expert reviews
in molecular medicine

Mammalian target of rapamycin (mTOR) pathway signalling in lymphomas

Elias Drakos[1], George Z. Rassidakis[1,2] and L. Jeffrey Medeiros[1,*]

The mammalian target of rapamycin mTOR is a central element in an evolutionary conserved signalling pathway that regulates cell growth, survival and proliferation, orchestrating signals originating from growth factors, nutrients or particular stress stimuli. Two important modulators of mTOR activity are the AKT and ERK/MAPK signalling pathways. Many studies have shown that mTOR plays an important role in the biology of malignant cells, including deregulation of the cell cycle, inactivation of apoptotic machinery and resistance to chemotherapeutic agents. The development of several mTOR inhibitors, in addition to rapamycin, has facilitated studies of the role of mTOR in cancer, and verified the antitumour effect of mTOR inhibition in many types of neoplasms, including lymphomas. Clinical trials of rapamycin derivatives in lymphoma patients are already in development and there are encouraging preliminary results, such as the substantial response of a subset of mantle cell lymphoma patients to the rapamycin analogue temsirolimus. Based on results obtained from in vitro and in vivo studies of the mTOR pathway in lymphomas, it seems that better understanding of mTOR regulation will reveal aspects of lymphomagenesis and contribute to the development of more powerful, targeted therapies for lymphoma patients.

In the 1970s, a soil sample collected from the Vai Atare region of Rapa Nui (also known as Easter Island) in the Pacific Ocean was found to contain a bacterial strain of *Streptomyces hygroscopicus* producing a compound with potent antifungal activity (Ref. 1). The purified antibiotic, named rapamycin after the location where it was discovered, was characterised as a lipophilic macrolidic lactone – practically insoluble in water but soluble in most organic solvents. In addition to antifungal activity, rapamycin was found to have impressive immunosuppressive qualities (Refs 2, 3). The National Cancer Institute (NCI) identified rapamycin as a potent, mainly cytostatic agent against many types of human cancer (Refs 4, 5). However, because of its low solubility in water and the fact that the patent for the drug had

[1]Department of Hematopathology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA.

[2]First Department of Pathology, National and Kapodistrian University of Athens, Athens, Greece.

*Corresponding author: L. Jeffrey Medeiros, Department of Hematopathology, Unit 72, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, USA. Tel: +1 713 794 5446; Fax: +1 713 745 0736; Email: ljmedeiros@mdanderson.org

Accession information: doi: 10.1017/S1462399408000586; Vol. 10; e4; February 2008
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https://doi.org/10.1017/S1462399408000586 Published online by Cambridge University Press

expired, the development of rapamycin as an antitumour agent was delayed considerably (Refs 5, 6).

Intensive investigation of the mechanism of action of rapamycin led to the discovery of an evolutionarily conserved pathway that integrates signals arising from growth factors, nutrients and energy status. This pathway regulates metabolism, growth and proliferation in normal cells and plays a central role in cell proliferation, survival and drug resistance in many human cancers (Refs 7, 8, 9). The core of this pathway corresponds to the target of rapamycin (TOR), discovered originally through two mutations conferring resistance to the growth inhibitory effect of rapamycin in the budding yeast (*Saccharomyces cerevisae*) (Refs 10, 11, 12, 13). All eukaryotes studied to date contain a *TOR* gene. There are two yeast genes (*TOR1* and *TOR2*); the mammalian homologue, named mammalian target of rapamycin (*MTOR* or *FRAP1*), is a single gene (Refs 14, 15, 16).

The core of the mTOR pathway: mammalian target of rapamycin complexes (mTORCs)

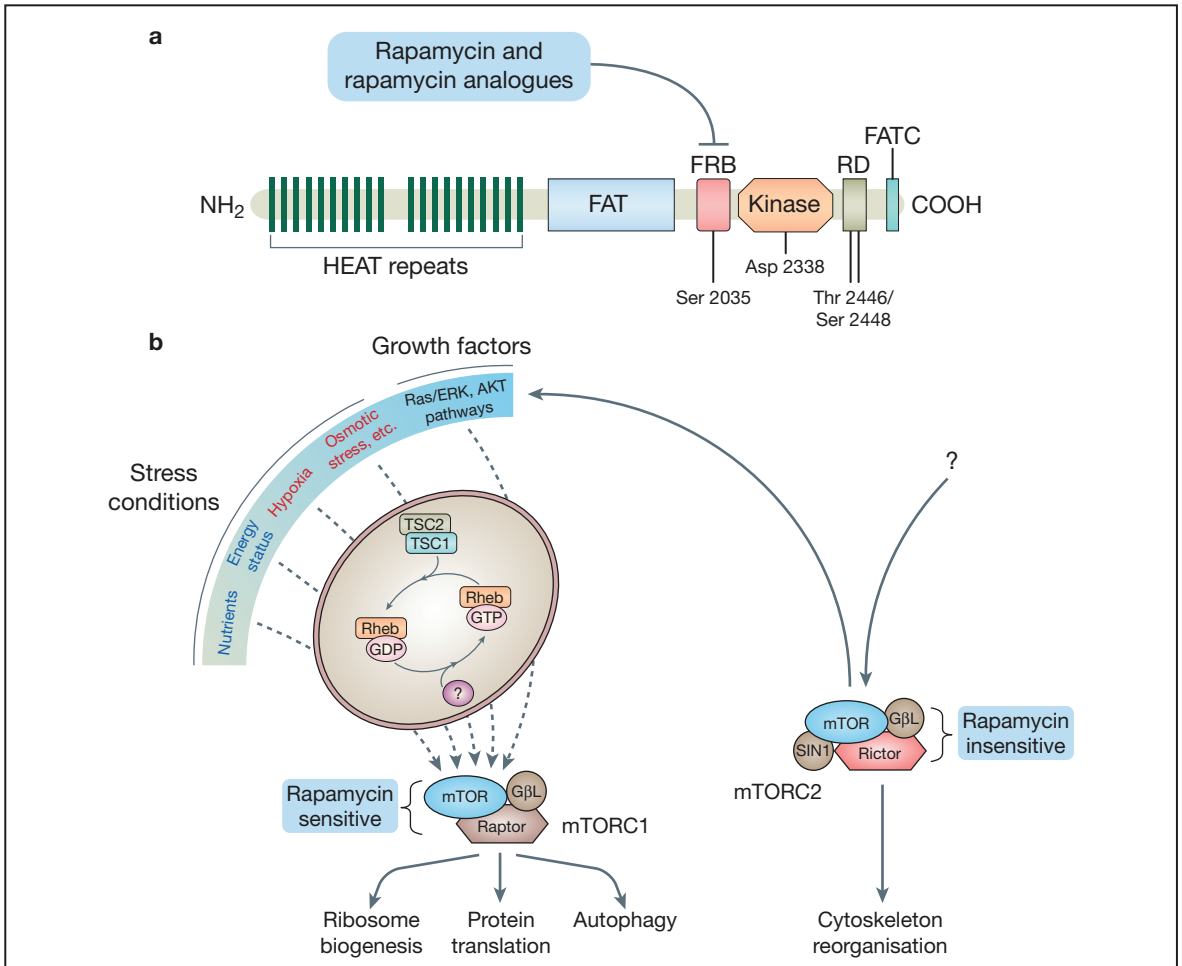
The *MTOR* gene maps to chromosome 1p36.2 in the human genome and encodes a 289 kDa protein that contains a kinase catalytic domain similar to that found in phosphoinositide 3-kinase (PI3K) (Refs 17, 18, 19). However, unlike PI3K, mTOR does not have lipid kinase activity and instead functions as a Ser/Thr protein kinase (Refs 17, 18). mTOR is the founding member of the PI3K-related kinase (PI3KK) family, which also includes DNA-dependent protein kinase, ATM (ataxia telangiectasia mutated), ATR (ATM- and Rad3-related) and SMG-1 ('human homologue of suppressor with morphogenetic effect on genitalia 1') (Ref. 20). In addition to the catalytic domain, the mTOR molecule contains 20 HEAT (Huntington elongation factor 1A–protein phosphatase 2A subunit–TOR) repeats that are crucial for protein–protein interactions, FAT (FRAP–ATM–TRAPP2) and FATC (FAT C-terminal) domains characteristic of the PI3KK family, a putative autoinhibitory repressor domain (RD) and an FKB12 rapamycin-binding domain (FRB). The FRB is the immediate target of rapamycin and rapamycin analogues (Fig. 1a) (Refs 12, 21, 22, 23, 24, 25, 26).

