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Review

Rapamycins

Mechanism of Action and Cellular Resistance

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ABSTRACT

Rapamycins are macrocyclic lactones that possess immunosuppressive, antifungal and antitumor properties. The parent compound, rapamycin, is approved as an immunosuppressive agent for preventing rejection in patients receiving organ transplantation. Two analogues, CCI-779 and RAD001 are currently being investigated as anticancer agents. Rapamycins first bind a cyclophilin FKBP12, and this complex binds and inhibits the function of mTOR (mammalian target of rapamycin) a serine/threonine (Ser/Thr) kinase with homology to phosphatidylinositol 3′ kinase. Currently, as mTOR is the only identified target, this places rapamycins in a unique position of being the most selective kinase inhibitor known. Consequently these agents have been powerful tools in elucidating the role of mTOR in cellular growth, proliferation, survival and tumorigenesis. Increasing evidence suggests that mTOR acts as a central controller sensing cellular environment (nutritional status or mitogenic stimulation) and regulating translation initiation through the eukaryotic initiation factor 4E, and ribosomal p70 S6 kinase pathways. Here we review the conserved TOR signaling pathways, conceptual basis for tumor selectivity, and the mechanisms of resistance to this class of antitumor agent.

INTRODUCTION

Rapamycin, a macrocyclic lactone product of the soil bacteria *Streptomyces hygroscopicus*, was isolated and identified as an antifungal agent in the mid-1970's.[1-3] Rapamycin (sirolimus), is a structural analogue of the macrolide antibiotic FK506 (tacrolimus, Prograf®) (Fig. 1), and like FK506 was found to potently suppress the immune system.[4-7]

The potential for rapamycin to act as an antitumor agent was recognized early in its development when the drug demonstrated potent inhibitory activity against numerous solid tumors in the NCI screening program.[8-10] However, the drug was not developed further due to stability and solubility problems that prevented development of a parenteral formulation for use in clinical trials. Also at that time in the early 1980's, the mechanism of action of rapamycin in blocking signal transduction was not understood.

Rapamycin (Rapamune®), as an immunosuppressive drug, was finally approved by the Food and Drug Administration (FDA) in the USA in 1999, and the European Commission in 2000, respectively. Results from many laboratories have demonstrated that rapamycin, in contrast to FK506, is not only a potent immunosuppressant, but also an active antitumor agent. Rapamycin can act as a cytostatic, slowing or arresting cells in G_1 phase. Under specific conditions, or in some tumor cell lines rapamycins may induce apoptosis 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] osteoscarcoma,[18] pancreatic cancer,[19,20] breast and prostate cancer,[21-23] murine melanoma and leukemia, and B-cell lymphoma.[9,24-26] In addition to broad spectrum activity in vitro, rapamycin and its derivatives (designated here as rapamycins) suppress growth of 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]

The use of rapamycin as an anticancer drug is clinically impractical, because of its poor water-solubility and stability in solution. Recently, 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), have entered clinical trials. These analogues have improved pharmaceutical properties. CCI-779 is being developed for both intravenous and oral administration, whereas RAD001 is only for oral administration. The antitumor activity of these analogues

is similar to that of rapamycin.[17,21-23,27-30] RAD001 is in Phase I trials whereas the development of CCI-779 is more advanced with several Phase II trials completed.

Why should it be anticipated that rapamycins could exhibit tumor-selectivity, in a manner analogous to the activity of another kinase inhibitor, Gleevec, in Bcr-Abl expressing chronic lymphocytic leukemia? Accumulating evidence suggests that genetic mutations or compensatory changes in tumor cells may affect sensitivity to rapamycins. At least in some systems mutations that occur frequently in malignant transformations such as *GLI* amplification, or mutations that inactivate p53, and the dual specificity phosphatase PTEN (phosphatase and tensin homolog deleted on chromosome ten, also known as MMAC1 for mutated in multiple advanced cancers) or lead to activation of Akt appear to determine rapamycin sensitivity. On the other hand there may be multiple loci that confer intrinsic or acquired resistance. This review will summarize the current knowledge of the role of mTOR in cellular regulation, the mechanism of action of rapamycins, and currently understood resistance mechanisms.

