

Abstract Rapamycins represent a novel family of anticancer agents, currently including rapamycin and its derivatives, CCI-779 and RAD001. Rapamycins inhibit the function of the mammalian target of rapamycin (mTOR), and potently suppress tumor cell growth by arresting cells in G1 phase or potentially inducing apoptosis of cells, in culture or in xenograft tumor models. However, recent data indicate that genetic mutations or compensatory changes in tumor cells influence the sensitivity of rapamycins. First, mutations of mTOR or FKBP12 prevent rapamycin from binding to mTOR, conferring rapamycin resistance. Second, mutations or defects of mTOR-regulated proteins, including S6K1, 4E-BP1, PP2A-related phosphatases, and p27^{Kip1} also render rapamycin insensitivity. In addition, the status of ATM, p53, PTEN/Akt and 14-3-3 are also associated with rapamycin sensitivity. To better explore the role of rapamycins against tumors, this review will summarize the current knowledge of the mechanism of action of rapamycins, and progress in understanding mechanisms of acquired or intrinsic resistance. © 2002 Elsevier Science Ltd.

Key words: Rapamycin, mTOR, signaling pathways, p27^{Kip1}, drug resistance

INTRODUCTION

Rapamycin, a macrocyclic lactone (Fig. 1), is produced by the soil bacteria *Streptomyces hygroscopicus* that was first found on Easter Island in the South Pacific. A group led by Dr. Suren Sehgal, then senior scientist at Ayerst Research Laboratories in Montreal, Canada, firstly isolated rapamycin from the bacteria and identified it as an antifungal agent.¹⁻³ Soon rapamycin (sirolimus), as a structural analogue of the macrolide antibiotic FK506 (tacrolimus, Prograf[®]) (Fig. 1), was also found to potently suppress the immune system.⁴⁻⁷ When rapamycin was sent to the National Cancer Institute (NCI) for testing, surprisingly, the drug also demonstrated potent inhibitory activity against numerous solid tumors.⁸⁻¹⁰ Whereas the NCI quickly designated rapamycin as a priority antitumor drug Ayerst abandoned it, because at that time company researchers failed to develop a satisfactory intravenous formulation for use in clinical trials. Also at that time, little was known about the mechanism of action of rapamycin in blocking signal transduction. Not until 1988, after Wyeth and Ayerst merged, did studies of rapamycin resume. While solid data convinced Wyeth-Ayerst to develop rapamycin as an immunosuppressant, the NCI and many other laboratories continued to study the antitumor activity of rapamycin. Rapamycin (Rapamune[®]), as an immunosuppressive drug, was finally approved by the Food and Drug

suppressant, but also a potential antiangiogenic agent. Rapamycin can act as a cytostatic, arresting cells in G1 phase or potentially inducing apoptosis in many malignant cells in culture. To date, studies have revealed that rapamycin potently arrests growth of cells derived from rhabdomyosarcoma, neuroblastoma and glioblastoma, small cell lung cancer,¹¹⁻¹⁷ osteosarcoma,¹⁸ pancreatic cancer,^{19,20} breast and prostate cancer,²¹⁻²³ murine melanoma and leukemia, and B-cell lymphoma.^{9,24-26}

