Review

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mTOR-targeted therapy of cancer with rapamycin derivatives

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Rapamycin and its derivatives (CCI-779, RAD001 and AP23576) are immunosuppressor macrolides that block mTOR (mammalian target of rapamycin) functions and yield antiproliferative activity in a variety of malignancies. Molecular characterization of upstream and downstream mTOR signaling pathways is thought to allow a better selection of rapamycin-sensitive tumours. For instance, a loss of PTEN functions results in Akt phosphorylation, cell growth and proliferation; circumstances that can be blocked using rapamycin derivatives. From recent studies, rapamycin derivatives appear to display a safe toxicity profile with skin rashes and mucositis being prominent and dose-limiting. Sporadic activity with no evidence of dose–effect relationship has been reported. Evidence suggests that rapamycin derivatives could induce G1–S cell cycle delay and eventually apoptosis depending on inner cellular characteristics of tumour cells. Surrogate molecular markers that could be used to monitor biological effects of rapamycin derivatives and narrow down biologically active doses in patients, such as the phosphorylation of P70S6K or expression of cyclin D1 and caspase 3, are currently evaluated. Since apoptosis induced by rapamycin is blocked by BCL-2, strategies aimed at detecting human tumours that express BCL-2 and other anti-apoptotic proteins might allow identification of rapamycin-resistant tumours. Finally, we discuss current and future placements of rapamycin derivatives and related translational research into novel therapeutic strategies against cancer.

Key words: cell signal inhibitors, phase I trial, rapamycin, signal transduction inhibitors, sirolimus

Introduction

Cancer cells need several kinases for cell cycle control, proliferation, invasion and angiogenesis [1]. Treatments targeted against cellular signalling pathways have shown promise in the management of solid tumours and hematological malignancies. mTOR (mammalian target of rapamycin) was shown to be a key kinase acting downstream of the activation of the phosphatidylinositol 3 kinase (PI3K). Cumulative evidence supports the hypothesis that mTOR acts as a 'master switch' of cellular catabolism and anabolism, signalling cells to expand, grow and proliferate. Although it is found in virtually all mammalian cells, it is particularly important in tumour cells that proliferate and invade aggressively. In addition, mTOR has recently been found to have profound effects in the regulation of apoptotic cell death, mainly dictated by the cellular context and downstream targets including P53, BAD, BCL-2, P27 and C-MYC.

Rapamycin (sirolimus) is a macrolide antibiotic produced by *Streptomyces hygroscopicus*, which binds FKBP-12 (FK506 binding protein). Thereby, the rapamycin–FKBP12 complex can inhibit mTOR preventing further phosphorylation of P70S6K, 4E-BP1 and, indirectly, other proteins involved in transcription and translation and cell cycle control. Rapamycin is currently used alone or in combination with cyclosporine as an immunosuppressive drug to prevent renal graft rejection.

Rapamycin analogues currently selected for clinical development are CCI-779 (intravenous formulation currently in phase III from Wyeth Ayest), RAD001 (oral formulation currently in phase I-II from Novartis Pharma) and AP23573 (intravenous formulation currently in phase I from Ariad Pharma). In clinical settings, using intermittent administration of CCI-779, RAD001 and AP23576, no evidence of immunosuppressive effects has been observed. Dose-limiting toxicities consist of skin reactions, mucositis and minimal myelosuppression. Evidence of antitumour activity has been reported in several patients with renal clear cell carcinoma and breast cancer. Interestingly, rapamycin and its analogues antagonise tumour growth induced by loss of the PI3K antagonist, PTEN. Selection of patients based on the detection of activated P70S6K/AKT and/or loss of PTEN expression might help to predict the sensitivity of tumour cells to rapamycin analogues. Pharmacodynamic monitoring of the biological activity of rapamycin in clinical trials using molecular endpoints such as the phosphorylation of AKT, P70S6K and/or 4E-BP1 might also help to determine biological relevant dose(s) and plasma

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concentration(s) in individuals treated with rapamycin analogues. In addition, rapamycin and its analogues may sensitise cancer cells to apoptosis induction by cisplatin and gemcitabine.

In this review, we will describe the molecular pathways involved in rapamycin activity and we will present recent preclinical and clinical data on rapamycin and its analogues. We will then discuss the current and future placement of those molecules into current therapeutic strategies against cancer.