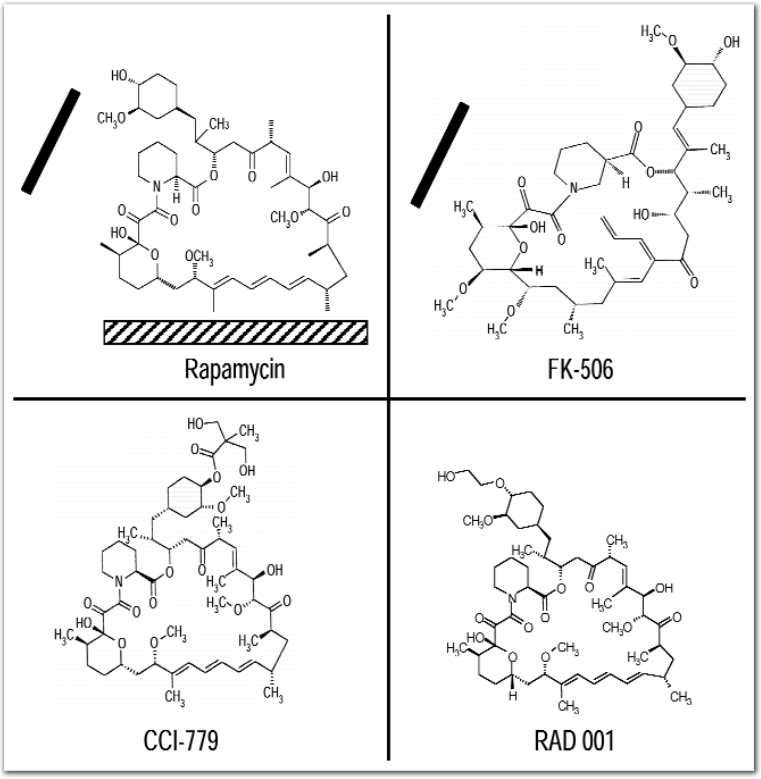

Figure 1. The structure of rapamycin and its analogues FK506, CCI-779 and RAD001. The FKBP12 binding face is shown by the filled bars, whereas the mTOR binding face of rapamycin is shown by the hatched bar.

THE RAPAMYCIN TARGET (MTOR)

The mammalian target of rapamycin, [also named FKBP12 and rapamycin-associated protein (FRAP), rapamycin and FKBP12 target 1 (RAFT1), rapamycin target 1 (RAPT1), or sirolimus effector protein (SEP)], is a 289 kDa Ser/Thr kinase orthologue of TOR1 and TOR2 in *Saccharomyces cerevisiae*.[35,36] TOR is an atypical serine/threonine kinase highly conserved from yeast to mammals. Human, mouse and rat mTOR proteins share 95% identity at the amino acid level.[36-38] Since the C-terminus of TOR is highly homologous to the catalytic domain of phosphatidylinositol 3′ kinase (PI3K), mTOR is considered to belong to the PI3K-related protein kinase (designated PIKK) family, which also includes Mec1, Tel1, RAD3, MEI-41, DNA-PK, ATM, ATR, and TRRAP.[36,37] Recently, single TOR homologs have also been identified in fungi (TOR1 in *Cryptococcus neoformans*), plants (AtTOR in *Arabidopsis thaliana*), worms (CeTOR in *Caenorhabditis elegans*), and flies (dTOR in *Drosophila menalogaster*).[37]

The domain structure of mTOR is depicted in Figure 2. The protein consists of a catalytic kinase domain, an FKBP12-rapamycin binding (FRB) domain and a putative auto-inhibitory domain ("repressor domain") near the 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-TRRAP) and FATC (FAT C-terminus) domains. HEAT motifs may serve as protein-protein interaction parts, whereas FAT and FATC domains may participate in modulation of catalytic kinase activity of mTOR.[36] The remarkable conservation of mTOR at the amino acid level suggests that multiple domains of this protein are essential for its cellular functions.

Tor Signaling in Yeast. In yeast, Tor kinase activity is regulated by availability of nutrients (amino acids and glucose), whereas in mammalian cells, mTOR is regulated also by phosphatidic acid, ATP, and growth factors.[37,39-42] The Tor signaling pathway in yeast is depicted in Figure 3, and controls translation initiation, protein turnover, transcription, and actin cytoskeleton organization. In yeast these pathways have been rigorously established,[37] and are at least in part maintained in mammalian cells. The Tor1/2 complex (designated TORC1) comprising Kog1 (the yeast homologue of the mammalian protein raptor) and Lst8 controls translation, protein stability and transcription,[43-45] whereas the TORC2 complex controls actin organization. As TORC2 is not a rapamycin target it will not be considered further. The evolutionarily conserved TORC1 complex controls translation initiation probably through activation of eIF4E, and transcription of ribosomal genes, stress response genes, ribosomal biogenesis and tRNA synthesis.