However, direct use of rapamycin as an anticancer drug is clinically impractical, because of its poor water-solubility and stability in solution. Recently, two rapamycin ester analogues (Fig. 1), CCI-779 [rapamycin-42, 2, 2-bis(hydroxymethyl)-propionic acid] (Wyeth-Ayerst, PA, USA) and RAD001 [everolimus, 40-O-(2-hydroxyethyl)-rapamycin] (Novartis, Basel, Switzerland), with improved pharmaceutical properties have been synthesized and evaluated. CCI-779 is designed for intravenous injection, whereas RAD001 for oral administration. Both have similar antitumor effects as rapamycin,^{17,21-23,27-30} and are currently being developed as antitumor agents and undergoing phase I/II clinical trials. So far, preclinical results have revealed that rapamycin and its derivatives (designated here as rapamycins) suppress growth of numerous human tumor cells in vitro, and in some human and murine tumor models in vivo.¹¹⁻³⁰ When combined with other chemotherapeutic agents, rapamycins generally show at least additive antitumor activity.^{10,12,17,31} Preliminary data from clinical trials have indicated that rapamycins are well tolerated and successfully suppress growth of various human tumors.³²⁻³⁴ However, increasing evidence has suggested that genetic mutations or compensatory changes in tumor cells may affect the sensitivity of rapamycins. For instance, mutations of the mammalian target of rapamycin (mTOR) or FKBP12 prevent rapamycin from binding to mTOR and confer rapamycin resistance. Mutations or defects of mTOR-controlled downstream effector molecules, such as S6K1, 4E-BP1, PP2A-related phosphatases, and p27^{Kip1}, also render rapamycin insensitivity. At least in some systems the status of ATM, p53, PTEN/Akt and 14-3-3 also determines rapamycin sensitivity. This review will summarize the current knowledge of action mechanism of rapamycins, and resistance mechanisms.

MECHANISM OF ACTION OF RAPAMYCINS

Rapamycins represent a novel family of anticancer agents, currently including rapamycin and its derivatives, CCI-779 and RAD001. Rapamycins share a common mechanism of antitumor action. Simply, they inhibit the function of mTOR that links mitogen stimulation to protein synthesis and cell cycle progression, and potently suppress tumor cell growth by arresting cells in G1 phase, potentially inducing apoptosis of cells.

mTOR and its inhibition by rapamycin

The mammalian target of rapamycin, mTOR [also designated FRAP (FKBP12 and rapamycin-associated protein), RAFT1