mTOR functions as part of a larger multiprotein signalling complex. Recent studies show that mTOR participates in at least two different signalling complexes – mTORC1 and mTORC2 – which have different functions (Fig. 1b) (Ref. 27). mTORC1, which is sensitive to rapamycin, is currently believed to have three components: mTOR, Raptor (regulatory-associated protein of mTOR; an adaptor protein approximately half the size of mTOR) and GβL (G protein β-subunit-like protein, also known as mLST8; a 36 kDa protein believed to be important for sensing upstream signals) (Refs 28, 29). Both Raptor and GβL are evolutionary conserved. However, the exact relationship between these components and their functions are not completely understood. It is believed that upstream signals associated with growth factors, energy status, nutrient availability and various conditions of stress, such as hypoxia, reactive oxygen species, DNA damage and hyperosmotic environment regulate the strength of association between mTOR and Raptor and, in this way, the recruitment of various downstream substrates of mTOR (Refs 30, 31). In turn, activation of mTORC1 promotes ribosome biogenesis and the rates of translation and protein synthesis. Activation of mTORC1 also inhibits autophagy, influencing metabolic mass, cell proliferation and cell survival (Ref. 32). All these functions are inhibited by rapamycin or rapamycin analogues (Ref. 30).

mTORC2, which is generally rapamycin insensitive, contains at least four components: mTOR, GβL, Rictor (rapamycin-independent companion of mTOR; a ~200 kDa adaptor protein) and mSIN1 (mammalian stress-activated protein kinase interacting protein 1) (Refs 33, 34, 35, 36). Very recently a fifth component of undetermined significance, named protor-1, was discovered (reviewed in Ref. 161). mTORC2 is regulated by unknown upstream signals, and the exact mechanisms of mTORC2 activation are poorly understood. However, it is believed that various growth factors contribute to mTORC2 activation. Compared with mTORC1, the function of mTORC2 is less well studied, but it is known that mTORC2 activity regulates cytoskeleton organisation and promotes activation of AKT (also known as protein kinase B) (Refs 31, 33, 34). Since AKT is an important upstream

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https://doi.org/10.1017/S1462399408000586 Published online by Cambridge University Press



Mammalian target of rapamycin protein structure and complexes

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Figure 1. Mammalian target of rapamycin protein structure and complexes. *(See next page for legend.)*

regulator for the activation of mTORC1, an autoregulatory loop between the two complexes seems to exist (Refs 31, 32).

Downstream effectors of mTOR

Although the regulation of protein production has been studied mainly at the genetic and transcriptional levels, it is becoming clear that regulation of translation is equally important (Ref. 37). mTORC1 acts mostly at this level, regulating the rate of mRNA translation and ribosome biosynthesis. Two critical mTORC1 downstream effectors of translation are the eukaryotic initiation factor 4E (eIF4E) binding protein 1 (4E-BP1) and p70 ribosomal protein S6 kinase (S6K1) (Fig. 2) (Refs 38, 39, 40, 41).

The rate of translation of most eukaryotic mRNAs is dependent on the binding of initiator factors (eIF) to the cap (m^7GpppN – where N is any nucleotide) structure at the 5′ untranslated mRNA terminus (Ref. 42). The eIF4E 5′CAP-binding subunit of the eIF4F initiator complex is recruited and neutralised by 4E-BP1. Direct or indirect phosphorylation of 4E-BP1 by activated mTORC1 disrupts the association between 4E-BP1 and eIF4E, facilitating the 5′CAP-binding function of eIF4E and thereby promoting translation (Fig. 2) (Refs 42, 43, 44).

S6K1, which is phosphorylated and activated by mTORC1 and PDK1, was previously thought to play a critical role in the translation of mRNAs with the TOP (terminal

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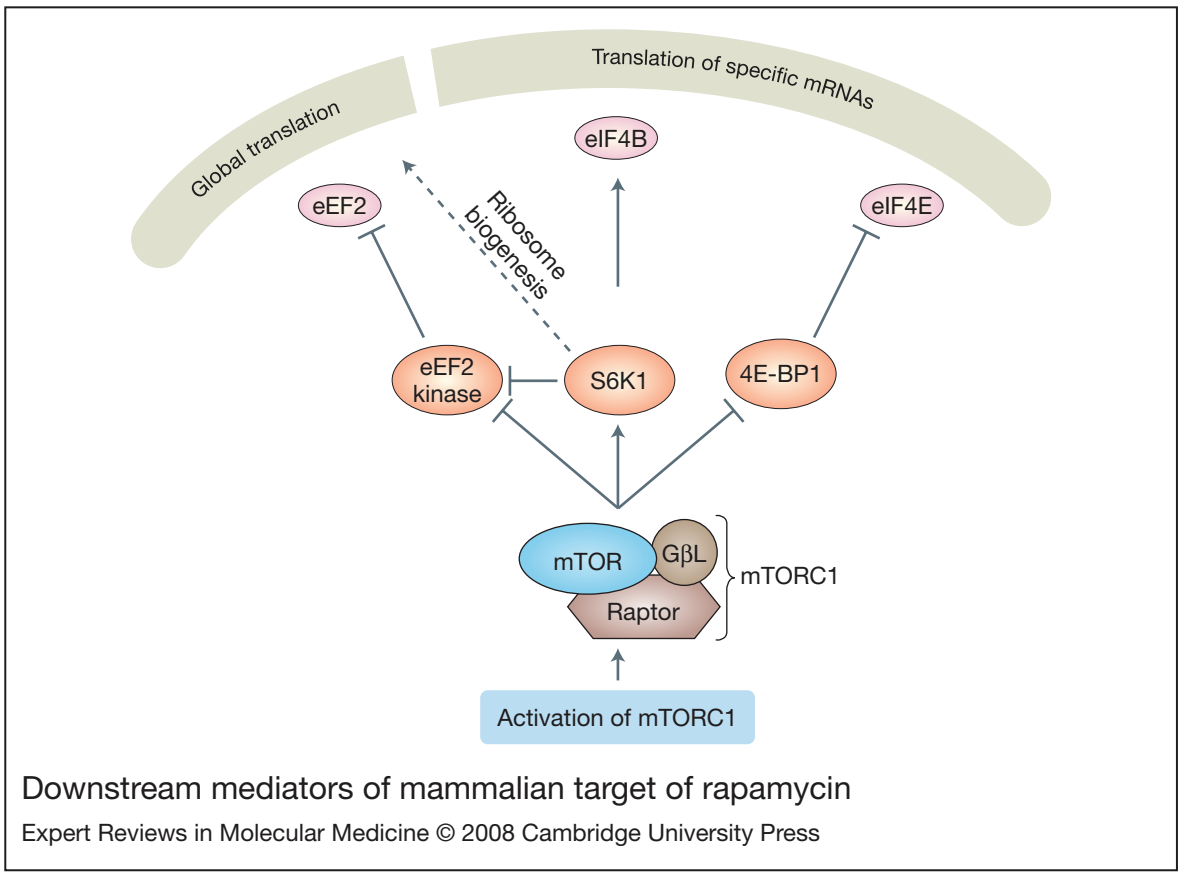
Figure 1. Mammalian target of rapamycin protein structure and complexes. *(Legend; see previous page for figure.)* (a) The human mammalian target of rapamycin (mTOR) gene encodes a protein of 2549 amino acids. Point mutation at the catalytic domain changing Asp2338 to Ala eliminates mTOR kinase activity. The FAT and FATC domains, flanking the catalytic domain are believed to be necessary for the appropriate folding or organisation of the catalytic domain and perhaps interact. The FRB region, just upstream of the catalytic domain, is characteristic of mTOR and the only region for which definite structural information exists. Mutation of Ser2035 to Arg in this region abolishes the binding of the FKBP12–rapamycin complex. The 20 HEAT repeats at the N-terminus, each ~39 amino acids long, contain several conserved hydrophobic residues. It is believed that each repeat forms a pair of antiparallel α-helices that stack in parallel with other repeats forming a large surface for protein–protein interactions. Between the catalytic and the FATC domain there is a poorly understood regulatory region containing two phosphorylation sites: Thr2446 and Ser2448. Deletion of this region results in activation of mTOR. Recently it was shown that both sites are phosphorylated by the downstream target of mTOR, S6K1, and not by AKT as it was initially believed. However, the functional significance of this regulatory loop between mTOR and S6K1 remains elusive. (b) There are at least two different mTOR protein complexes: mTORC1 and mTORC2. Most of the known functions of mTOR, and particularly the regulatory effect on protein translation and autophagy, are attributable to mTORC1 and can be inhibited by rapamycin. The two other proteins of the complex, GβL and Raptor, have no catalytic activity. The human gene for Raptor encodes a protein 1335 amino acids long, which contains a unique N-terminal region, three HEAT motifs and seven WD40 repeats. GβL protein, which is 260 amino acids long, consists almost entirely of seven WD40 repeats, is similar in sequence to the β subunits of heterotrimeric G proteins and interacts with the kinase domain of mTOR. Collectively, mTOR, GβL and Raptor have 23 HEAT and 14 WT40 motifs, increasing the potential of protein–protein interaction. No definite model exists for mTORC1 function; however, it seems that Raptor acts as adaptor that presents substrates to mTOR, and that Raptor and GβL both modulate mTOR activity. Many of the signals that regulate mTORC1 activity concentrate on the TSC1–TSC2 complex. For example, activated AKT or ERK pathways result in phosphorylation of TSC2 and inactivation of TSC1–TSC2. TSC1–TSC2, when active, inactivates the small protein Rheb, promoting the hydrolysis of GTP bound to Rheb. The protein that catalyses the opposite step remains elusive. Rheb seems to regulate mTOR indirectly, through FKBP38, a member of the FK506-binding protein (FKBP) family. FKBP38 binds to mTOR and inhibits its activity. Rheb interacts directly with FKBP38 and prevents its association with mTOR in a GTP-dependent manner. The second complex – mTORC2 – is known to influence cytoskeleton organisation and cell polarity and contains the evolutionary conserved protein Rictor (instead of Raptor), SIN1 and protor-1. SIN1 exists in at least three different isoforms defining three different mTORC2 complexes with different target specificities. However, all of these isoforms contribute to AKT activation, creating a regulatory loop for the activation of mTORC1. Insulin regulates the activity of two of these mTORC2 variations. However, the exact mechanism of mTOR2 activation and whether it is upstream of mTORC1 remains unclear. mTORC2 function is not generally inhibited by rapamycin. Abbreviations: FAT, FRAP–ATM–TRAPP2; FATC, FAT C-terminal; HEAT, Huntington elongation factor 1A–protein phosphatase 2A subunit–TOR; FKBP12, FK507-binding protein 12; FRB, FKBP-rapamycin binding; mTORC1/2, mammalian target of rapamycin complex 1/2.