Tor, through the TORC1 complex, controls protein turnover and some aspects of transcription through regulation of protein phos-

Figure 2. Schematic representation of the domains of mTOR. Structural domains of mTOR. HEAT :(huntingtin elongation factor A subunit of PP2A and 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.

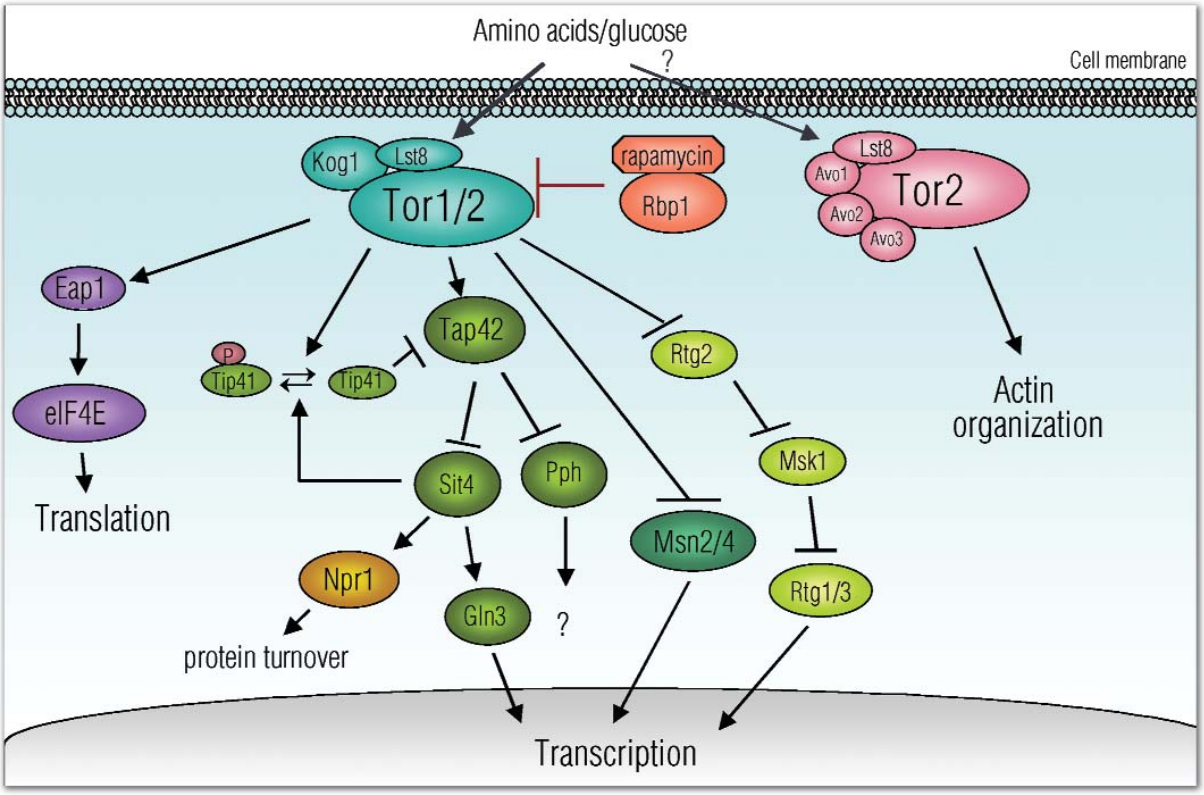

Figure 3. Nutrient signaling in yeast. (Adapted from Jacinto and Hall.[37])

