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Inhibitors of the mammalian target of rapamycin

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The mammalian target of rapamycin (mTOR) is a downstream protein kinase of the phosphatidylinositol 3′-kinase–Akt signalling pathway. As a result of its position within this pathway and its central role in controlling cellular growth, mTOR is viewed as an important target for anticancer therapeutics development. Currently, the mTOR inhibitor rapamycin (sirolimus, Wyeth) and its derivatives temsirolimus (CCI-779, Wyeth), everolimus (RAD-001, Novartis Pharma AG) and AP-23573 (Ariad Pharmaceuticals) are being evaluated in cancer clinical trials. Preclinical studies suggest that sensitivity to mTOR inhibition may correlate with aberrant activation of the phosphatidylinositol 3′-kinase pathway and/or with aberrant expression of cell-cycle regulatory or antiapoptotic proteins. Clinical trial results show that mTOR inhibitors are generally well tolerated and may induce prolonged stable disease and even tumour regressions in a subset of patients. Questions remain regarding optimal dose, schedule, patient selection and combination strategies for this novel class of agents.

Keywords: AP-34573, everolimus, mammalian target of rapamycin, sirolimus, temsirolimus

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1. Introduction

The mammalian target of rapamycin (mTOR) is a downstream protein kinase of the phosphatidylinositol 3′-kinase (PI3K)–Akt signalling pathway. As a result of its position within this pathway and its central role in controlling cellular growth, mTOR is considered to be an important target for anticancer therapeutics development. By targeting mTOR, the immunosuppressant and antiproliferative agent rapamycin inhibits the signals required for cell-cycle progression, cell growth and proliferation in both normal and malignant cells. Currently, mTOR inhibitors rapamycin (sirolimus, Rapamune™, Wyeth) and its derivatives temsirolimus (CCI-779, Wyeth), everolimus (RAD-001, Novartis Pharma AG) and AP-23573 (Ariad Pharmaceuticals) are being evaluated in cancer clinical trials. An additional agent, TAFA-93 (isotechnika), has recently entered human trials in the prevention of organ rejection after transplantation.

2. Biochemistry of protein kinase of the phosphatidylinositol 3′-kinase–Akt–mammalian target of rapamycin pathway

mTOR is an evolutionarily conserved 290-kDa serine-threonine kinase that regulates both cell growth and cell-cycle progression through its ability to integrate signals from nutrient and growth factor stimuli [1,2]. mTOR, a member of the PI3K-kinase-related kinase (PIKK) superfamily, is composed of 2549 amino acids that are grouped into highly conserved, yet functionally poorly understood, domains. Modelling of the tertiary structure of mTOR suggests that most of the protein consists of helical repeat units that may form an extended superhelical structure to create multiple interfaces for protein–protein interactions [3]. mTOR