oligopyrimidine) sequence at the 5′ untranslated region, among which are many that encode components of the translational machinery (Ref. 45). However, more recent studies have shown that S6K1 (and the similar S6K2), as well as the phosphorylation status of its well-known target, ribosomal protein S6, are dispensable for 5′TOP mRNA translation, although mTORC1 activation remains crucial (Refs 46, 47, 48). Recent studies have established two more connections between mTORC1-mediated S6K1 activation and translation (Ref. 49). First, activated S6K1 phosphorylates the RNA helicase eIF4B, promoting the association of eIF4B with the eIF3 scaffold component of the initiator complex, and the association of eIF3 with the eIF4G scaffold component of the eIF4F initiator complex (Refs 50, 51). Second, activated S6K1 phosphorylates and inactivates the eukaryotic elongation factor 2 (eEF2) kinase, resulting in underphosphorylated and functional eEF2. The latter is important for the promotion of the elongation steps of translation (Fig. 2) (Refs 52, 53).

Regulation of ribosomal biogenesis is a central mechanism for the control of global levels of translation and cell growth in eukaryotes, and is tightly regulated by mTORC1 (Ref. 54). Activation of mTORC1 promotes the biosynthesis of ribosomal RNAs and proteins by activating transcription, mediated by RNA polymerase (Pol) I, Pol II

Accession information: doi: 10.1017/S1462399408000586; Vol. 10; e4; February 2008
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https://doi.org/10.1017/S1462399408000586 Published online by Cambridge University Press



Downstream mediators of mammalian target of rapamycin

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Figure 2. Downstream mediators of mammalian target of rapamycin. 4E-BP1, S6K1 and eEF2 kinase are among the crucial downstream mediators of mammalian target of rapamycin (mTOR) that orchestrate the response of the translational machinery to various stress signals and growth factors. In the inactive state, 4E-BP1 blocks eIF4E from binding the cap structure of mRNA, and the translation elongation factor eEF2 is phosphorylated and inactivated by the corresponding eEF2 kinase. In the active state, activated mTORC1 phosphorylates and neutralises 4E-BP1, so that eIF4E can bind the cap structure of mRNA. In addition, S6K1, activated by mTORC1, phosphorylates and activates the eIF4B RNA helicase. Activated S6K1 phosphorylates and inhibits eEF2 kinase so that the underphosphorylated and active eEF2 can contribute to the elongation step of translation. Finally, activation of mTORC1 enhances ribosome biogenesis through many intermediate steps generally promoting the rate of translation. Abbreviations: 4E-BP1, 4E-binding protein-1; eEF2, eukaryotic elongation factor 2; eIF-4E, eukaryotic initiator factor 4E; mTORC, mammalian target of rapamycin complex; S6K1, p70 ribosomal protein S6 kinase.

and Pol III in the nucleus and accelerating the translation of 5′TOP mRNA into ribosomal proteins in the cytoplasm (Ref. 54). Although the exact mechanisms for the regulation 5′TOP mRNA in the cytoplasm remain elusive, it seems likely that enhancement of transcription in the nucleus by Pol I is mediated partly by S6K1, which activates and increases the availability of TIF-IA (transcription initiator factor IA) and UBF (upstream binding factor), essential cofactors of Pol I (Refs 55, 56).

Autophagy, more specifically macroautophagy, the process by which cellular components including organelles are catabolised and recycled, is an important survival mechanism that is tightly regulated by mTORC1 (Ref. 57). The exact mechanisms by which activated mTORC1 inhibits autophagy are poorly understood, although it seems probable that negative regulation of a homologue of ATG1 kinase that mediates early activation steps of the autophagic process is involved (Refs 58, 59).

Downstream targets of mTORC2 that mediate cytoskeleton reorganisation seem to include the small GTPases Rho and Rac, and the protein kinase PKCα (Refs 33, 34). However, knowledge

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about the pathway downstream of mTORC2 is limited.

Upstream regulators of mTOR

Pivotal to the understanding of upstream regulation of mTOR activity was the discovery of the importance of TSC1 and TSC2 (tuberous sclerosis complex 1 and 2, also known as amartin and tuberin, respectively) (Refs 60, 61). Lack of TSC1 or TSC2 expression results in overactivation of mTOR (Refs 62, 63). The heterodimer of TSC1/TSC2 is a GTPase-activating protein (GAP) for the small GTP-binding protein Rheb (RAS homologue enriched in brain), which catalyses the hydrolysis of Rheb-bound GTP and promotes the conversion of Rheb-GTP to Rheb-GDP (Refs 64, 65, 66, 67). In turn, Rheb-GTP activates mTOR kinase (Ref. 68). Signals regulating mTORC1 activity including those associated with growth factors, energy status and various stressful stimuli (e.g. hypoxia) target the TSC1/TSC2 heterodimer (Fig. 1B) (Refs 32, 41).