phatases. Tor positively regulates Tap42, which binds to and inactivates the Sit4 and Pph protein phosphatases.[46,47] Pph21 and Pph22 are calaytic subunits of PP2A, and Sit4 is the catalytic subunit of a PP2A-related phosphatase in yeast. Nutrient deficiency or rapamycin leads to dissociation of these phosphatases from Tap42, resulting in increased phosphatase activity. This leads to dephosphorylation of Npr1 and Gln3 involved in protein turnover and transcription, respectively. Control of protein turnover and some aspects of transcription appear to be regulated through Tap42 binding and inactivating Sit4, whereas pathways regulated by release of Pph phosphatases are less well defined. In the presence of nutrients Tor signaling represses autophagy and leads to stabilization of proteins by suppressing ubiquitin-dependent degradation.[48] For example, Tor signaling prevents ubiquitylation, vacuolar targeting and degradation of the tryptophan transporter Tat2 by maintaining phosphorylation and inactivation of Npr1 a putative Tat2 kinase.[49,50] Under conditions of starvation Sit4 becomes activated leading to dephosphorylation of Npr1 and degradation of Tat2. The Tap42-Sit4 pathway also controls the Gln3 transcription factor. Under nutrient replete conditions Gln3 is phosphorylated and is bound to the Ure2 protein in the cytoplasm. Inhibition of Tor by rapamycin or nitrogen starvation leads to dephosphorylation of Gln3, its nuclear translocation and transcription of genes required for the use of secondary nitrogen sources.[43,44] The pathway(s) downstream of Tap42 involving Pph are less clear. Similarly, Tor negatively regulates the heterodimeric transcription factor Rtg1-Rtg3 through an unknown mechanism.[51] The Tor pathway also is important in control of stress-responses through modulation of transcription. The TORC1 complex negatively controls transcription of stress-responsive genes through the cytoplasmic sequestration of the general stress transcription factors Msn2 and Msn4. Although the mechanism is not fully understood this may occur through Tor signaling promoting the binding of these transcription factors to the 14-3-3 homologues Bmh1 and Bmh2.[50]

Proximal Signaling in Mammalian Cells. In mammalian cells, mTOR is regulated not only by nutrients but also by growth factors.[37,39-42] It appears that growth factors regulate mTOR signaling through both PI3K and Akt pathways, whereas proximal activators regulated by nutrients and ATP are less well characterized. In mammalian cells mTOR is activated as a consequence of ligand binding to various growth factor receptors that result in activation of PI3K, Figure 4. Activated PI3K catalyzes the conversion of phostidylinositol (4,5)-bisphosphate (PIP2) to phosphatidylinositol-3,4,5-trisphosphate (PIP3). This pathway is negatively regulated by a dual-specificity protein and lipid phosphatase PTEN. Full activation of Akt, downstream of PI3K requires binding of PIP3 to the pleckstrin homology domain of Akt, and phosphorylation by phosphoinositide-dependent kinases 1/2 (PDK1/2) and other unidentified kinases. Pharmacological studies with albeit relatively non-specific inhibitors of PI3K (wortmannin and LY294002) indicate that mTOR is downstream of PI3K. How mTOR is regulated by PI3K or Akt, however, is still not well understood. Akt can phosphorylate mTOR (Ser2448) directly, although the significance remains to be determined.[37,38] Recent studies have placed the tuberous sclerosis (TSC1/2) complex as a modulator between PI3K/Akt and mTOR.[52-54] The TSC1/2 complex comprises harmartin (TSC1) and tuberin (TSC2). These proteins form a physical and functional complex in