PI3K signaling pathway and mTOR

Overview of the PI3K-related kinases (PIKKs)

Following activation of membrane receptors by a variety of growth factors, secondary molecular signals are generated to transmit the stimulus toward the nucleus and activate a number of events. Many of these signals involve the phosphorylation of proteins known as kinases (Figure 1). Among those kinases, PI3K and PI3K-related kinases (PIKK) belong to a family of high molecular mass kinases whose catalytic domains show a strong resemblance. This family and the ribosomal protein P70S6K, mTOR, the DNA-dependent protein kinase, the ataxia telangiectasia mutated gene (ATM), the ataxia-telangiectasia related (ATR) protein and key components of the histone acetylase complex are involved in checkpoint regulation of cell cycle, DNA repair, telomere length and cell death [2].

The PI3K pathway is very often activated in cancer and contributes to cell cycle progression, to decrease apoptosis and to increase metastatic capabilities of cancer cells [3, 4]. The uncontrolled activation of the PI3K pathway has been implicated in cell transformation and tumour progression in several tumour types including brain tumours, breast, ovarian and renal carcinomas [5–7]. Activation of the PI3K pathway is mediated by activated RAS or directly by some tyrosine-kinase receptors, under the control of several growth factors and cytokines including interleukin 1 (IL-1), IL-2, IL-3, IL-4,

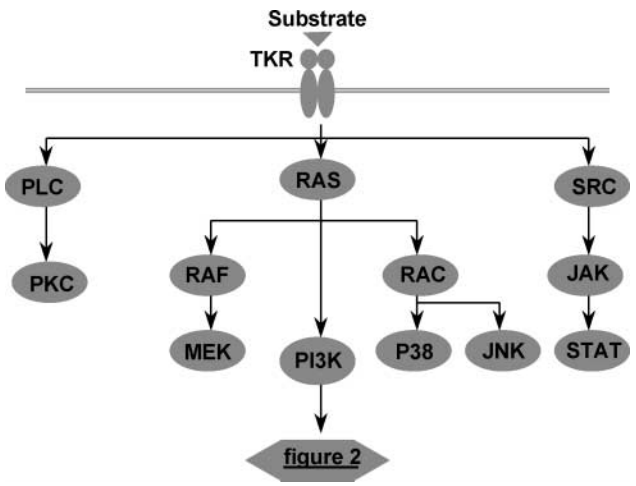

Figure 1. Multiple signaling pathways involved in signal transduction from tyrosine kinase receptors (TKR).

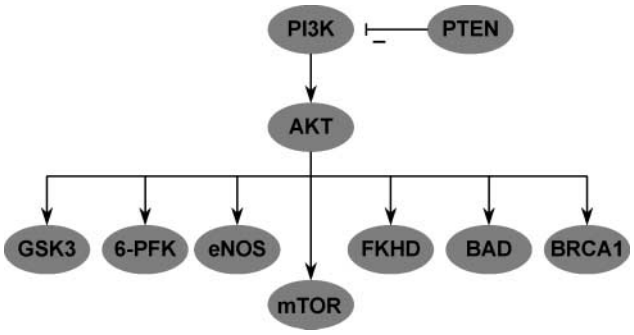

Figure 2. Several molecules involved in cell survival, including mTOR, are regulated by the PI3K/AKT pathway.

IL-6, insulin-like growth factor (IGF), epidermal growth factor (EGF), platelet derived growth factor (PDGF), insulin growth factors (IGF-1 and IGF-2) and colony stimulating factor (CSF). Activated PI3K phosphorylates inositol lipids at the 3′ position of the ring inositol, generating the lipid products PI3-phosphate [PI(3)P], PI3,4-biphosphonate [PI(3,4)P2] and PI3,4,5-triphosphate [PI(3,4,5)P3]. These lipid products are involved in a number of cellular processes including cell proliferation, survival, cytoskeletal reorganisation, membrane trafficking, cell adhesion, motility, angiogenesis and insulin action [8, 9]. Downstream to PI3K, protein kinase B (PKB), also named AKT, impacts on cell survival at multiple levels [10]. Substrates of AKT include glycogen synthase kinase (GSK3), 6-phosphofructo-2-kinase, the protein BAD, forkhead family of transcription factors, endothelial nitric oxide synthase (eNOS), mTOR, BRCA1 and others (Figure 2). GSK3 appears negatively regulated by AKT-dependent phosphorylation. Reduced GSK-3 activity leads to increased levels of the growth stimulator beta-catenin [11]. The pro-apoptotic protein BAD is also inactivated by AKT-dependent phosphorylation, thus enhancing cell survival. On the contrary, AKT indirectly activates mTOR via TSC, which in turn phosphorylates and activates several targets involved in translation of specific mRNAs, apoptosis and/or cell cycle, as we will discuss later [12].