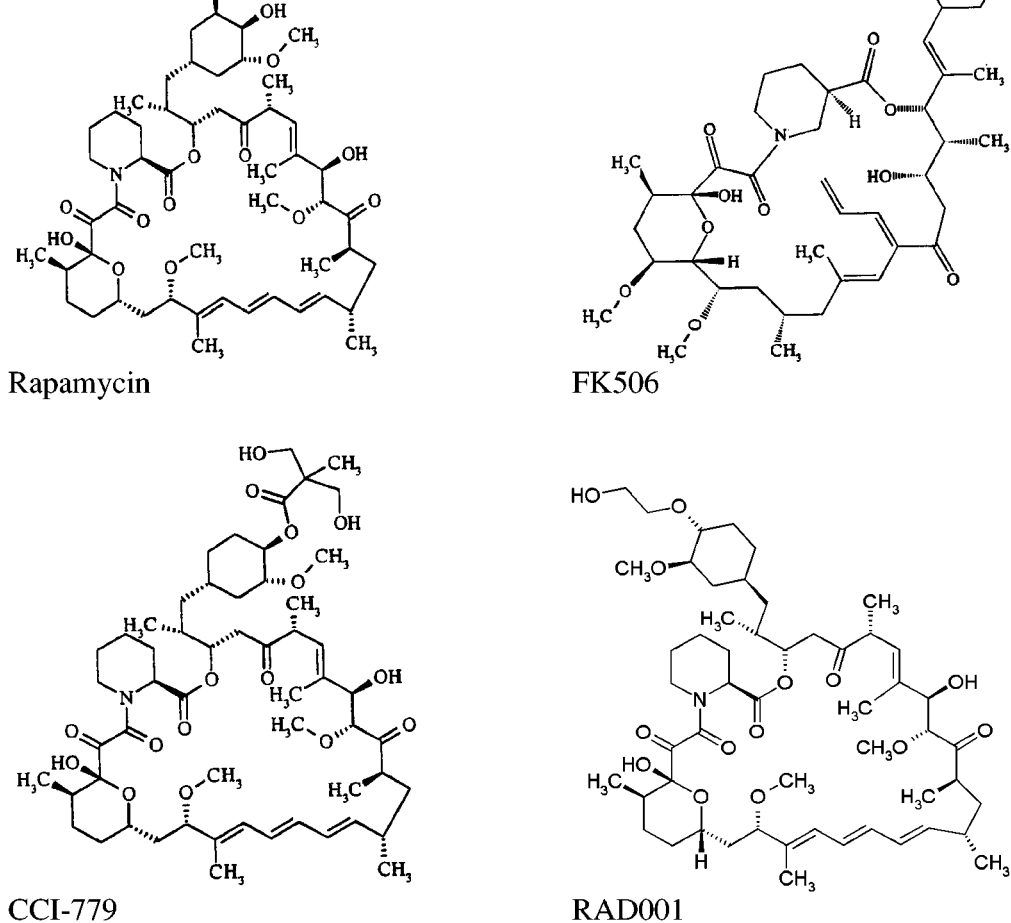


Fig. 1 Structures of rapamycin, FK506, and two rapamycin analogues in clinical trials, CCI-779 and RAD001.

(rapamycin and FKBP12 target 1), RAPT1 (rapamycin target 1) or SEP (sirolimus effector protein)], was identified as a 289 kDa serine/threonine kinase from mammalian cells.³⁵⁻³⁸ According to Genebank database, TOR proteins are evolutionarily conserved from yeast to human beings in the catalytic domain. In the yeasts, *Saccharomyces cerevisiae* and *Schizosaccharomyces pombe*, two TOR genes, designated TOR1 and TOR2, have been cloned, both sharing 67% homology and encoding ~280 kDa proteins.³⁹⁻⁴¹ In the fruit fly, *Drosophila melanogaster*, a single TOR orthologue, termed dTOR, has been characterized, sharing 38% identity with TOR2 from *Sac-*

charomyces cerevisiae.^{42,43} Mammalian TOR (mTOR) shares ~45% identity with TOR1 and TOR2 from the yeast *Saccharomyces cerevisiae*, and 56% identity with dTOR in overall sequence.^{44,45} Human, mouse and rat mTOR proteins share 95% identity at the amino acid level.^{46,47} Structurally, mTOR is composed of a catalytic kinase domain, FRB (FKBP-rapamycin binding) domain and a putative auto-inhibitory domain ("repressor domain") near C-terminus, and up to 20 tandemly repeated HEAT (Huntingtin, EF3, A subunit of PP2A and TOR) motifs at the N-terminus, as well as FAT (FRAP-ATM-TRAPP) and FATC (FAT C-terminus) domains (Fig. 2).^{47,48} Since the

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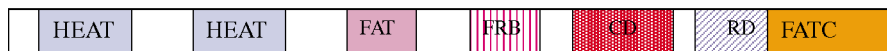


Fig. 2 Schematic representation of the domains of mTOR. Structural domains of mTOR. HEAT: (huntingtin elongation A subunit TOR) repeats (positions 71-522 and 628-1147); FAT: (FRAP-ATM-TRAPP) domain, which is unique to PIK-related kinases located N-terminal to the FKBP12-rapamycin binding domain (FRB); the role of FAT sequences is less clear, but they are associated with C-terminal FAT (FATC) sequences in mTOR Interaction between FAT and FATC domains may facilitate protein binding or act as a structural scaffold; CD: Catalytic domain; RD: regulatory domain.