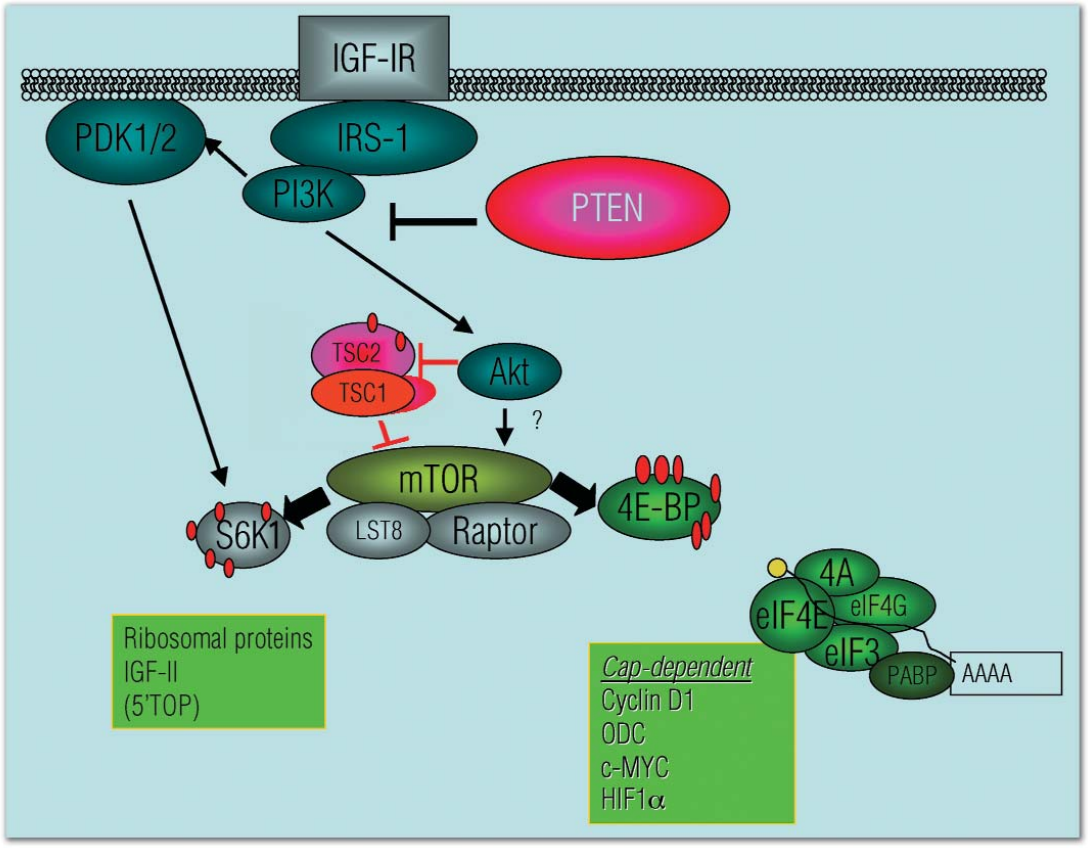

Figure 4. Growth factor signaling in mammalian cells.

vivo, which binds and inhibits mTOR.[52-54] Loss of TSC1/2 results in mTOR-dependent increase of ribosomal p70 S6 kinase (S6K1) activity, and confers resistance of cells to amino acid starvation.[53] Conversely co-expression of TSC1 and TSC2 inhibits amino acid-induced activation of S6K1 in nutrient-deprived cells.[54] Mitogenic stimuli, such as insulin or serum, activate Akt which can directly phosphorylate TSC2 on multiple sites in vitro and in vivo.[52,55,56] Phosphorylation of TSC2 at Ser939 and Thr1462 is PI3K-dependent.[52,56] Akt-mediated phosphorylation of TSC2 destabilizes TSC2 and thereby inhibits the formation of TSC1/2 complex, leading to de-repression of mTOR, and consequently increasing the kinase activity of mTOR. By contrast, treatment with rapamycin does not influence the phosphorylation of TSC2,[52] and together with other data,[53,54] suggests that mTOR lies downstream of TSC2. Other results[57,58] imply that the TSC1/2 complex may mediate S6K1 activation through a pathway parallel to mTOR. However, further studies will be required to address the relationship of mTOR and TSC1/2.

mTOR Associated Proteins. mTOR forms a scaffold complex with other proteins, such as raptor (regulatory associated protein of mTOR) and mLST8,[59,60] which are the mammalian counterparts of yeast Kog1 (kontroller of growth 1) and Lst8,[61] respectively. The exact role of raptor remains unclear.[38,59-61] Raptor may act as a scaffold protein linking mTOR to S6K1 and 4E-BP1.[60] Alternatively, it may have a dual function, inhibiting mTOR under nutrient-deficient conditions and stimulating mTOR in a nutrient-replete environment.[59] Thus TSC1/2, raptor and possibly mLST8 act as potential modulators of mTOR function in response to availability of nutrients.