Kinase activities are regulated by phosphatases that act in opposition to kinases by removing phosphates from the target proteins. The phosphatase and tensin homologue gene (*PTEN*, also named *MMAC1* or *TEP1*) is a tumour suppressor gene, located on human chromosome 10q23 [13]. *PTEN* was found to be mutated in several human sporadic cancers such as breast, endometrial, ovarian (type endometroid), brain, renal carcinoma, melanoma and prostate tumour cell lines and primary tumours. Patients with germline mutations of *PTEN* develop inherited Bannayan Zoanna syndrome characterised by multiple hamartomas and Cowden disease, and subsequently are susceptible to developing breast, thyroid and several others cancers [14, 15].

The *PTEN* product has a protein tyrosine phosphatase domain and extensive homology to tensin (related protein with focal adhesions), suggesting that PTEN suppresses tumour cell growth by antagonising protein tyrosine kinases, and regulates tumour cell invasion and metastasis through interactions

at focal adhesions. Davies *et al.* [16] and others, have demonstrated that PTEN plays an important role in anchorage-dependant cell survival. Additionally, loss of PTEN protects cells from apoptosis triggered by matrix detachment (anoikis), and the re-expression of PTEN in PTEN-mutated cells causes apoptosis in cells in suspension.

PTEN is involved in the regulation of the PI3K pathway [3]. There is evidence that PTEN dephosphorylates phosphatydilinositol 3,4,5-triphosphate while mutated PTEN cannot dephosphorylate phosphoinositides at the D3 position (D3-PPI). PTEN ± mice spontaneously develop neoplasia, associated with loss of the normal *PTEN* allele and an increased activation of AKT, mTOR and P70S6K. *In vitro* and *in vivo*, the growth of PTEN-deleted human cancer cells and PTEN−/− mouse cells can be preferentially inhibited by pharmacologic mTOR inhibition [17]. This growth inhibition then involves both a decrease in proliferation and an increase in apoptosis.

However, although PTEN inactivation might be required, it might not be sufficient to explain the sensitivity to rapamycin since there is also evidence to show that cancer cells with PTEN inactivation might remain resistant to rapamycin. Conversely, a dose dependent tumour growth delay is observed in mice bearing PTEN proficient cancer cells. In that case, reports have suggested that the effects of rapamycin might be related to the inhibitory effects against endothelial cells blocking tumour angiogenesis.

Several studies have suggested that genomic integrity, transcript and protein levels, phosphorylation and activity of all the multiples components of the PI3K pathway, should be evaluated to determine whether they predict prognosis or response to therapy in several cancers. The members of the PIKK family are key components of signals that coordinate the activity of the cell cycle and their functional characterisation gives important insights into cell growth and cell cycle checkpoint function. Further, development of molecular therapeutics targeting the PI3K pathway is clearly warranted in different types of cancer. Wortmannin inhibits the multiple effects of PI3Ks and yield anti-inflammatory, immunosuppressive, cytotoxic and radio-sensitising properties with potential as an anti-neoplastic drug [18, 19]. The multiple molecular targets inhibited by this agent (PI3, PI4 and PIKK) raise caution about its clinical use. Besides, wortmannin presents chemical instability and hepatotoxicity, limiting its development. Thus, we need to evaluate more specific molecules in this pathway as individual targets.

Focus on mTOR (Figure 3)

mTOR was identified in 1994 by several groups of investigators as the kinase targeted by rapamycin linked to the cellular protein FKBP12 (FK506-binding protein). It was therefore also named FKBP-RAP associated protein (FRAP), RAP FKBP12 target (RAFT1) and RAP target (RAPT1) [20, 21].