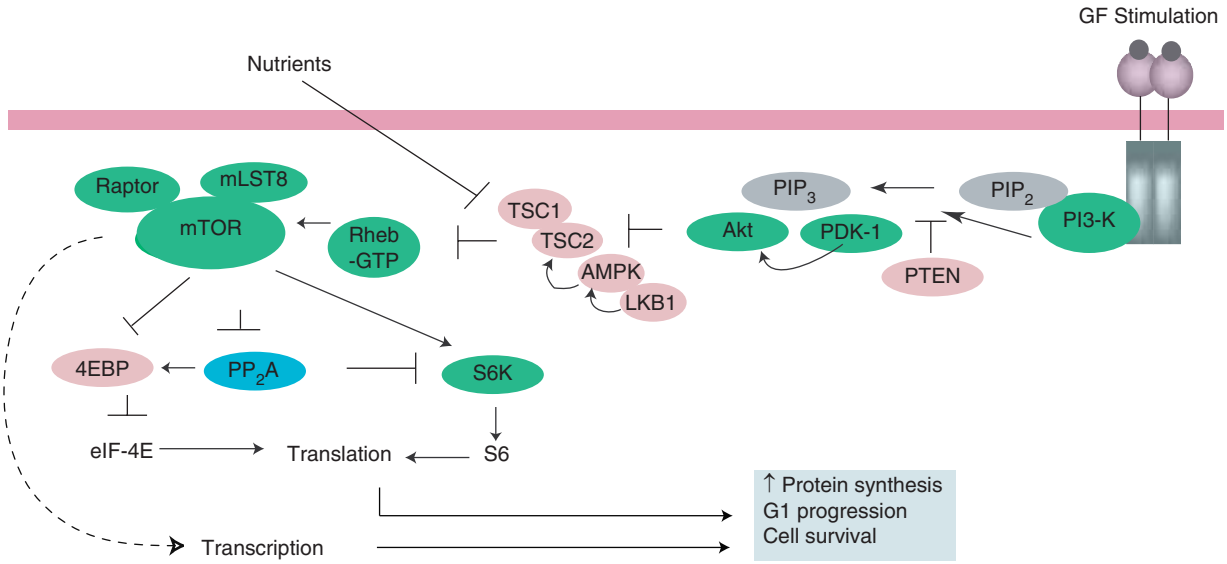

Figure 1. mTOR signalling. GF receptor stimulation leads to activation of PI3K and 3'-OH phosphorylation of PIP_2 to generate PIP_3. PIP_3 then recruits PDK-1 and Akt to the plasma membrane to be activated. The tumour suppressor phosphatase PTEN dephosphorylates PIP_3 at the D3 position of the inositol ring. Activated Akt phosphorylates and inhibits TSC, removing its inhibitory effect on Ras-related small GTPase Rheb, which acts as a positive upstream regulator of TOR. TSC2 is also inhibited by the presence of amino acids, thus allowing Rheb to activate mTOR through an unknown mechanism. Activation of mTOR in complex with other proteins such as raptor and possibly other proteins such as mLST8 leads to phosphorylation of eIF-4E-binding protein (4E-BP) and ribosomal protein S6 kinase 1. This interaction results in an increase in translation rates of a subset of mRNAs including those encoding proteins required for cell-cycle progression. See Section 2 for additional details.

BP: Binding protein; eIF: Eukaryotic initiation factor; GF: Growth factor; mLST8: Mammalian orthologue of LST8; mTOR: Mammalian target of rapamycin; PDK: Phosphatidylinositol-dependent kinase; PDK-1: Phosphatidylinositol-dependent kinase-1; PI3K: Phosphatidylinositol 3′-kinase; PIP_2: Phosphatidylinositol-4,5-bisphosphate; PIP_3: Phosphatidylinositol-3,4,5-triphosphate; PP_2A: Protein phosphatase 2A; PTEN: Phosphatase and tensin homologue; Raptor: Regulatory-associated protein of mTOR; Rheb: Ras homologue enriched in brain; SC: Tuberous sclerosis complex.

functions in a protein complex that integrates signals from a variety of sources, including growth factors, energy stores and hypoxia, with the protein translation apparatus [4]. There remains a number of unresolved questions regarding the function and the mechanism of action of mTOR. For example, it is not clear whether the intrinsic kinase activity of mTOR is sufficient for its full activity *in vivo* or if some mTOR functions may be mediated through protein interactions independent of its kinase function [5]. Furthermore, it is not clear whether mTOR may also serve as a scaffold for other proteins with catalytic activity, such as kinases and phosphatases that may regulate its overall activity *in vivo* [6]. However, it does seem clear that not all the cellular activities of mTOR are sensitive to inhibition by rapamycin [5]. Thus, mTOR function in normal and malignant cells requires further elucidation, and a further understanding of these functions is likely to lead to optimal strategies for therapeutic interventions.

The pathway from growth factor receptor stimulation to mTOR activation proceeds through and in parallel to PI3-K and Akt (Figure 1). In response to extracellular stimuli, PI3K phosphorylates the 3′-hydroxyl of phosphatidylinositol-4,5-bisphosphate (PIP_2) to generate phosphatidylinositol-3,4,5-triphosphate (PIP_3). The formation of PIP_3 leads to the binding through their pleckstrin homology (PH) regions and activation of phosphatidylinositol-dependent kinase-1 (PDK-1) and Akt at the plasma membrane [1]. The tumour suppressor phosphatase PTEN (phosphatase and tensin homologue deleted on chromosome 10) dephosphorylates PIP_3 at the 3′ position of the inositol ring, reversing the action of PI3K. Activated Akt phosphorylates and inhibits the tuberous sclerosis complex (TSC). In mammals, TSC1 (hamartin) and TSC2 (tuberin) associate to form a heterodimer that inhibits cell-cycle progression and cell proliferation [7,8] that, at least in part, is mediated through mTOR inhibition. A current model suggests that PI3K-dependent activation of Akt results in the phosphorylation and inactivation of TSC2 in mammalian cells [9]. Following its phosphorylation, TSC2 destabilises, disrupting the formation of functional TSC1/2 complexes and removing their inhibitory effect on mTOR [10-12]. Conversely, energy deprivation activates the tumour suppressor gene product LKB1, which in turn phosphorylates and activates TSC2 [13,14]. TSC2 acts as a GTPase-activating protein (GAP) toward the Ras-related small GTPase Rheb (Ras homologue enriched in brain) [15], a positive upstream regulator of mTOR. Therefore, activation of TSC2 by LKB1, as may occur in a nutrient-deprived state, inhibits Rheb and results in the downregulation of mTOR. In contrast, inhibition of TSC2 as occurs in the presence of amino acids, as well as binding to 14-3-3 proteins [16-18], with Akt phosphorylation