Signaling Distal to mTOR. mTOR controls translation initiation through two pathways, S6K1 and eukaryotic initiation factor 4E (eIF4E) binding proteins (4E-BPs). mTOR either directly phosphorylates Thr389 of S6K1, or suppresses a phosphatase responsible for maintaining the hypophosphoryalted state of this residue. Activation of S6K1 enhances translation of mRNAs bearing a 5′ terminal oligopyrimidine tract (5′ TOP).[62,63] Inactivation of S6K1 decreases synthesis of ribosomal proteins and translation factors.[62,63] Activation of S6K1 is complex. The process involves interplay between four different domains and at least seven specific sites mediated by multiple upstream kinases.[64] At least 12 sites (Ser17, Thr229, Thr367, Thr371, Thr389, Ser404, Ser411, Ser418, Tr421, Ser424, Ser429, and Thr447) can be phosphorylated in response to serum stimulation.[65] However, the responsible kinases have not been fully characterized. Phosphoinositide-dependent protein kinase 1 (PDK1) phosphorylates Thr229 in vitro and in vivo.[66] Atypical PKC isoforms and the Rho family of small G proteins (cdc42 and Rac1) may contribute to phosphorylation of S6K1,[65] although the specific sites regulated by these kinases remain to be determined. In vitro, mTOR phosphorylates only Thr389 in the regulatory domain.[67-69] However, whether this phosphorylation is directly or indirectly regulated by mTOR is in question, since recent data suggest that mTOR may regulate S6K1 activation by inhibiting phosphatases rather than directly phosphorylating S6K1.[64,70]

mTOR phosphorylates and inactivates the 4E-BP suppressor proteins causing their dissociation from the RNA cap-binding protein eIF4E. In response to mitogens, six sites (Thr37, Thr46, Ser65, Thr70, Ser83, and Ser112) of 4E-BP1 can be phosphorylated.[65] So far, only mTOR and ATM have been identified to be involved in phosphorylation of 4E-BP1.[71-74] Other kinases that phosphorylate 4E-BP1 remain to be characterized. ATM phosphorylates 4E-BP1 at Ser112,[74] however the physiological significance of this remains to be elucidated. In vitro mTOR phosphorylates 4E-BP1 at two sites (Thr37, Thr46) and possibly at two additional Ser/Thr residues (Thr70 and Ser65) in the N-terminal region.[73,75] Phosphorylation is a hierarchical process.[73,75-77] Phosphorylation of Thr37/Thr46 is followed by Thr70 phosphorylation. Ser65 is phosphorylated last[77] and is dependent on phosphorylation of all three Thr/Pro sites.[75,76] Mutation of Thr37 and/or Thr46 to alanine(s) prevents phosphorylation of Ser65 and Thr70, indicating that phosphorylation of Thr37 and Thr46 serves as a requisite "priming" event.[36] Single phosphorylation of these residues is not sufficient to dissociate 4E-BP1 from eIF4E, indicating the requirement of combined phosphorylation of at least Thr37, Thr46, Ser65, and Thr70 in 4E-BP1 to suppress association with eIF4E.[36,78] Inhibition of mTOR leads to rapid hypophosphorylation of 4E-BP1 which then tightly binds to eIF4E. This prevents formation of eIF4F complex that contains eIF4E, eIF4G, eIF4A and eIF3, and inhibits cap-dependent translation initiation.[36] Once 4E-BP1 is hyperphosphorylated, it releases eIF4E, facilitating eIF4F complex formation and promoting cap-dependent protein synthesis.[36] Overall inhibition of mTOR by rapamycin leads to a decrease in protein synthesis of 15 to 20 percent. However, as the eIF4E pathway is required for translation of mRNA's encoding cyclin D1,[79,80] and ornithine decarboxylase[81] inhibition of mTOR leads to slowing or arrest of cells in G_1 phase of the cell cycle. However, the exact mechanism(s) by which mTOR regulates cell cycle progression are complex, poorly understood, and potentially context specific. Although rapamycins are highly specific inhibitors, the TOR pathway regulates multiple cellular processes. The mTOR pathway regulates translation initiation of survival factors such as c-MYC[82] and hypoxia-inducible factor 1α, and consequently vascular endothelial growth factor.[83,84] In addition, mTOR is involved in the regulation of cyclin A, cyclin dependent kinases (cdk1/2), cdk inhibitors ($p21^{Cip1}$ and $p27^{Kip1}$), retinoblastoma protein, RNA polymerase I/II/III-transcription and translation of rRNA and tRNA, protein phosphatases (PP2A, PP4 and PP6), and CLIP-170.[36,37,85-91]

