, and renal cancer cells that

lack the tumour suppressor VHL (von Hippel Lindau), which normally inhibits HIF1α, are particularly sensitive to rapamycin in culture and in tumour xenografts[77]. The expression in the cancer cells of a *HIF1α* mRNA that is engineered to make its translation resistant to rapamycin can largely eliminate the sensitivity of the cells to the antiproliferative effects of the drug[77]. In this case, rapamycin is clearly functioning through its action on the cancer rather than endothelial cells.

Tumours with cyclin D1 overexpression. Tumours with cyclin D1 overexpression deserve their own special mention because this characteristic might underlie one of the more promising indications for rapamycin. In clinical trials rapamycin slowed the progression of nearly 40% of advanced MCLs[49]. A hallmark of MCL is the translocation-induced overexpression of cyclin D1 (reviewed in REF. 81). The mTORC1 pathway positively regulates cyclin D1 transcription, translation and stability in many types of cancer cell[82–86]. Despite the clear rationale for the use of rapamycin in MCL, in tissue culture experiments the drug had the unexpected effect of arresting MCL cells without decreasing their high levels of cyclin D1 (REF. 87). Recent work reveals that hyperactive PI3K–Akt signalling (in some cases caused by PTEN loss) occurs in about 50% of MCLs[88] and it is tempting to speculate that rapamycin-mediated inhibition of Akt might contribute to the effectiveness of the drug in the treatment of some cases of MCL.

Beyond rapamycin

The likely approval in the near future of a rapamycin analogue for an anticancer indication is almost certainly only the first foray into the oncology arena for mTOR inhibitors. Only recently has work begun on trying to identify compounds that perturb the mTOR complexes through mechanisms other than rapamycin and its analogues. Of particular interest will be molecules that directly inhibit the mTOR kinase domain, the assumption being that such molecules will inhibit both mTORC1 and mTORC2. Of course, this remains to be proven as structural changes that are induced by interacting proteins in the mTORC1 and mTORC2 kinase domains might not permit a single molecule to inhibit both while retaining specificity for mTOR. mTOR is essential for cell proliferation in mice[89,90], so the expectation is that a direct mTOR kinase inhibitor will have more pronounced effects than rapamycin, which rarely completely arrests or kills cells on its own. On the other hand, there is no formal proof that the cell-essential functions of mTOR depend on its kinase activity as mTOR might have scaffolding functions that do not require an active kinase domain. Still, it is interesting to consider the potential anti-tumour activity of a hypothetical molecule that directly inhibits the kinase function of mTOR so that, unlike rapamycin, it suppresses both mTOR-dependent pathways in all cancer cells. Such a molecule should inhibit both the mTORC1 growth pathway that is regulated by S6K1 and 4EBP1, and the mTORC2-dependent Akt pathway, and so should prevent the activation of Akt that is caused by mTORC1-only inhibitors. If activation of Akt by rapamycin and its analogues explains their ineffectiveness in certain tumours, such a molecule should overcome this. Currently, this idea cannot be tested because all molecules that inhibit the kinase domains of mTORC1 and mTORC2 also inhibit PI3K p110α. Because acute inhibition of mTORC2 or PI3K p110α both suppress Akt[27] it is difficult to distinguish the effects of an mTORC2 inhibitor from that of a PI3K p110α inhibitor when using Akt activity as a read-out. This raises the question of whether the greater effectiveness compared with rapamycin of molecules such as PI-103, which inhibit both PI3K p110α and mTOR[67], depends on their capacity to inhibit mTORC2, PI3K p110α or both kinases.

We have known since the early 1980s that rapamycin has anti-tumour properties[91], but it has taken two decades for our understanding of mTOR and its connection with cancer-related pathways to progress to the point where we can begin to consider using mTOR inhibitors in a logical fashion. For those of us who have wrestled with the maddening complexity of the mTOR pathway, it is exciting that this time is finally here.

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Competing interests statement

The author declares no competing financial interests.

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