or through loss of TSC2 function through mutation, as occurs in TS patients, allows Rheb to activate mTOR and leads to the phosphorylation of the downstream mTOR targets [8]. The molecular mechanism by which Rheb activates mTOR is currently unknown. The net result of these signalling interactions suggests a model in which growth factor signalling through PI3K–Akt is coordinated with nutrient availability signalling through LKB1–TSC1/2 to Rheb and mTOR.

mTOR functions in a complex with at least two other proteins: regulatory associated protein of mTOR (raptor) [19,20] and mammalian orthologue of LST8 (mLST8, also known as G-protein β-subunit-like protein [GβL]) [20,21]. The function of raptor is not completely understood; however, it appears to be essential for mTOR signalling *in vivo* and is critical for mTOR substrate phosphorylation *in vitro* [6]. One model that has been proposed to explain the role of mTOR–raptor–mLST8 suggests that a change in the configuration of the mTOR–raptor complex, which is mediated by nutrient conditions such as amino acid availability, affects the ability of mTOR to interact with and phosphorylate its substrates [6]. In the absence of amino acids, the mTOR–raptor–mLST8 complex prevents mTOR from binding to its substrates and/or prevents the access of mTOR (or mTOR-associated kinases) to the substrates [6]. In the presence of amino acids, a conformational change promotes the interaction between raptor and mTOR substrates and/or increases access of the substrates to mTOR and its associated kinases [6]. Further studies are required to address how amino acids elicit these proposed changes in mTOR–raptor complex and verify this model [6]. However, current evidence suggests that activated mTOR, in complex with raptor, and possibly other proteins, leads to phosphorylation of two key proteins; eukaryotic initiation factor-4E (eIF-4E) binding protein 1 (4E-BP1) and protein S6 kinase 1 (S6K1) [3,22]. S6K1 or 4E-BP1 phosphorylation is often used as *in vitro* and *in vivo* readouts of mTOR activity (described in this section) in laboratory and clinical research studies.

Unphosphorylated 4E-BP1 binds to RNA cap-binding protein eIF-4E, inhibiting its coupling to mRNA methyl-7 GpppN cap and the multi-protein translational–initiation complex, required for initiating translation of cap-dependent mRNAs, a subset of mRNAs with regulatory elements located in the 5′-untranslated regions (UTRs) [23]. Stimulation of cells by hormones, mitogens, growth factors, cytokines and G-protein-coupled agonists results in the activation of mTOR, leading to multi-site phosphorylation of 4E-BP1, release of eIF4E to bind to cap mRNA transcripts and other initiation complex proteins and the initiation of cap-dependent translation. This interaction results in an increase in translation rates of cap-dependent mRNAs, which include those encoding a number of proteins required for cell-cycle progression, such as mRNAs that encode cell-cycle regulator proteins cyclin D and ornithine decarboxylase [24]. This effect on translation of certain regulatory mRNAs may be one means by which mTOR regulates cell growth.

The second target of mTOR is the phosphorylation and activation of S6K1. Previously, activation of S6K1 had been correlated with increased translation of 5′-terminal oligopyrimidine tract (TOP) mRNAs, which encode components of the translational apparatus [25]. However, the requirement for S6K1 activity in translation of TOP-containing mRNAs has been disputed. Recent studies indicate that the translation of TOP mRNAs may occur independently of S6K1 function, as S6K1 activation is insufficient to relieve translational repression of TOP RNAs and complete inhibition of mTOR by rapamycin had only a slight repressive effect on translation of TOP mRNAs [24,26]. These recent studies led to the conclusion that the regulation of TOP translation by growth factors and mitogens is primarily through the PI3K pathway with little role for mTOR [24]. Instead, S6K1 has been implicated in glucose homeostasis and regulation of eukaryotic elongation factor 2 kinase [24]. The exact mechanism(s) by which mTOR regulates translation and cell growth are complex and require further study.