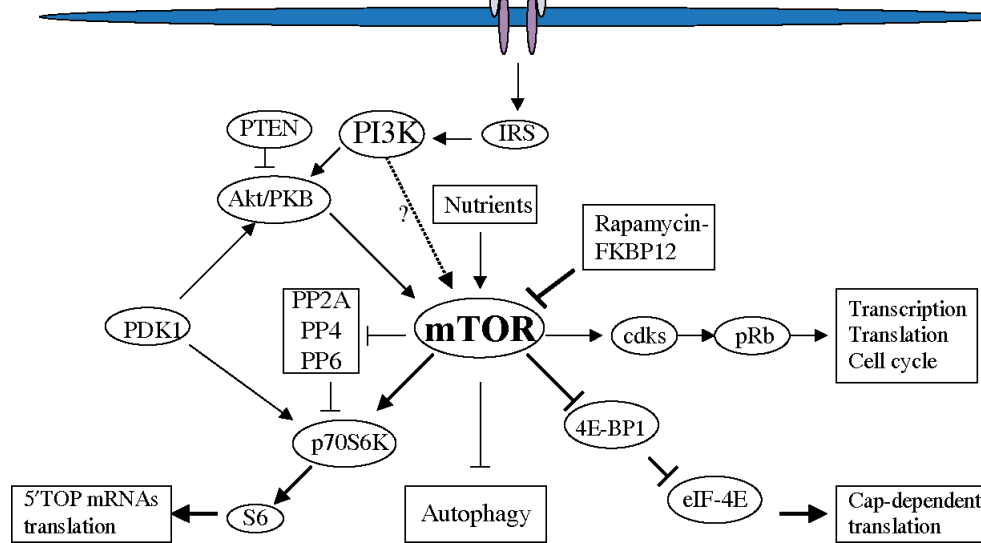


Fig. 3 Scheme of the mTOR signaling pathway. Arrows represent activation, whereas bars represent inhibition. IRS, insulin receptor substrates; PI3K, phosphatidylinositol 3' kinase; PIP₂, phosphatidylinositide (4,5)-P₂; PIP₃, phosphatidylinositide (3,4,5)-P₃; PTEN, phosphatase and tensin homologue deleted on chromosome ten; PDK1, phosphoinositide-dependent protein kinase I; Akt/PKB, protein kinase B; rapamycin-FKBP12, rapamycin-FK506-binding protein 12 complex; mTOR, mammalian target of rapamycin; pRb, retinoblastoma protein; Pol I/II/III, RNA polymerase I/II/III; 4E-BP1, eIF-4E-binding protein I; eIF-4A/4E/4F/4G/3, eukaryotic initiation factor-4A/4E/4F/4G/3; S6K1, p70 S6 kinase; S6, 40S ribosomal protein; 5'TOP, 5'-terminal oligopyrimidine.

C-terminus of mTOR is highly homologous to the catalytic domain of phosphatidylinositol 3 kinase (PI3K), mTOR is considered a member of PI3K-related kinase family (designated PIKK), which also includes MEC1, TEL1, RAD3, MEI-41, DNA-PK, ATM, ATR, and TRRAP.^{47,49} Both PI3K and, potentially, Akt/PKB lie upstream of mTOR, whereas two translational components, ribosomal p70S6 kinase (S6K1) and eukaryotic translation initiation factor-4E (eIF4E) binding protein 1 (4E-BP1), are the best characterized downstream effector molecules of mTOR (Fig. 3). However, the full spectrum of cellular events controlled by mTOR extends beyond these pathways. Increasing evidence has implicated mTOR as a sensor that integrates extracellular and intracellular events, coordinating growth and proliferation. mTOR may directly or indirectly regulate translation initiation, actin organization, membrane traffic and protein degradation, protein kinase C signaling, ribosome biogenesis and tRNA synthesis, as well as transcription.⁴⁷ Recent results suggest that mTOR may also sense cellular ATP levels, suppressing protein synthesis when ATP levels decrease.⁵⁰