Two of the most important mTORC1-regulating pathways are the AKT and the Ras–ERK (extracellular-signal-regulated kinase)/MAPK (mitogen-activated protein kinase) pathways emanating from cell membrane growth-factor-activated tyrosine kinase or seven-transmembrane receptors (Refs 69, 70, 71). A critical step for AKT activation is phosphorylation at the D3 position of the inositol ring of the plasma membrane lipid phosphatidylinositol 4,5-bisphosphate [PtdIns(4,5)P_2] by PI3K. PI3K is activated by interaction with activated receptor tyrosine kinases (RTKs) and/or associated adaptors, such as those of the IRS family. Phosphorylation of PtdIns(4,5)P_2 produces PtdIns(3,4,5)P_3, which offers plasma membrane docking sites for proteins that contain the pleckstrin homology (PH) domain, such as AKT and PDK1 (phosphoinositide-dependent kinase). In this way, PtdIns(3,4,5)P_3-associated AKT is phosphorylated in the catalytic domain by the proximal PtdIns(3,4,5)P_3-associated PDK1 and becomes activated (Ref. 69). However, full activation of AKT requires a second phosphorylation at the conserved C-terminal hydrophobic motif by a second 'PDK2' kinase. A recent study has shown that this 'PDK2' is, in fact, mTOR kinase nucleated at mTORC2 (Ref. 31). Activated AKT, in turn, phosphorylates TSC2 and inactivates the TSC1/TSC2 heterodimer, neutralising the inhibitory activity of TSC1/TSC2 on mTORC1 (Refs 61, 72, 73).

In the Ras–ERK pathway, activated RTKs, through adaptors, recruit guanine-nucleotide exchange factors, such as SOS (son of sevenless), which stimulate the exchange of GDP for GTP on the GTPase Ras, allowing the activation of downstream effectors such as the MAPKKK Raf. It has been shown that downstream effectors of the Ras–ERK pathway – ERK (a MAPK) and the MAPK-activated protein kinase (MP) p90 ribosomal S6 kinase – can phosphorylate TSC2 and inactivate the TSC1/TSC2 heterodimer (Refs 74, 75, 76).

The AMP-activated protein kinase (AMPK) has a central place in the energy-status-associated mTOR signalling pathway (Ref. 77). AMPK is a Ser/Thr kinase that senses the AMP:ATP ratio and is activated by conditions that impinge on the energy balance of the cell, thereby increasing the relative AMP concentration. Fully activated AMPK, for which the additional step of its phosphorylation by the Ser/Thr kinase LBK1 is necessary, is able to phosphorylate TSC2, inactivating TSC1/TSC2 (Refs 78, 79, 80). AMPK regulation of mTORC1 is also noteworthy because it has been shown to be used by DNA-damage-response signals mediated by activated p53 (Ref. 81).

When there is a scarcity of nutrients (particularly amino acids leucine and arginine), the activity of the mTORC1 is low; nutrient abundance boosts mTORC1 activity (Ref. 77). Where the exact nutrient input signal is localised within the mTOR regulatory network is controversial. There are contradictory data placing the input above the level of TSC1/TSC2, or lower, at Rheb, or even at the level of mTORC1. Recently, it was shown that hVps34, a class III PI3K (totally unrelated to the PI3K mentioned in the AKT pathway), can be activated by amino acids and inhibited by AMPK (Refs 82, 83). However, the exact mechanism by which hVps34 regulates mTORC1 activity, and whether this occurs in parallel with the TSC–Rheb–mTORC1 pathway, remains uncertain.

In addition, the links between many stress signals, including those associated with hyperosmotic conditions, overproduction of reactive oxygen species, mechanical stressors

Accession information: doi: 10.1017/S1462399408000586; Vol. 10; e4; February 2008
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and the mTOR regulatory network is generally poorly understood (Ref. 84). Interestingly, the hypoxia input that culminates in mTORC1 downregulation was shown recently to be above the TSC1/TSC2 level and to depend on a hypoxia-induced 34 kDa protein, Redd1/RTP801 (Refs 85, 86). However, the exact mechanism by which Redd1 leads to TSC1/TSC2 inhibition remains unknown.

mTOR is a major integrator of oncogenic pathways

The importance of the mTOR pathway for human cancer may be better appreciated after realising that almost every member of the mTOR regulatory network behaves as an oncogene or tumour suppressor gene. Although mutations of the *MTOR* gene itself have not been described in cancers to date, genetic alterations or deregulated expression of RTKs, RAS, ERK, PI3K, PTEN, AKT, TSC1/TSC2, 4EBP-1, eIF4E and S6K1 have been identified in many types of cancer (Refs 5, 87, 88). In addition, germline genetic alterations of PTEN, TSC1/TSC2, NF1 and LBK1 are the cause of various tumour-prone syndromes, each one characterised by a specific spectrum of neoplasms (Refs 5, 87, 88).

The mechanisms by which overactivation of the mTOR pathway promotes the oncogenic phenotype are under intense investigation and are not fully elucidated. However, it seems that both deregulation of autophagy and protein translation by mTOR play major roles. On the one hand, suppression of autophagy (also a consequence of mTOR activation) by inactivation of beclin – an important downstream autophagy regulator – is oncogenic in animal models (Refs 89, 90). On the other hand, the translation of many proteins that promote cell-cycle progression, including cyclins and other oncogenes (e.g. Myc), are promoted by mTOR activation (Ref. 91). Accordingly, the mTOR downstream regulator of translation eIF4E has been shown to be oncogenic in many studies including animal models of lymphoma (Refs 92, 93).

Clinical aspects of mTOR signalling in lymphomas

The therapy of patients with haematological malignancies, including lymphomas, is in flux because efforts are focusing on the development of biologically targeted therapies, as opposed to the traditional, and mostly empirical, chemotherapeutical approaches. Here we summarise the findings of recent studies regarding the activation status, regulation and downstream targets of mTOR signalling in lymphomas (Table 1), as well as clinical efforts to exploit mTOR inhibition as part of clinical trials of lymphoma patients.

Hodgkin lymphoma

Hodgkin lymphoma (HL), previously known as Hodgkin's disease, represents ~30% of all lymphoma cases worldwide. HL is further divided into nodular lymphocyte predominant and classical types, with the latter representing ~94% of all cases. Classical HL is typically composed of a small number (often <1%) of large neoplastic cells, known as Hodgkin/Reed–Sternberg cells (HRS), within a reactive cellular background (Ref. 94). As mTOR activity and its downstream effector, S6K1, are known to be important determinants of cell size, it is not surprising that the mTOR pathway is activated in HL cell lines and primary tumours (Refs 95, 96, 97). Expression of activated mTOR, S6K1 and phosphorylated 4E-BP1 proteins in primary HRS cells has been reported in most HL tumours by using immunohistochemistry (Ref. 98). Treatment of HRS cells with rapamycin or the rapamycin analogue RAD0001 results in G1–S cell-cycle arrest, but not apoptosis (Ref. 99). However, rapamycin was shown to enhance the cytotoxicity of a chemotherapeutic agent (doxorubicin) against HRS cells (Ref. 99). Also, RAD0001 has an antitumour effect in HL murine xenograft models. The growth-inhibitory effect of RAD001 on HRS cells is accompanied by decreased NF-κB activity – an important survival factor for HRS cells, mediated by stabilisation of IκBα – as a result of translational regulation (Ref. 99). The exact mechanism of mTOR activation in HRS cells is not completely understood. It seems that AKT, an upstream regulator of mTOR, plays an important role. Activated (phosphorylated) AKT was found to be expressed by 64% of primary HL tumours in one study, and by most cases in another (Refs 100, 101). Furthermore, activation of tumour necrosis factor (TNF) receptors, including CD40, CD30 and RANK, which are characteristic of HRS cells, seems to contribute to AKT activation (Ref. 100). ERK1/2, another

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important upstream regulator of mTOR, is also activated in HRS cells (Refs 102, 103). However, the functional significance of this ERK–mTOR link in HL is unknown.