Consistent with its role as a central controller of cellular growth, mTOR activation leads to the phosphorylation of several downstream signalling effectors and transcription factors in addition to its effects on 4E-BP1 and S6K1, which in turn influence cell proliferation, survival and angiogenesis. Of particular note for therapeutics development is that many, although not all, of the protean functions of mTOR appear to be sensitive to inhibition by rapamycin. The additional cellular effects of mTOR include its direct phosphorylation of signal transducer and activator of transcription-3 (STAT3) [27]. Similarly, S6K1 phosphorylation of the transcription factor cAMP response element modulator (CREM) [27,28] is reported to be rapamycin sensitive. mTOR has been reported to regulate autophagy [29,30]. mTOR signalling may also provide an antiapoptotic function; Akt-mediated protection from apoptosis is mediated, at least in part, by mTOR-dependent stabilisation of cell surface amino acid transporters [31], and the proapoptotic protein BAD has been reported to be a substrate of S6K1 [32]. In addition, microarray analysis of RNA isolated from cells deprived of nutrients or treated with rapamycin has demonstrated an important role for mTOR in controlling the expression of genes involved in many metabolic and biosynthetic pathways [33]. Clearly, the biochemical effects of mTOR signalling are multiple, incompletely catalogued, poorly understood and potentially context specific [24]. However, the multitude of cellular signalling processes in which mTOR participates in normal and malignant cells and the inhibition of some of these processes by pharmacological inhibition has contributed to the keen interest in mTOR inhibition as a strategy for development of therapeutics.

3. Mammalian target of rapamycin in human cancer

Although mutations of mTOR have not been reported in human cancers, both aberrant PI3K-dependent signalling and

aberrant protein translation have been identified in a wide variety of malignancies and may contribute to the oncogenesis and malignant progression. For example, components of the PI3K pathway that are mutated in different human tumours include activation mutations of growth factor receptors, amplification and/or overexpression of PI3K and Akt. The resultant aberrant pathway signalling not only leads to a growth advantage during carcinogenesis and stimulates cancer cell proliferation but also contributes to treatment resistance due to a high PI3K–Akt-mediated survival threshold [1]. If such cancer cells are 'addicted' to the growth and survival-signalling effects of the PI3K–Akt pathway, it is possible that this dependency will result in cancer-cell sensitivity to mTOR inhibition [1].

In addition to cancer-cell dependency on aberrant PI3K signalling for proliferation and survival, endothelial cell proliferation may also be dependent on mTOR signalling. Endothelial cell proliferation is stimulated by vascular endothelial cell growth factor (VEGF) activation of the PI3K–Akt–mTOR pathway and, furthermore, VEGF production may be partly controlled by mTOR signalling through mTOR effects on the expression of hypoxia-inducible factor-1α (HIF-1α) [34-36]. HIF-1α is a heterodimeric transcription factor containing an inducibly expressed HIF-1α subunit and a constititutively expressed HIF-1β subunit. Under hypoxic conditions, the HIF-1α subunit accumulates due to a decrease in the rate of proteolytic degradation through the ubiquitin–proteasome pathway. The resulting HIF-1α–HIF-1β heterodimers lead to the transcription of certain gene products, including VEGF. Recent studies suggest that amplified signalling through PI3K and its downstream target, mTOR, enhances HIF-1-dependent gene expression *in vitro* and that this expression is partially sensitive to mTOR inhibition [37]. Therefore, tumour angiogenesis may depend on mTOR signalling in two ways: through hypoxia-induced production of VEGF by tumour and stromal cells, and through VEGF stimulation of endothelial cell proliferation and survival through PI3K–Akt–mTOR pathway. Furthermore, the antitumour effects noted by inhibiting mTOR may be related to antiproliferative effects within tumour cells as well as endothelial cells.