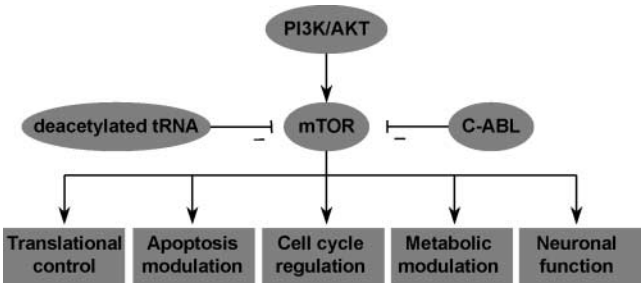

Figure 3. Overview on mTOR main activities in normal cells.

mTOR is a serine/threonine kinase of 289 kDa, highly related to yeast TORs that belong to the PIKK family with a dual regulation by amino acid availability and by mitogen activated PI3K/AKT. TOR proteins in *Sacharomyces cerevisae* and the mammalian related proteins (mTOR) are required for signalling translational initiation and therefore cell cycle progression from the G0/G1 to S phase [22]. Yeast TOR 2 protein also controls the actin cytoskeleton during cell cycle progression but it is not clear whether this function is conserved by mTOR [23].

In humans, mTOR primarily appears to be a nutrient-sensing protein: mTOR is constitutively activated in the presence of growth factor and nutrients and acts as a master switch of cellular catabolism and anabolism [12, 24]. mTOR is also regulated by hypoxia and by AMP levels. mTOR is inhibited through deacetylated tRNA species accumulating as a result of amino acid shortage (but the exact pathway remains to be elucidated) and via C-ABL protein tyrosine kinase that phosphorylates mTOR and inhibits its action. mTOR is also activated by TSC2 mutations or loss of LKB1.

As discussed above, upregulation of mTOR can be related to loss of the tumour suppressor gene *PTEN* and activation of *AKT*.

Translational control by mTOR

mTOR modulates translation of specific mRNAs via the regulation of the phosphorylation state of several different translation proteins, mainly 4E-BP1, P70S6K and eEF2.

4E-BP1. Protein synthesis is regulated in many instances at the initiation phase, when a ribosome is recruited to the 5′ end of an mRNA. Eukaryotic ribosomes do not have the ability to locate and bind to the 5′ end of mRNA and need translation initiation factors to guide them. The cap structure at the 5′ end of an mRNA is recognised by the eukaryotic translation initiation factor 4E(eIF4E). eIF4E, in association with eIF4G, directs the translation machinery to the 5′ end of the mRNA. The 4E-binding proteins (4E-BP) are essential in the regulation of the interaction between eIF4E and eIF4G. The mTOR signalling pathway modulates 4E-BP1 phosphorylation and mediates its dissociation from eIF-4E [25, 26]. This dissociation is a crucial step toward activating translation of mRNAs with specific regulatory elements in the 5′-untranslated terminal region (5′UTR), especially c-myc, cyclin D1 and ornithine decarboxylase. In contrast, when

growth factor or nutrients are lacking, or in the presence of mTOR inhibitors, 4E-BP1 becomes hypophosphorylated, which increases its binding with EIF-4E and prevents initiation of translation.

P70S6K. mTOR also phosphorylates and activates P70S6K to favour the recruitment of the 40S ribosomal subunit into actively translating polysomes and enhance the translation of mRNAs with 5′ terminal oligopyrimidine tracts. These transcripts can encode up to 20% of the mRNAs [27].

eEF2. Finally, mTOR also acts at the level of the elongation phase. The eukaryotic elongation factor 2 (eEF2) promotes translocation of the mRNA and mTOR regulates the activity of eEF2 kinase, apparently via regulation of a phosphatase activity (PP2A) [28].

Anti-apoptotic and pro-apoptotic effects

There is evidence that the downstream target of mTOR, P70S6K, binds to mitochondrial membranes and phosphorylates the pro-apoptotic molecule BAD [29]. The binding of P70S6K to BAD inactivates BAD and increases cell survival. In contrast, mTOR might translocate from the cytoplasm to the nucleus shortly after the formation of syncitium between cells expressing the HIV envelope and CD4 cells. Once in the nucleus, it causes phosphorylation of P53, transcriptional activation and induction of pro-apoptotic proteins such as BAX, and activation of the intrinsic cell death pathway [30].

Cell cycle regulation

mTOR inhibition results in an increase in the turnover of cyclin D1, at both mRNA and protein levels [31], and a decrease in the elimination of the cyclin dependant kinase inhibitor P27. Additionally, mTOR downregulates cyclin-A-dependent kinase activity in exponentially growing cells. The pharmacological inhibition of mTOR decreases G1 transit in the cell cycle [32].