Anaplastic large cell lymphoma

Activation of the mTOR pathway has been shown in several types of non-Hodgkin lymphoma (NHL). Anaplastic large-cell lymphoma (ALCL) is a type of NHL of T- or null-cell lineage that represents approximately 2% of NHLs in North America and Europe (Ref. 94). A large subset of ALCL cases, more frequent in children and young adults, is characterised by constitutive overactivation of anaplastic lymphoma kinase (ALK) as a result of the t(2;5)(p23;q35) or other chromosomal abnormalities involving the *ALK* gene (Ref. 94).

ALK^+ ALCL cell lines and most tumours (as well as ALK^- tumours to a lesser degree) express activated constituents of the mTOR pathway, including phosphorylated 4E-BP1,

Table 1. mTOR signalling in lymphomas

Lymphoma type	Upstream regulators of mTOR	Downstream targets of mTOR	Refs
Hodgkin lymphoma	AKT, CD30, CD40, ERK1/2	S6K1, 4E-BP1, IKBα, NF-κB	95, 96, 97, 98, 99, 100, 102, 103
Anaplastic large cell lymphoma	AKT, ERK1/2, CD30, nutrients	S6K1, 4E-BP1, eIF4E, MCL-1, BCL-XL, FLIP, C/EBPβ	99, 100, 101, 102, 103, 104, 105, 106, 107, 108
Mantle cell lymphoma	AKT	S6K1, 4E-BP1, eIF4E, Cyclin D1, MCL-1, BCL-XL	111, 112, 113, 114
Chronic lymphocytic leukaemia/small lymphocytic lymphoma	AKT	S6K1, 4E-BP1, eIF-4E, Cyclin D3, cyclin A, cyclin E, survivin	115, 116, 117, 118, 119
Acute lymphoblastic leukaemia/lymphoma	AKT, Notch1, BCR–ABL kinase	S6K1, 4E-BP1, NF-κB, FKBP51, MCL1	120, 121, 122, 123, 124, 125, 126, 127, 128, 129
Diffuse large B-cell lymphoma	AKT	S6K1, 4E-BP1, cyclin D3, cyclin A, XIAP IL-6/10 (PEL)	130, 131, 132, 133
Follicular lymphoma	BCR, Syk, AKT, phospholipase D	S6K1, 4E-BP1	134
Plasma cell myeloma	AKT, ERK1/2	S6K1, 4E-BP1, cyclin D1/D2/D3, SKP2, XIAP, cIAP1, survivin, IGF-1, IGF-2, IL-6, VEGF	136, 137, 138, 139, 140, 141, 142, 143, 144, 145

Abbreviations: AKT, akt murine thymoma viral oncogene homologue; BCL-XL, long isoform of the BCL-2-related gene; BCR, B-cell receptor; BCR–ABL, fusion product of breakpoint cluster region gene on chromosome 22 and Abelson kinase; C/EBPβ; CCAAT enhancer binding protein β; cIAP1, cellular inhibitor of apoptosis 1; 4E-BP1, 4E-binding protein 1; eIF-4E, eukaryotic initiator factor 4E; ERK, extracellular-signal-regulated kinase; FLIP, FLICE-inhibitory protein; IGF, insulin-like growth factor; IL, interleukin; MCL-1, myeloid cell leukaemia 1; NF, nuclear factor; PEL, pleural effusion lymphoma; S6K1, p70 ribosomal protein S6 kinase; SKP2, S-phase kinase-associated protein 2; Syk, spleen tyrosine kinase; VEGF, vascular endothelial growth factor; XIAP, X-linked inhibitor of apoptosis.

Accession information: doi: 10.1017/S1462399408000586; Vol. 10; e4; February 2008
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p70S6K1 and mTOR, and elevated levels of eIF4E (Ref. 104). Rapamycin treatment or downregulation of mTOR by *MTOR*-specific siRNA was shown to induce G1–S cell-cycle arrest and apoptosis of ALK^+ ALCL cells, accompanied by downregulation of anti-apoptotic molecules, such as MCL-1, BCL-XL and FLIP, and cell-cycle-promoting proteins, including cyclin D2. Rapamycin was also shown to enhance the cytotoxicity of chemotherapeutic agents in ALK^+ ALCL cells (Ref. 104). Similar results were obtained using the rapamycin analogue RAD0001, which was also shown to have antitumour activity in ALCL xenograft animal models (Ref. 99). Interestingly, downregulation of a truncated isoform of the transcription factor CCAAT enhancer-binding protein β (CEBPβ) as a result of RAD001 treatment was shown to be essential for antitumour activity in one study (Ref. 99). AKT and ERK activation, as well as nutrient availability, contribute to mTOR activation in ALCL cells (Refs 104, 105). Activation of both AKT and ERK has been shown by immunohistochemistry in most ALCL tumours (Refs 103, 106). ALK has been causally linked to AKT and ERK activation in ALK^+ tumours (Refs 107, 108, 109, 110). By contrast, the cause of AKT, ERK and consequently mTOR activation in ALK^- ALCL tumours is less well understood. However, TNF-receptor signalling, including CD30 and AP-1 transcription factor activity, may play an important role (Ref. 103).

Mantle cell lymphoma

Mantle cell lymphoma (MCL) is a type of B-cell NHL characterised by t(11;14)(q13;q32) and cyclin D1 overexpression (Ref. 94). These tumours represent approximately 6% of all NHLs in North America and Europe. Because patients with MCL are usually elderly and have poor long-term survival, attempts to develop novel and biological targeted therapies are of particular importance.

Recent studies have shown that the mTOR pathway is activated in MCL cell lines and a substantial subset of MCL tumours (Ref. 111). Inhibition of the mTOR pathway by rapamycin or rapamycin analogues resulted mainly in cell-cycle arrest of MCL cells (Refs 111, 112, 113). In addition, rapamycin or its analogues enhanced the cytotoxic effect of chemotherapeutic agents, such as doxorubicin, vincristine or rituximab, which are traditional components of MCL treatment regimens (Ref. 113). In addition, total mTOR inhibition using *MTOR*-specific siRNA induced cell-cycle arrest and apoptosis of MCL cells accompanied by downregulation of cyclin D1 and anti-apoptotic proteins, including MCL-1 and BCL-XL (Ref. 111). Interestingly, downregulation of eIF4E, a downstream target of mTOR, recapitulated most of the effects of mTOR inhibition, underlining the importance of the regulation of translational machinery for the biological effects of mTOR inhibition in MCL cells (Ref. 111). Activation of AKT seems to contribute to mTOR activation in MCL cells, and specific inhibition of AKT induces cell-cycle arrest and apoptosis of MCL cells through mTOR downregulation, as well as involving targets that are independent of the mTOR pathway, including mdm2, p27, FRKHL-1, BAD and GSK-3β (Ref. 114). The cause of AKT activation in MCL, observed more frequently in the clinically aggressive blastoid variant of MCL, is not well understood. PTEN, a known AKT inhibitor, is expressed in most cases of MCL. Furthermore, activating mutations of PI3K have not been detected (Ref. 114). It seems that other factors, in addition to AKT, contribute to mTOR activation in MCL (Ref. 111).

Chronic lymphocytic leukaemia/small lymphocytic lymphoma

Chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) is a B-cell NHL that can present as either leukaemia or lymphoma. CLL/SLL is the most common type of human leukaemia and represents approximately 6% of all lymphomas. CLL/SLL affects adults, usually over 50 years of age, and it is practically incurable by standard chemotherapeutic approaches (Ref. 94). Although the pathogenesis of CLL/SLL is unknown, it is believed that the accumulation of long-lived apoptosis-defective B cells is an important pathogenetic mechanism. However, as has been shown relatively recently, aberrant proliferation of the neoplastic cells also appears to be involved (Refs 115, 116).