Rapamycins are specific inhibitors of mTOR. Although rapamycin and FK506 are both potent immunosuppressive agents, their mechanisms of action are quite different. Both rapamycin and FK506 competitively binds to a *M_r* 12,000 cytosolic protein termed FK-binding protein (FKBP-12). The FKBP-FK506 complex inhibits calcineurin, preventing dephosphorylation, nuclear translocation of NF-ATp, and activation of interleukin 2 transcription.⁴⁶ The FKBP-rapamycin complex binds to the FRB domain of mTOR, resulting in inhibition of

the function of mTOR. The specific binding of rapamycin has been confirmed by studies of genetic mutations of mTOR and FKBP12 (see review below for details). Currently, a major unresolved issue is how rapamycin inhibits the function of mTOR. As we know, many small molecule kinase inhibitors reduce the activity of kinases by direct competition for ATP binding, thus preventing ligand-induced autophosphorylation and signaling. However, whether rapamycin or FKBP-rapamycin complex directly inhibits the kinase activity of mTOR is controversial. FKBP-rapamycin complex inhibited autokinase activity of mTOR in vitro at high concentration (500 nM).⁵¹ Rapamycin in vitro also blocked the modest insulin-induced increase of kinase activity of immunoprecipitated mTOR.⁵² However, treatment of cells with rapamycin did not alter autophosphorylation level of Ser2481, and had little or no effect on the kinase activity of immunoprecipitated mTOR.^{42,45,53} Possibly, mTOR may repress a phosphatase activity associated with downstream targets. Binding of FKBP-rapamycin complex to mTOR may first result in de-repression of this phosphatase, which then dephosphorylates downstream effector molecules, e.g. S6K1^{54,55} and p44/42 MAP kinases (our unpublished data).⁵⁶ More recently, phosphatidic acid has been identified as a critical component of mTOR signaling, and its binding to mTOR is necessary for activation of mTOR downstream effector molecules.⁵⁷ It is also possible that FKBP-rapamycin complex may compete with phosphatidic acid to bind the FRB domain of mTOR, preventing mTOR from activating downstream effectors although without inhibiting mTOR's catalytic activity.⁵⁷ Alternatively, mTOR may act as a scaffold

Rapamycin signaling pathways mediated by mTOR

As mentioned above, 4E-BP1 and S6K1 are the best characterized downstream effector molecules of mTOR (Fig. 3). Both are translational components. 4E-BP1 functions as a suppressor of eIF4E. In response to mitogens, six sites (Thr37, Thr46, Ser65, Thr70, Ser83, and Ser112) of 4E-BP1 (also termed PHAS-I) can be phosphorylated.⁵⁸ So far, only mTOR and ATM have been identified to be involved in phosphorylation of 4E-BP1.⁵⁹⁻⁶² Little is known whether other kinases participate in phosphorylation of 4E-BP1. ATM phosphorylates 4E-BP1 at Ser112,⁶² whereas mTOR in vitro selectively phosphorylates 4E-BP1 at two and possibly four Ser/Thr residues (Thr37, Thr46, Thr70 and Ser65) in the N-terminal region.^{61,63} 4E-BP1 phosphorylation is a hierarchical process.^{61,63-65} Phosphorylation of Thr37/Thr46 is followed by Thr70 phosphorylation, and Ser65 is phosphorylated last.⁶⁵ Phosphorylation of Ser65 depends on phosphorylation of all three Thr/Pro sites,^{63,64} whereas mutations of Thr37 and/or Thr46 to alanine(s) prevents phosphorylation of Ser65 and Thr70, suggesting that phosphorylation of Thr37 and Thr46 serves as a requisite 'priming' event.⁵⁵ Single phosphorylation of above residues is not sufficient to dissociate 4E-BP1 from eIF4E, indicating that a combined phosphorylation of at least Thr37, Thr46, Ser65, and Thr70 in 4E-BP1 is essential to suppress association with eIF4E.^{55,66} In the presence of rapamycin, 4E-BP1 becomes hypo-phosphorylated and associates with eIF4E. This prevents binding of eIF4E to the scaffold protein eIF4G and formation of the eIF4F initiation complex required for cap-dependent translation of mRNA. As a result, rapamycin may downregulate mTOR-controlled synthesis of essential proteins involved in cell cycle progression, such as cyclin D1,^{67,68} and ornithine decarboxylase,⁶⁹ and survival (c-MYC).⁷⁰