TUMOR SELECTIVITY OF RAPAMYCINS

To date there are no reports suggesting that activating mutations of mTOR, or overexpression occur as primary events in malignant transformation. However, activation of signaling pathways both proximal and distal to mTOR appear to occur frequently in human cancer. Loss of the phosphatase PTEN by deletion, silencing or mutation leads to constitutive activation of Akt,[29,30,92] and upregulation of mTOR-dependent pathways. In PTEN-deficient tumor cells or mouse embryo fibroblasts (MEFs), activated Akt is associated with enhanced activity of S6K1 and hyperphosphorylation of 4E-BP1,[29,30] or increased levels of c-MYC.[92] It is speculated that Akt-activated cells become dependent on upregulated mTOR signaling for proliferation, hence become more susceptible to rapamycin or CCI-779. Increased sensitivity to rapamycins has been demonstrated in a panel of brain, prostate, and breast cancer cells, multiple myeloma cells and in MEFs.[23,29] The association of PTEN deficiency and sensitivity to rapamycin is further supported by the activity of CCI-779 against the growth of human tumors implanted in athymic nude mice.[23,30] There are, however, some exceptions; cells with functional PTEN and low constitutive activation of Akt are equally sensitive to inhibition of proliferation by rapamycins. Consequently the role of PTEN as an independent variable predicting for rapamycin sensitivity remains to be demonstrated. Disruption of the TSC1 or TSC2 gene leads to the development of tumors in multiple organs, notably kidney brain heart and lung. Even low doses of rapamycin causes apoptosis and necrosis of spontaneous renal tumors in Eker rats with germline mutation in TSC2 and results in tumor regression.[93] These studies suggest that tumors developing in patients with tuberous sclerosis may be sensitive to rapamycins. Oncogene expression may also regulate the response to rapamycin. For example, in RK3E cells transformed with c-MYC or Ras rapamycin treatment increased global protein synthesis. In contrast rapamycin inhibited global protein synthesis and turnover in GLI transformed isogenic lines leading to inhibition of proliferation.[94]

Although generally considered to be cytostatic agents, rapamycins can induce apoptosis in some cell systems. Rapamycins induce apoptosis of B-cells, rhabdomyosarcoma cells, renal tubular cells and dendritic cells.[16,95-97] Rapamycin enhances transforming growth factor-β induced cell cycle arrest,[98] and through blocking survival factor signaling[99] rapamycins enhance cell death. Our results suggest that the functional status of the p53 tumor suppressor may dictate the cellular fate of rapamycin treated cells, as depicted in Figure 5. For example, under serum free conditions, the response to rapamycin in cells lacking functional p53 is apoptosis, suggesting that only in the absence of p53/p21 inhibition of mTOR becomes lethal (so-called synthetic lethality). Ectopic expression of p53 or $p21^{Cip1}$ protects cells from rapamycin-induced apoptosis. The implication is that rapamycins may have potential tumor-selective therapeutic effects.[16] Recent results show that inhibition of mTOR by rapamycin induces a cellular stress response characterized by rapid and sustained activation of ASK1 (apoptosis signal-regulating kinase 1) signaling in p53-mutant cells.[100] This leads to sustained phosphorylation of c-JUN (Ser63) that appears to be responsible for inducing apoptosis. Rapamycin-induced stress appears distinct from that induced by ultra violet radiation in that MEKK1 is not activated, and from cytotoxic agents such as DNA damaging agents where other stress pathways (p38 or ERK1/2) are also activated.[101,102] In contrast, cells expressing wild type p53, (or constitutive $p21^{Cip1}$ expression) there is only transient activation of ASK1.[100] Suppression of ASK1 is associated with binding of $p21^{Cip1}$ in rapamycin treated cells, and protection from apoptosis. Since the rapamycin-induced apoptosis is specifically prevented by insulin-like growth factors (IGF-I/II) and insulin,[96] combination of IGF receptor inhibitors with rapamycins may be selectively cytotoxic and induce regression of tumors with p53 mutations. Whether such anticipation is justified requires vigorous testing.

MECHANISMS OF RESISTANCE TO RAPAMYCINS

Intrinsic sensitivity to rapamycins between cell lines may vary by several orders of magnitude. For example, rhabdomyosarcoma cells in vitro are very sensitive (concentration for 50% inhibition (IC50) of proliferation ~ 1 nM) compared to colon carcinoma cells (IC50 > 5000 nM).[11] Mechanisms of intrinsic and acquired resistance may have either a genetic or epigenetic basis.

Mutations in FKBP12 and mTOR. Rapamycins first bind to the cyclophilin FKBP12 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.

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