Inhibition of the mTOR pathway by rapamycin has been shown to decrease dramatically the proliferative potential of primary CLL/SLL cells stimulated by interleukin 2 (IL-2) or CpG oligonucleotides (Ref. 117). The rapamycin-induced G1–S cell-cycle arrest of CLL/SLL cells

Accession information: doi: 10.1017/S1462399408000586; Vol. 10; e4; February 2008
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https://doi.org/10.1017/S1462399408000586 Published online by Cambridge University Press

was accompanied by downregulation of cyclin D3, phosphorylated Rb, cyclin A and cyclin E and consequently decreased CDK2 activity, as well as by downregulation of survivin, a molecule involved in both apoptotic and proliferation pathways (Ref. 117). Interestingly, rapamycin had no effect on apoptosis of CLL/SLL cells (Ref. 117). The potential of using mTOR inhibition in CLL/SLL was shown in a recent animal model study (Ref. 118). Genetically modified mice that overexpress the TCL1 oncogene in the B-cell compartment (Eμ-TCL1 transgenic) develop in advanced age a B-cell lymphoproliferative disorder similar to human CLL/SLL (Ref. 119). Rapamycin treatment was shown to prolong significantly the life of syngeneic mice serially transplanted with Eμ-TCL1 B leukaemic cells (Ref. 118).

Acute lymphoblastic leukaemia/lymphoma

Precursor B-cell acute lymphoblastic leukaemia/lymphoma (pre-B-ALL) is one of the most common lymphoid leukaemias in children. Pre-B-ALL also can affect adults, usually the elderly. Although affected children are frequently cured by conventional chemotherapy, adult pre-B-ALL is often chemotherapy resistant (Ref. 94).

In vitro studies show that rapamycin treatment induces G1 cell-cycle arrest and apoptosis of pre-B-ALL cells, and these effects can be reversed by pretreatment with IL-7, an important regulator of B- and T-cell development (Ref. 120). These observations were further extended in a mouse model of pre-B-ALL. Transgenic mice that overexpress the tyrosine kinase receptor ret in the B-cell compartment (Eμ-ret transgenic) develop a lymphoproliferative disorder similar to human pre-B-ALL (Refs 121, 122, 123). Daily treatment of these mice in advanced stages of disease with rapamycin substantially extended survival time (Ref. 120). Also, treatment with the rapamycin analogue CCI-779 dramatically decreased the burden of the disease in severe combined immunodeficient nonobese diabetic (SCID/NOD) mice that were transplanted with primary human pre-B-ALL cells (Ref. 124).

In a recent study, BCR–ABL kinase was shown to contribute to activation of the translation machinery by inhibiting 4E-BP1 (Ref. 125). BCR–ABL kinase is the gene product of t(9;22)(q34;q11), also known as the Philadelphia chromosome (Ph), which is the hallmark of chronic myelogenous leukaemia (CML). BCR–ABL kinase is also present in approximately 25–33% of Ph^+ pre-B-ALL, mostly in adults. This provides a rationale for combining BCR–ABL kinase inhibitors (e.g. imatinib) and mTOR inhibitors, and this combination appears to offer promise for the treatment of patients with Ph^+ pre-B-ALL (Ref. 126).

In general, precursor T-cell lymphoblastic leukaemia/lymphoma (pre-T-ALL) has been relatively less well studied. However, rapamycin induces cell-cycle arrest and apoptosis in pre-T-ALL cells as in pre-B-ALL cells, and enhances the cytotoxic effects of doxorubicin in both cell types (Ref. 127). AKT activation seems to contribute to mTOR activation of ALL cells because all rapamycin-sensitive ALL samples were found to express phosphorylated AKT, and selective inhibition of AKT resulted in cell-cycle arrest and apoptosis (Ref. 128). The biological effects of rapamycin in ALL cells were also shown to be mediated partly by downregulation of the NF-κB pathway, through inhibition of the immunophilin FKBP51, a protein that belongs to the same family as FKBP12, which mediates the direct inhibition of mTOR by rapamycin (Ref. 127). Rapamycin was also found to reverse the resistance of ALL cells to glucocorticoids, through downregulation of the anti-apoptotic molecule MCL-1 (Ref. 128). In addition, inhibition of the mTOR pathway by rapamycin reversed the chemoresistance of pre-T-ALL cells caused by overactivation of Notch1, a cell membrane receptor frequently deregulated in pre-T-ALL cells as a result of activating mutations in the *Notch1* gene (Ref. 129).

Diffuse large B-cell lymphoma

Diffuse large B-cell lymphoma (DLBCL), the most common type of NHL in western countries, represents approximately a third of all NHLs. DLBCL is a heterogeneous group of diseases in terms of its pathogenesis (Ref. 94). Although a subset of patients with DLBCL is curable with current chemotherapy, many patients succumb to disease and novel therapeutic approaches are very much needed.

An in vitro study of DLBCL cell lines of the germinal centre type showed that the rapamycin analogue RAD001 induces G1 cell-cycle arrest but not apoptosis, accompanied by downregulation of cyclins D3 and A (Ref. 130).

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In the same study, RAD001 enhanced the cytotoxicity of rituximab (a monoclonal humanised anti-CD20 antibody) against DLBCL cells, whereas it seemed to decrease the effectiveness of classical chemotherapeutic agents. In an immunohistochemical investigation of primary DLBCL tumours, approximately half of cases were found to express activated AKT, an upstream regulator of mTOR (Ref. 131). Accordingly, treatment with the PI3K inhibitor LY29002 was shown to result in apoptotic cell death in a subset of DLBCL cell lines in vitro, accompanied by downregulation of XIAP, an inhibitor of the intrinsic apoptotic pathway (Ref. 131). However, LY29002 is not specific and can inhibit PI3K as well as mTOR. Therefore, the biological effects of LY29002 on DLBCL cannot be localised with certainty to either AKT or mTOR.

In another study, rapamycin was shown to inhibit the growth of primary effusion lymphoma (PEL) cell lines in vitro and in SCID mouse xenograft models. PEL is a rare type of lymphoma, currently considered to be a variant of DLBCL, affecting immunocompromised individuals, including HIV^+ patients. PEL is aetiologically linked with infections by human herpesvirus 8 (HHV-8), also known as Kaposi sarcoma-associated herpesvirus (Refs 94, 132). The growth-inhibitory effect of rapamycin was attributed partly to cell-cycle arrest mediated by dramatically decreased production of IL-6 and IL-10, which are important autocrine growth factors promoting the survival of PEL cells. Importantly, restimulation with IL-6 or IL-10 reversed the growth-inhibitory effects of rapamycin on PEL cells (Ref. 132). Also, the AKT pathway was shown to contribute to mTOR activation in PEL cells, because phosphorylated AKT, mTOR and p70S6K – a downstream effector of mTOR – were all expressed in most tumour cells (Refs 132, 133).

Follicular lymphoma

Follicular lymphoma (FL), the second most common type of B-cell NHL in adults from western countries, represents approximately 25% of all NHLs in western countries. FL is a neoplasm of germinal centre B cells, usually associated with overexpression of BCL-2 as a result of t(14;18)(q32;q21) (Ref. 94). Although patients with FL usually have an indolent clinical course, they gradually evolve to a treatment refractory phase and many patients actually die of disease.

Activation of the mTOR pathway in FL has been shown in a subset of primary FL tumours and in B-cell lymphoma cell lines that carry t(14;18) (Ref. 134). It was also shown that Syk tyrosine kinase, a protein in the B-cell-receptor signalling pathway, contributes to mTOR activation in FL cells (Ref. 134). In addition, it was proved that this link operates independently of AKT or phospholipase D, the latter also contributing to mTOR activation in FL cells (Ref. 134). Interestingly, the Syk–mTOR link was shown to be of functional importance in cell lines derived from other B-cell NHL types, including DLBCL, Burkitt lymphoma and MCL (Ref. 134). However, the clinical potential of mTOR inhibition has not been tested in an FL animal model to date. This is of particular importance because rapamycin treatment was shown to increase the levels of BCL-2 protein in B-cell lymphoma cell lines with t(14;18) (Ref. 135).