Metabolic modulation

Cells have the ability to adapt to the dynamic pool of nutrients in their immediate environment. Mammalian cells respond continually to changes in available blood glucose and amino acids. mTOR plays an important role in the modulation of metabolic pathways, including those related to insulin [12, 33]. The initiation of translation appears to be the limiting phase in protein synthesis. The central role played by mTOR in protein translation leads to the control of skeletal muscle protein synthesis. Because mTOR inhibition causes cellular responses indicating the physiological state of starvation, these proteins are thought to be mediators of nutrient-sensing pathways. mTOR can detect nutrients such as carbon and nitrogen, signaling cells to grow and proliferate, a fact particularly important in tumour cells that proliferate aggressively. In yeast, TOR functions are well established genetically, with somewhat less compelling data in mammalian cells. In yeast, TOR signaling modulates the transcription of genes that are involved in amino acid biosynthesis, regulates the activity of amino acid permeases and represses autophagy. In the absence of the TOR signal, ribosomal biosynthesis is inhibited and autophagy is activated.

Neuronal function and role in brain development

Recent evidence also suggests that mTOR may be involved in neuronal protein synthesis. mTOR could play a role in embryonic brain development and in the learning and memory process [34]. mTOR could inhibit eEF2 phosphorylation in active synapses to locally unrepress translation, whereas some studies have reported an increase of eEF2 phosphorylation in response to various neurotransmitters.

Rapamycin and analogues

Rapamycin development

Rapamycin, also named sirolimus, is a natural antibiotic produced by *S. hygroscopicus*. This molecule was found 30 years ago in the Easter Island Rapa Nui soil from which rapamycin was named. Rapamycin was subsequently isolated in Montreal by Ayerst Research laboratories in 1972. Rapamycin is a macrocyclic lactone developed initially as an anti-fungal drug directed against *Candida albicans*, *Cryptococcus neoformans*, and *Aspergillus fumigatus* [35–38]. It is a white crystalline solid insoluble in aqueous solutions, but soluble in organic solvents. The chemical structure is shown in Figure 4.

Recently, rapamycin has been tested by the Developmental Therapeutic Branch, National Cancer Institute (NCI) and identified as a noncytotoxic agent that delays tumour proliferation, finding evidence of cytostatic activity against several human cancers *in vitro* and *in vivo*. However, the development program of rapamycin as an anticancer agent was halted in 1982 and only resumed in 1988 after demonstration of a safe toxicological profile in animals.

In the meantime, rapamycin was developed as an immunosupressive agent and those studies have enabled us to understand the mechanism of action of this agent. Rapamycin, via

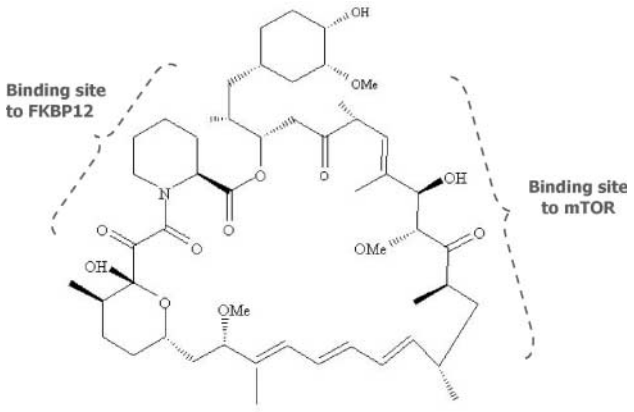

Figure 4. Rapamycin's chemical structure including FKBP12 and mTOR binding domains.

its methoxy group, crosslinks the immunophilin FK506 binding protein (FKBP12). The rapamycin–FKBP12 complex specifically interacts with mTOR to inhibit mTOR signalling to downstream targets [38]. Rapamycin inhibits T-cell proliferation induced by antigen, mitogenic lectins, alloantigen and crosslinking of T-cell surface markers with monoclonal antibodies. Rapamycin can inhibit proliferative responses induced by cytokines, including IL-1, IL-2, IL-3, IL-4 and IL-6, IGF, PDGF and CSFs.

The preclinical development of rapamycin as an immunosuppressor has been extensively reviewed [39, 40]. It has demonstrated a high degree of synergy with cyclosporin [41] both *in vitro* and *in vivo*, lowering the dose of cyclosporin necessary for immunosuppression, enhancing the rejection prevention in renal transplantation and minimising cyclosporin-induced toxicity [42, 43]. There are observations that high doses of rapamycin block the proliferative responses to cytokines by vascular and smooth muscle cells after mechanical injury, such as balloon angioplasty or allo-rejection [44, 45]. In a non-human primate model, supra-therapeutic concentration of rapamycin stabilised and possibly reversed the intimal vascular lesion caused by the progression of immune injury in aortic allograft [46]. Rapamycin treatment concomitant with monoclonal antibody blockade of the co-stimulatory signal by anti-CD154 in mice induces tolerance, and the combination of rapamycin with anti-B7 in non-human primates seems to facilitate tolerance induction [47]. IC_{50} values of rapamycin as an immunosuppressor are in the range of 0.1–300 nM.