More directly related to mTOR effects on protein translation in cancer cells, aberrantly high rates of protein biosynthesis are observed in tumours [38], and certain tumour suppressors and proto-oncogenes may regulate malignant progression by altering the protein synthesis machinery [39]. For example, signalling through Ras and Akt acts rapidly to increase the association of mRNA transcripts with polyribosomes, and, therefore, may immediately and broadly influence protein translation [40]. In addition, dysregulation of cap-dependent translation through overexpression of eIF-4E confers malignant characteristics and induces cancer by suppressing apoptosis in a breast-cancer model, underscoring the potential of therapeutics that selectively target the Akt–mTOR–eIF-4E pathway [41,42]. Further investigation will be needed to clarify to what extent deregulation of translation of total or specific mRNAs contributes to tumorigenesis. However, deregulated components of the translational machinery, or specific oncoproteins that are overexpressed in cancer cells and that are under mTOR translational control, could be sensitive to mTOR targeted therapy. Thus, mTOR inhibition may lead to the inhibition of malignant progression by altering the translation of multiple proteins including those that control cell size, cell-cycle progression and cell survival as well as angiogenesis.

4. Rapamycin and derivatives

Rapamycin is a macrocyclic lactone produced by *Streptomyces hygroscopicus*, a soil bacterium native to Easter Island (Rapa Nui). Rapamycin possesses fungicidal, immunosuppressive and antiproliferative properties [43]. Because of its ability to suppress lymphocyte activation, rapamycin was developed and received regulatory approval as an immunosuppressant for the prophylaxis of renal allograft rejection. Rapamycin's immunosuppressant effects are due to its inhibition of the biochemical events required for the progression of IL-2-stimulated T cells from G1 to S phase of the cell cycle. However, rapamycin and derivatives temsirolimus, everolimus and AP-23573 also inhibit cellular proliferation in a variety of tumour models, and are currently under clinical evaluation as potential cancer therapeutics. These clinical studies will help to validate mTOR as an anticancer drug target. A review of the mechanisms of action and resistance and a summary of clinical trial results for these agents is described in Section 4.1 – 4.8.

4.1 Mechanism of action

For many years, rapamycin has been used as a pharmacological probe; thus, much is known about its mechanism of action and by inference, if not actual experimentation, about the other agents of this pharmaceutical class. Rapamycin targets the ubiquitously expressed peptidyl-prolyl *cis-trans* isomerase FK506-binding protein of 12 kDa (FKBP12) and the rapamycin–FKBP12 complex binds to the FKBP12–rapamycin-binding (FRB) domain adjacent to the kinase domain of mTOR. The mechanism by which rapamycin inhibits mTOR is unclear. The rapamycin–FKBP12 complex may act by altering the composition and/or conformation of the multi-protein mTOR complexes. By disrupting these protein complexes, rapamycin may impair either upstream signalling leading to mTOR activation or kinase access to downstream substrates [44,45]. Rapamycin and its derivatives share the following features: inhibition of cellular proliferation by inducing G1 phase arrest, induction of apoptosis in selected models and limited normal tissue toxicity.

The antiproliferative effects of rapamycins have been evaluated in numerous *in vitro* and *in vivo* tumour models. Results from these experiments indicate that these agents may inhibit tumour and endothelial cell proliferation in picomolar to nanomolar concentrations, and may add to the cytotoxicity of

other chemotherapeutic agents and radiation [46-51]. The means by which rapamycin induces antiproliferative effects are not completely understood but are associated with the inhibition of transition from G1 to S phase of the cell cycle. Among the reported cellular alterations in the presence of rapamycin include reduction of cyclins, particularly cyclin D [52,53], which would lead to inhibition of cyclin-dependent kinase activity and phosphorylation of retinoblastoma protein (pRb) as well as increases in cyclin-dependent kinase inhibitors $p21^{cip1}$ and $p27^{kip1}$ [54,55]. These observed effects would be consistent with the ability of rapamycin to impede G1 progression.

In most instances, inhibition of mTOR by rapamycin leads to an antiproliferative response. However, there are examples in which rapamycin induces apoptosis of certain cell lines [56,57]. The molecular determinants of the antiproliferative versus apoptotic response of cells after exposure to rapamycins are poorly understood. One proposed trigger for rapamycin-induced apoptosis may depend on the functions of p53, $p27^{cip1}$ and $p27^{kip1}$. In a series of studies, Huang and colleagues reported that rapamycin induced a cellular stress response characterised by rapid and sustained activation of the apoptosis signal-regulating kinase 1 (ASK1) signalling pathway. Selective apoptosis was seen in cells lacking functional p53 or $p27^{kip1}$, and the apoptotic response correlated with and was dependent on 4E-BP1 expression. In contrast, wild-type p53 or $p27^{cip1}$ suppressed the apoptotic response to rapamycin [56-58]. Thus, the antitumour activity of rapamycin may depend on the function of cell-cycle regulatory proteins as well as upstream cellular signalling through mTOR. Based on these laboratory models, the expected clinical activity of rapamycin would be delayed tumour progression rather than tumour regression in most patients with sensitive disease. However, tumour regression through rapamycin-induced apoptosis could occur.