Plasma cell myeloma

Plasma cell myeloma (PCM) is a molecularly heterogeneous disease characterised by uncontrolled proliferation of plasma cells in the bone marrow. Most affected patients are adults over 40 years of age and African Americans are affected more often than Caucasian Americans (Ref. 94). Although considerable improvement in prognosis has been achieved with current chemotherapeutic regimens, many patients die of this disease.

Preliminary studies have shown that two important upstream regulators of the mTOR pathway – ERK and PI3K–AKT – are frequently activated and contribute to survival and growth of PCM cells (Refs 136, 137, 138, 139). AKT activation in particular was shown by immunohistochemical methods to be common in PCM, particularly in patients with disease progression (Ref. 137). Also, AKT inhibition was shown to induce cell-cycle arrest and apoptosis of PCM cells in vitro (Refs 137, 138). Consequently, it was found that rapamycin, or the rapamycin analogue CCI-779, induced cell-cycle arrest and apoptosis in PCM cell lines or primary tumour cells in vitro, and enhanced the growth inhibitory effect of dexamethasone in vitro in PCM xenograft models (Refs 140, 141, 142). In some studies, the

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PCM inhibitory effects of mTOR inhibitors were shown to be limited to PCM cells harbouring PTEN-inactivating mutations and overactivation of the AKT pathway (Ref. 141). The effects of mTOR pathway inhibition on PCM cells are mainly mediated by downregulation of the translational machinery. This results in decreased expression of anti-apoptotic proteins, including XIAP, cIAP1 and survivin, as well as cell-cycle-promoting proteins, including cyclin D1, cyclin D2 and cyclin D3. This occurs with a concordant increase of the cell-cycle inhibitor p27, partly as a consequence of diminished degradation because of decreased levels of SKP2 (Refs 138, 140, 142, 143). It must be added that mTOR inhibition in PCM cells interferes with nonautonomous cell-survival mechanisms because two important growth factors for PCM cells, insulin-like growth factor (IGF)-1/2 and IL-6, which are produced by non-neoplastic bone marrow cells, stimulate the PI3K-AKT pathway (Ref. 144). Another nonautonomous cell effect of mTOR inhibition in PCM is decreased angiogenesis in PCM animal models, which is, in part, due to decreased production of vascular endothelial growth factor by the neoplastic cells (Ref. 145).

Post-transplant lymphoproliferative disorders

Post-transplant lymphoproliferative disorders (PTLD) encompass a spectrum of polyclonal, oligoclonal or monoclonal lymphoproliferations of B-cell or T-cell lineage, which occur because of iatrogenic immunosuppression in patients after organ transplantation. Most cases of B-cell PTLD are associated with Epstein–Barr virus infection (Ref. 94). Although a subset of PTLD resolves spontaneously after reduction of immunosuppression, always with increased danger of graft rejection, other cases of PTLD can be clinically aggressive and difficult to manage.

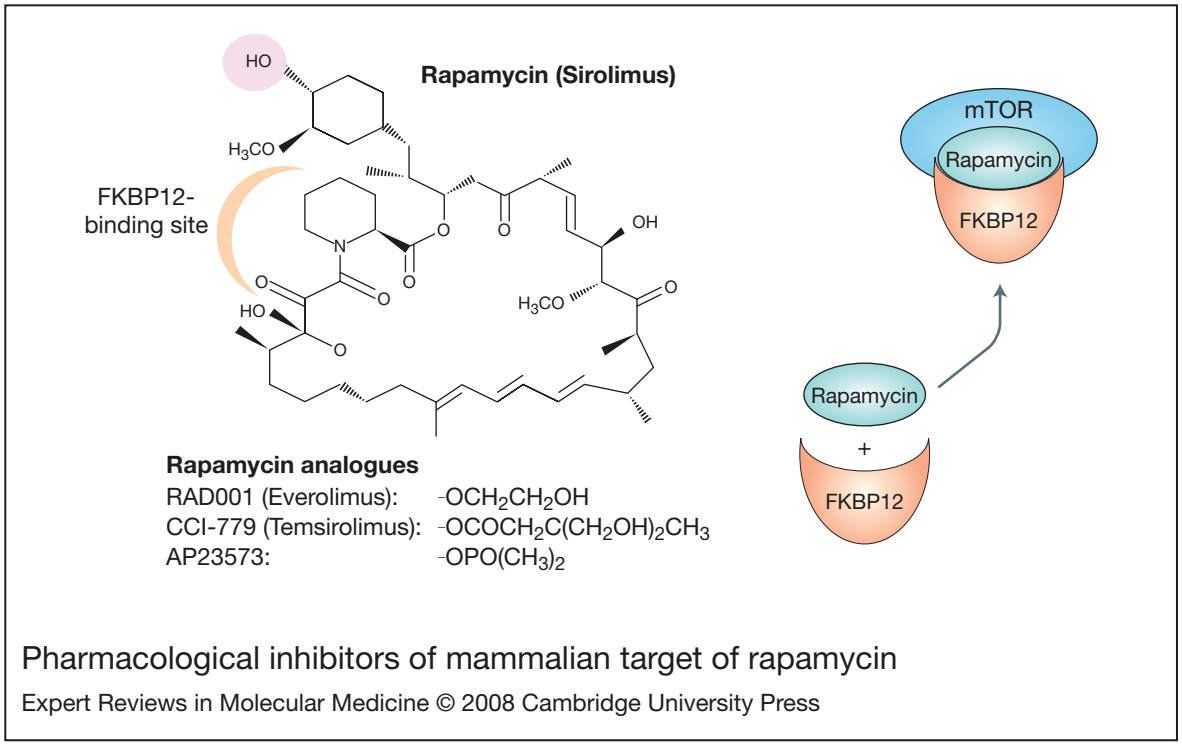
In vitro studies have shown that rapamycin or RAD001 induces G1 cell-cycle arrest and apoptosis in lymphoid cell lines established from patients with PTLD (Refs 146, 147, 148). In addition, it was shown that treatment with rapamycin or RAD001 was able to postpone the onset and delay the growth of tumours established from PTLD cell lines in SCID mice xenograft models (Ref. 148). One mechanism involved in the growth-inhibitory effect of rapamycin on PTLD, as a result of mTOR inhibition, involves downregulation of IL-10 production by tumour cells, consequently decreasing STAT-3 activation (Ref. 149). In vitro studies investigating the function of the mTOR network in EBV^+ lymphoid cells in more detail have shown that mTOR is activated in lymphoma cells with type III latency EBV infection (e.g. PTLD) and type I latency EBV infection (e.g. Burkitt lymphoma). However, activation of AKT and ERK, which may contribute to mTOR activation, was observed only in cells with type III latency EBV infection. In addition, in EBV^+ lymphoma cells, signals related to nutrient availability were also shown to be crucial for mTOR activation (Ref. 149).

Pharmacological inhibitors of mTOR

In addition to the prototype mTOR inhibitor rapamycin (sirolimus), three more mTOR inhibitors are available for clinical trials: CCI-779 (temsirolimus), RAD001 (everolimus) and AP23573 (Refs 5, 150). All inhibitors are derivatives of rapamycin with which they share the same basic chemical structure; however, each has a different chemical group at the position of the C40 hydroxyl group of rapamycin. CCI-779 is essentially a prodrug because it is metabolised to rapamycin inside the organism, whereas RAD001 and AP23573 are metabolised differently (Fig. 3). To inhibit mTOR, all must initially form an intracellular complex with the immunophilin FKB12. This complex, in turn, binds the FRB domain of mTOR, inhibiting mTOR function. The inhibition of mTOR by rapamycin and its derivatives is regarded as quite specific, and rapamycin treatment of mice embryos induces the same developmental defects as knockout of the *mTOR* gene (Refs 151, 152). Until recently, it was thought that rapamycin and its derivatives inhibit only the mTOR protein nucleated in mTORC1, which is mostly responsible for regulation of protein translation and autophagy. However, it has now been shown that prolonged treatment with rapamycin, in some types of cells, also can inhibit mTORC2, which is mainly responsible for activation of AKT (Ref. 153). This finding can be explained by the assumption that within the cell there exists an equilibrium between the pool of mTOR associated with Raptor (mTORC1) and that of