S6K1 is the other well documented downstream target of mTOR. To date, two ribosomal p70S6 kinases have been identified: S6K1 and S6K2, and both can be inhibited by rapamycin.^{71,72} S6K1 contains a nuclear localization signal domain at the N-terminus, followed by an acidic domain, a catalytic domain, a regulatory domain, an auto-inhibitory domain and C-terminal domain.⁷³ Activation of S6K1 is a complex process that involves the interplay between four different domains and at least seven specific sites mediated by multiple upstream kinases.⁷³ It has been reported that at least 12 sites (Ser17, Thr229, Thr367, Thr371, Thr389, Ser404, Ser411, Ser418, Thr421, Ser424, Ser429, and Thr447) can be phosphorylated in response to serum stimulation.⁵⁸ However, the kinases responsible for the phosphorylation of these sites are not fully characterized. Phosphoinositide-dependent protein kinase 1 (PDK1) phosphorylates Thr229 in vitro and in vivo.⁷⁴ Atypical PKC isoforms and the Rho family of small G proteins (cdc42 and Rac1) may partially contribute to phosphorylation of S6K1⁵⁸, but the specific sites regulated by these kinases remain to be determined. In vitro, mTOR phosphorylates only Thr389 in the regulatory domain.⁷⁵⁻⁷⁷ However, whether this phosphorylation is directly or indirectly regulated by mTOR is in question, since recent data suggest that mTOR may regulate

Ser/Thr-Pro sites in the auto-inhibitory domain, which then cooperates with the N-terminus to allow phosphorylation of Thr389. This presumably disrupts the interaction of the C-terminus with the N-terminus, allowing phosphorylation of Thr229 and resulting in S6K1 activation.⁷³ As phosphorylation of Thr389 is a primary event for phosphorylation of other sites, in vivo rapamycin may affect phosphorylation of more sites, including Thr229 in the catalytic domain, and Ser404 in the regulatory domain.⁷⁵ S6K1 functions to increase translation of mRNA species with 5' terminal oligopyrimidine (5'TOP) tracts. These mRNAs primarily code for ribosomal proteins and other elements of the translational machinery, such as ribosomal proteins, elongation factors, the poly(A) binding proteins,⁷² and IGF-II.⁷⁸ Therefore, inhibition of mTOR by rapamycin primarily downregulates translation of 5'TOP-containing mRNAs.

In addition to inhibition of translation of specific mRNAs through 4E-BP1 and S6K1 pathways, rapamycin may also suppress RNA polymerase (Pol) I/II/III-mediated transcription and translation by decrease of mTOR-controlled phosphorylation of retinoblastoma protein (pRb).⁶⁶ Furthermore, rapamycin may also inhibit activation of G1 cyclin-dependent kinases (cdks) causing hypophosphorylation of pRb protein, and slow or arrest cell cycle transition from G1 to S-phase.⁷⁹ The mechanism by which rapamycin inhibits activity of cdks may be cell type dependent, either by upregulation of cdk inhibitors, or downregulation of cyclins or cdks, or inhibition of association of cyclin-cdks. For example, in T lymphocytes, rapamycin increases the level of cdk inhibitory protein p27^{Kip1} by prevention of its degradation induced by mitogens.^{80,81} Involvement of p27^{Kip1} being an effector of rapamycin-induced G1 cell cycle arrest is strengthened by the observation that p27^{Kip1} deficient T lymphocytes or fibroblasts are relatively resistant to rapamycin inhibition of growth.⁸² In NIH3T3 cells rapamycin may inhibit the G1 to S transition through inhibition of cdks by decrease of the cyclin D1 mRNA level and protein stability,⁶⁸ or delay of the expression of cyclin A.⁸³ In vascular smooth muscle cells, growth factors elevate the levels of cell cycle proteins, such as cyclins (D1, E, B) and cdks (cdk1 and cdk2), whereas rapamycin blocks the upregulation of these proteins, but not mRNA, and arrests the cells before S phase.⁸⁴ In contrast to findings in other cell types, in vascular smooth muscle cells rapamycin does not affect growth factor-induced downregulation of p27^{Kip1}.⁸⁴ In MG-63 human osteosarcoma cells, rapamycin inhibits cdk activity and cyclin D1-cdk association during early G1.⁸⁵ Similarly, in T lymphocytes, rapamycin also blocks activation of cdk1 (p34^{cdc2}) and cdk2 (p33^{cdc2}) by inhibition of cyclin A expression, and formation of active cyclin A-cdk1/2 complexes and cyclin E-cdk2 complex, resulting in late G1 arrest.⁸⁶