In addition to the effects on tumour cell proliferation, inhibition of mTOR by rapamycin also potently inhibits angiogenesis and endothelial cell proliferation *in vitro* and *in vivo*. Humar and colleagues showed that hypoxia directly enhances dose-dependent induction of DNA synthesis and cellular proliferation by platelet-derived growth factor (PDGF) and basic fibroblast growth factor (bFGF) and rapamycin specifically blocked the increase in proliferation observed under hypoxia in mouse and rat vascular smooth muscle and endothelial cell angiogenesis models [36]. The antiangiogenic properties of rapamycin are also associated with a decrease in VEGF production and a reduction in the response of vascular endothelial cells to stimulation by VEGF [36,59]. *In vitro* studies revealed that rapamycin is capable of blocking the activation of HIF-1 through enhanced degradation of HIF-1α [37]. In summary, there is considerable evidence that rapamycin is antiangiogeneic, and these antiangiogenic effects may be multifold in that the agent inhibits endothelial cell proliferation in the presence of hypoxia, inhibits endothelial cell proliferation to VEGF stimulation through inhibition of mTOR, and decreases VEGF synthesis through enhanced HIF-1α degradation [59-61].

4.2 Determinants of sensitivity and resistance to mammalian target of rapamycin inhibition

Considerable research is underway to identify markers associated with tumour cell sensitivity and resistance to rapamycin. Laboratory studies suggest that genetic mutations and/or compensatory changes leading to aberrant signal transduction, both upstream and downstream of mTOR, influence tumour cell sensitivity to rapamycins [62,63]. Among the described abnormalities in cellular molecules that correlated with rapamycin resistance are mutations of mTOR or FKBP12 that prevent rapamycin from binding to mTOR [62,63]. Although such mutations have been induced in laboratory models, these mutations have not been described in human cancers. Mutations or defects of mTOR-regulated proteins, including S6K1 and 4E-BP1, which impair their interaction with mTOR, also render cells insensitive to rapamycin [62]. Although inhibition of phosphorylation of S6K1, its target ribosomal S6 protein, and 4E-BP1 correlates with rapamycin sensitivity in laboratory models, inhibition of S6K1 and 4E-BP1 is not sufficient to guarantee sensitivity to rapamycin as hypophosphorylation of these mTOR targets has been seen in rapamycin-resistant as well as -sensitive cells [62,64]. Thus, additional factors must mediate cellular dependency on mTOR signalling. Expression and function of ataxia-telangiectasia gene product ATM, as well as 14-3-3, p53, PI3K–Akt and PTEN have been reported to correlate with rapamycin sensitivity [62,63]. Data supporting these last two potential mechanisms of sensitivity will be discussed in greater detail.

There is considerable evidence that aberrant stimulation of the PI3K–Akt signalling pathway in cancer cells may increase the dependency of such tumours on mTOR signalling functions and their sensitivity to signal modulation by inhibiting mTOR [1]. Studies have reported that rapamycin and related compounds exert selective cytostatic/cytotoxic effects on $PTEN^{-/-}$ tumours *in vivo* [65,66]. *In vitro* and *in vivo* studies of isogenic $PTEN^{+/+}$ and $PTEN^{-/-}$ mouse cells, as well as human cancer cells with defined PTEN status. showed that the growth of PTEN null cells was blocked preferentially by mTOR inhibition [65]. However, the loss of PTEN function does not correlate with rapamycin sensitivity in all models. In a series of breast cancer cell lines, overexpression of S6K1 and phosphorylated Akt, independent of PTEN status, was associated with rapamycin sensitivity [64]. As noted in other studies, the differential sensitivity to mTOR inhibition was not explained by differences in biochemical blockade of the mTOR pathway because S6 phosphorylation was inhibited in sensitive and resistant cell lines. Thus, aberrant stimulation of the PI3K–Akt pathway, which may occur through hyperaction growth factor receptor, PI3K, Akt or loss of PTEN may be markers of tumour cell responsiveness to rapamycins.

Loss of functional TSC, as occurs in patients with tuberous sclerosis syndrome (TS), may also confer sensitivity to rapamycins. Although TS-associated tumours are usually benign, they can affect almost every major organ system and

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