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Pharmacological inhibitors of mammalian target of rapamycin

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Figure 3. Pharmacological inhibitors of mammalian target of rapamycin. The basic chemical structure of rapamycin is shared among all rapamycin derivatives (left). The shaded area corresponds to the position of different chemical groups in the derivatives shown below. This area is distinct from the rapamycin sites for binding to immunophilin FKBP12 and mammalian target of rapamycin (mTOR), so that the mechanism of mTOR inhibition is common for rapamycin and its analogues. Rapamycin, as well its analogues, associates initially with FKBP12, in order to inhibit mTOR (right). The combined surface of the rapamycin–FKBP12 complex binds, in turn, the FRB domain of mTOR in mTORC1 and inhibits its activity. It seems that FKBP12 presents rapamycin to mTOR in a conformation-favourable state for interaction with the FRB domain. Immunophilins, such as FKBP12, belong to a protein family with at least 12 members in humans, and function as accessory helper enzymes or chaperones, contributing to the stability of multiprotein complexes. A common feature of immunophilins is they can catalyse the interconversion of *cis* and *trans* amide bonds adjacent to proline residues in peptide substrates, the so-called PPIase (prolyl isomerase) activity altering the spatial rearrangement of protein domains. This activity is inhibited by binding of each immunophilin with the corresponding drug. However, it has been shown that inhibition of PPIase activity of FKBP12 by rapamycin binding is not essential for mTOR inhibition. Abbreviations: FKBP12, FK507 binding protein 12; FRB, FKBP-rapamycin binding; mTORC, mammalian target of rapamycin complex.

mTOR associated with Rictor (mTORC2). Inhibition of mTORC2 by prolonged treatment with rapamycin is attributed to the exhaustion of mTOR available for binding to Rictor, because of the direct inhibition of mTOR bound to Raptor (Ref. 153).

Unlike rapamycin, its derivatives do not induce significant immunosuppression when administered intermittently in the appropriate clinical setting (Refs 5, 150). Rapamycin is produced in oral formulation for immunosuppression after kidney transplantation. CCI-779 (Wyeth Pharmaceuticals, Madison, NJ, USA) can be administered orally or intravenously. RAD001 (Novartis, Basel, Switzerland) is available in oral formulation and is in the advanced stage of development for use as an immunosuppressive in solid-organ transplantation. AP23573 (Ariad Pharmaceuticals, Cambridge, MA, USA) can be given orally or intravenously. Side effects common to all mTOR inhibitors include hypertension, oedema, hyperlipidaemia and gastrointestinal symptoms. Also, dose-limiting toxicities of rapamycin derivatives include reversible mucositis, asthaenia and thromphocytopaenia (Refs 5, 150).

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Clinical trials of mTOR inhibitors in lymphomas

Although rapamycin has been studied meticulously as an immunosuppressive drug, clinical experience using it as an antineoplastic agent is limited, especially for haematological malignancies (Ref. 154). However, all rapamycin derivatives are currently used in Phase I/II clinical trials as antineoplastic agents and some Phase III clinical trials are in progress (Refs 5, 154, 155).

One of the more promising results published to date regarding using mTOR inhibitors in lymphoma patients comes from a Phase II trial using CCI-779 in the treatment of MCL patients (Ref. 156). In this study, 34 patients with MCL, either refractory to previous therapy or relapsed, received CCI-779 as a single agent. Twelve patients showed partial response and one patient had a complete response, with an overall response rate of 38%. No deaths from the treatment were reported. The most frequent toxicity, which was also a cause for dose reduction, was thrombocytopaenia. Interestingly, reduction of the dose (from 250 mg to 25 mg intravenously once a week) seemed to decrease toxicities without affecting the response rate. Currently an international randomised Phase III trial comparing CCI-779 with control chemotherapy in MCL patients is ongoing.

In a Phase I/II trial of RAD001, which included four patients with MCL and six with CLL/SLL, three patients showed a 27–34% reduction of lymphadenopathy in radiological studies, and the drug was considered safe and worthy of further investigation (Ref. 157). In another trial using AP23573 to treat patients with lymphoid malignancies one of nine CLL/SLL patients showed a partial response (Ref. 155).

Additional clinical trials using rapamycin derivatives to treat Hodgkin lymphoma, PCM and other lymphomas, as monotherapy or in combination with other agents such as rituximab, are in progress, but the results are not yet published.

Research in progress and outstanding questions

Since preliminary clinical studies of mTOR inhibitors in cancer patients have shown promising results, further investigation will continue to accumulate considerable empirical knowledge about the spectrum of neoplastic diseases that will be successful targets for mTOR inhibitors. This will lead to better drug design and dosing, as well as the development of combinations of mTOR inhibitors with classical chemotherapeutical agents or new cell-signalling inhibitors that will be beneficial in various clinical settings.

However, many questions regarding the mTOR-signalling pathway that have clinical implications remain to be answered. What is the molecular signature that determines mTOR inhibition sensitivity in each clinical setting? Preliminary in vitro studies in PCM cells have shown that PTEN mutation and AKT overactivation are the most critical parameters of rapamycin sensitivity (Ref. 141). Does this hold true for other lymphoid malignancies and, if not, what are the critical pathways that contribute to mTOR activation in each case? Also, why does mTOR inhibition induce only cell-cycle arrest in some lymphomas, whereas in others mTOR inhibition also induces apoptotic cell death? Regarding the resistance of some cancer cells to rapamycin, it seems that the internal wiring of the mTOR network may play an important role. For example, in vitro studies in PCM cells showed in a subset of cases that rapamycin treatment induced overactivation of AKT. This was due to decreased IRS serine phosphorylation as a result of cancellation of the inhibitory feedback between the downstream mTOR effector S6K1 and the IRS–PI3K link upstream of AKT (Ref. 158). In which other neoplasms is this feedback connection important for rapamycin resistance? Will simultaneous inhibition at the level of AKT and mTOR by two independent inhibitors be able to overcome rapamycin resistance, as suggested in some studies (Refs 158, 159)? Some recent in vitro results suggest that prolonged rapamycin treatment – in addition to directly inhibiting mTORC1 – also has an indirect inhibitory effect on mTORC2 and therefore AKT activation through mTOR depletion (Refs 153, 160). Why is this true in some types of neoplasm and not in others, and is this a critical parameter of rapamycin resistance? The answers to these questions and many others of importance to our understanding of biology and patient care are likely to be forthcoming.

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https://doi.org/10.1017/S1462399408000586 Published online by Cambridge University Press

Acknowledgements and funding

We thank the referees for helpful suggestions to improve this manuscript.

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Further reading, resources and contacts

Guertin, D.A. and Sabatini, D.M. (2007) Defining the role of mTOR in cancer. Cancer Cell 12, 9-22
This recent review paper provides detailed molecular information about the role of mTOR pathway in cancer and its intricate molecular wiring.

Jaffe, E. et al. (eds) (2001) Pathology and Genetics of Tumors of Hematopoietic and Lymphoid Tissues. World Health Organization Classification of Tumours, IARC Press, Lyon
This book provides detailed clinical and biological information about lymphomas.

Detailed information for ongoing clinical trials with rapamycin analogues can be found at:

http://www.cancer.gov/clinicaltrials and http://www.citeline.com.

Features associated with this article

Figures
Figure 1. Mammalian target of rapamycin protein structure and complexes.
Figure 2. Downstream mediators of mammalian target of rapamycin.
Figure 3. Pharmacological inhibitors of mammalian target of rapamycin.

Table
Table 1. mTOR signalling in lymphomas.

Citation details for this article

Elias Drakos, George Z. Rassidakis and L. Jeffrey Medeiros (2008) Mammalian target of rapamycin (mTOR) pathway signalling in lymphomas. Expert Rev. Mol. Med. Vol. 10, e4, February 2008, doi: 10.1017/S1462399408000586

Accession information: doi: 10.1017/S1462399408000586; Vol. 10; e4; February 2008
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