MECHANISMS OF RESISTANCE TO RAPAMYCINS

As observed by Dilling et al.¹¹ various cell lines exhibit several thousand-fold differences in their intrinsic sensitivity to rapamycin under similar growth conditions. Further studies indicate that the response to rapamycin is different

or without mutagenesis. Obviously, the mechanisms of rapamycin resistance are complicated and multiple, some of which have been identified whereas others remain to be determined. Reported mechanisms of rapamycin resistance are summarized below.

Mutations in FKBP12 and mTOR

As aforementioned, rapamycin has a specific mode of action. It cannot directly bind to mTOR. It first has to bind to FKBP-12 in mammalian cells, forming the FKBP-rapamycin complex. This complex then interacts with the FRB domain in mTOR (Fig. 2), and inhibits the function of mTOR. Therefore, during such sequential interactions, either specific mutations in FKBP12 that prevent the formation of FKBP-rapamycin complex, or certain mutations in the FRB domain of mTOR that block binding of FKBP-rapamycin complex to mTOR would finally abrogate the effect of rapamycin on mTOR, causing rapamycin resistance. Such mutations were first found in yeast. For example, *S. cerevisiae* treated with rapamycin irreversibly arrested in the G1 phase. A mutational screen identified rapamycin-resistant alleles with mutations in genes designated TOR1 and TOR2. Strains with mutated to TOR1-1 (Ser1972 → Arg) and TOR2-1 (Ser1975 → Arg), were completely resistant to the growth-inhibitory effect of rapamycin. These resistant alleles encode mutant TOR proteins that lack the ability for FKBP-rapamycin complex binding.⁸⁷⁻⁹² The results suggest that a conserved serine residue (Ser1972 in TOR1; Ser1975 in TOR2) in yeast TOR proteins is critical for FKBP-rapamycin binding. In mammalian cells, resistance to rapamycin selected after mutagenesis is related to a dominant phenotype also consistent with mutation in the FRB domain of mTOR,⁹³ that results in decreased affinity for binding of the FKBP-rapamycin complex. Expression of a mutant mTOR (Ser2035 → Ile), having reduced affinity for binding the FKBP-rapamycin complex, confers high level resistance.^{14,93,94} Alternatively, in the yeast *S. cerevisiae*, deletion of the RBP1 gene, a homologue of mammalian FKBP-12, resulted in a recessive rapamycin resistance, whereas expression of RBP1 restored rapamycin sensitivity.⁸⁷ This observation has been further confirmed by RBP1 disruption experiments using the pathogenic yeast *Candida albicans*, in which the wild-type RBP1/RBP1 parental strain and the *rbp1*/RBP1 heterozygous mutant were sensitive to rapamycin inhibition, whereas *rbp1*/*rbp1* homozygous mutant was rapamycin resistant.⁹⁵ In addition, in *S. cerevisiae* mutation of a specific residue (Tyr89) which is conserved in RBP1 or FKBP, also resulted in decreased binding of rapamycin and conferred a recessive resistance phenotype.⁹⁶ In murine mast cells, two distinct point mutations in FKBP12, one altering a hydrophobic residue within the drug-binding pocket (Trp59 → Leu) and the other changing a charged surface residue (Arg49 → Gln), substantially reduced binding affinity of FKBP12 for rapamycin, rendered rapamycin resistance.⁹⁷