A relevant point of rapamycin as an immunosuppressor is the absence of the vasomotor renal side effects exhibited by CsA and tacrolimus. Treatment with rapamycin preserves glomerular filtration and renal blood flow in normal, salt-depleted and spontaneously hypertensive rats [48]. The renal tissue seems to be protected during the rapamycin treatment by an inhibition of the intrarenal angiotensin II cascade. However, rapamycin does produce a dose-dependent tubular toxicity in rats, which is related to the delayed recovery of tubular epithelial function after injury [49].

Over the last 8 years, rapamycin has undergone clinical trials as an immunosuppressive agent, progressing from phase I safety, tolerability and pharmacokinetic investigation to phase II dose-finding studies and limited sized evaluations of drug combination regimens. The completion of phase III trials led to approval of rapamycin by the Food and Drug Administration (FDA) of the USA in 1999 to prevent acute rejection in combination with cyclosporin and steroids. One year later, the drug was approved by the European Agency as an alternative to calcineurin antagonists for long-term maintenance therapy to avoid graft rejection. Interestingly, rapamycin, unlike cyclosporin, does not seem to increase the risk of malignancy but rather to decrease the risk of post-transplant lymphoproliferative disorders.

Apart from its immunosupressive capacity, rapamycin was also recently shown to be capable of preventing coronary artery re-stenosis [50, 51]. Growth, migration and differentiation of vascular smooth-muscle cells are two major features of neointimal proliferation after vascular injury. The proposed mechanism of inhibition of proliferation of vascular smooth-muscle cells by sirolimus includes binding of the immunophilin FKBP12, blockage of P70S6K, impairment of retinoblastoma protein phosphorylation, and prevention of p27 downregulation. Additionally, rapamycin has been shown to be effective in inhibiting PDGF-induced migration of human vascular smooth cells *in vitro*, without affecting the ability of these cells to bind collagen and without disrupting their cytoskeletal components [52, 53]. To avoid the systemic effects of rapamycin, it has been used locally in an impregnated stent to prevent coronary restenosis [51].

Pharmacokinetic and metabolic information

These data were initially obtained from studies that evaluated rapamycin as an immunosuppressor [54, 55]. The systemic bio-availability of rapamycin is approximately 15%, it has a maximal concentration at about 1 h and is widely distributed in tissues compared with plasma. The ratio blood cells/plasma ranges between 36 in renal transplant cases to 79 in healthy volunteers. *In vitro* experiments using human liver microsomes suggest that cytochrome Cyp450 3A4 is the major biotransformation system, generating the inactive metabolites, hydroxy, dihydroxy, hydroxy-demethyl, didemethyl, 7-0 demethyl and 41-0 demethyl. More than 90% of the drug is recovered in the faeces. Urine represents only 2% of the drug elimination. The average elimination half life is variable, ranging from 10 h in children to 110 h in patients with hepatic impairment.

Rapamycin exposure is increased by diltiazem and ketoconazole and decreased by rifamycin and anticonvulsants [56]. Regarding the interaction between rapamycin and cyclosporin (CsA), rapamycin concentrations are increased by concomitant administration of Neoral, the microemulsion formulation of CsA, and rapamycin increases CsA exposure approximately 2-fold, presumably because of competition for metabolism by Cyp450 3A4 and, possibly, drug extrusion by P-glycoprotein [57].

Initial clinical studies show that a dose-dependent reversible reduction in mean platelet number and, to a far lesser extent, leukocyte count, was accompanied by increased serum cholesterol and triglyceride values. There were no changes in blood pressure, kidney or liver function test results.

Corroborating preclinical studies, rapamycin does not affect glomerular filtration, but hypokalemia and hypophosphatemia has been reported as evidence of renal tubular abnormalities [58, 59].

Additionally, rapamycin augments reactions to CsA: hypertension, acne and hirsutism. It has been associated with minor adverse effects such as diarrhea, tachycardia and arthralgia, as well as with non-infectious pneumonitis [60].

Rapamycin as an anticancer drug

Rapamycin was shown to inhibit the growth of several murine and human cancer cell lines in a concentration-dependent

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