Mutations in S6K1

As described above, S6K1 is a principal downstream effector of mTOR. So far, data have revealed that rapamycin primarily

phosphorylation of more sites, including Thr229 in the catalytic domain, and Ser404 in the regulatory domain.⁷⁵ Therefore, site mutation of Thr389 → Glu abrogates the ability of rapamycin to inhibit S6K1 activation.^{72,75} Similarly, substitution of Thr229 by either a neutral amino acid Ala (Thr229 → Ala) or by an acidic amino acid Glu (Thr229 → Glu), renders S6K1 insensitive to rapamycin.⁹⁸ In addition, deletion of the 77 N-terminal codons (Δ N77) conferred rapamycin resistance.⁹⁹ It turns out that truncation of the first 54 residues of N-terminus (otherwise identical to Δ N77 above) blocked the serum-induced phosphorylation of three rapamycin-sensitive sites, Thr229, Thr389 and Ser404, causing rapamycin insensitivity.⁷⁵ Whether this results in resistance to the growth inhibitory effect of rapamycin is less clear, and may be cell context specific.

De-regulation of eIF4E

Besides S6K1, 4E-BP1, the suppressor of eIF4E, has been widely recognized as the other primary downstream effector of mTOR.⁵⁵ Recently, our group has found that acquired resistance to rapamycin was associated with decreased levels of 4E-BP1 (Dilling et al. submitted).¹⁰⁰ Briefly, rapamycin-resistant cell lines, Rh30/Rapa10K and C2 clones, were obtained by continuously culturing Rh30 parental cells in the presence of increasing concentrations of rapamycin, without prior mutagenesis. In the absence of selective pressure, resistance was unstable. Within 10 weeks after rapamycin was withdrawn from the medium, resistant clones reverted to being sensitive to growth inhibition of rapamycin. The molecular basis of rapamycin resistance in this case has been investigated. It turns out that in Rh30/Rapa10K and C2 cells, the levels of the suppressor protein 4E-BP1 bound to eIF4E were significantly lower (~10-fold), as were total cellular levels of 4E-BP1. However, mRNA levels of 4E-BP1 were unaltered, indicating post-translational regulation. Further studies indicate that the synthesis of 4E-BP1 did significantly decrease in rapamycin-resistant clones, but whether the steady state level of 4E-BP1 is also regulated by increased degradation remains to be determined. Thus, the changes in 4E-BP1 levels are reminiscent of those reported for p27^{Kip1} in BC3H cells.⁸² In cells (Rh30/Rapa10-revertant) that reverted to sensitive to rapamycin, total levels of 4E-BP1 became similar to those in parental cells, and 4E-BP1 bound to eIF4E had similar response to serum starvation and IGF-I stimulation as found in parental cells. In contrast, no significant changes were detected for S6K1 levels or activity between parental and resistant clones. Activation of S6K1 was equally inhibited in parental and rapamycin-resistant clones. Both Rh30/Rapa10K cells and Rh30/Rapa10K-revertant cells exhibited elevated c-MYC levels, and increased anchorage-independent growth, indicating that inhibition of c-MYC translation by rapamycin is not critical in determining rapamycin sensitivity. These data suggest that decrease of 4E-BP1 expression results in de-regulation of eIF4E, conferring rapamycin resistance.

According to the above findings, rapamycin-regulated eIF4E pathway is crucial in inducing growth arrest, and de-regulation of eIF4E may facilitate malignant phenotype. This

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