The Enigma of Rapamycin Dosage
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Abstract
The mTOR pathway is a critical regulator of cell growth, proliferation, metabolism, and survival. Dysregulation of mTOR signaling has been observed in most cancers and, thus, the mTOR pathway has been extensively studied for therapeutic intervention. Rapamycin is a natural product that inhibits mTOR with high specificity. However, its efficacy varies by dose in several contexts. First, different doses of rapamycin are needed to suppress mTOR in different cell lines; second, different doses of rapamycin are needed to suppress the phosphorylation of different mTOR substrates; and third, there is a differential sensitivity of the two mTOR complexes mTORC1 and mTORC2 to rapamycin. Intriguingly, the enigmatic properties of rapamycin dosage can be explained in large part by the competition between rapamycin and phosphatidic acid (PA) for mTOR. Rapamycin and PA have opposite effects on mTOR whereby rapamycin destabilizes and PA stabilizes both mTOR complexes. In this review, we discuss the properties of rapamycin dosage in the context of anticancer therapeutics. Mol Cancer Ther; 15(3); 347–53. ©2016 AACR.

Introduction
mTOR is a serine/threonine protein kinase that regulates cell metabolism, growth, proliferation, and survival in response to environmental signals such as growth factors, nutrients, oxygen, energy, and stress (1). mTOR acts as the catalytic subunit in two large multiprotein complexes: mTORC1 and mTORC2. The binding partners Raptor and Rictor are specific components of mTORC1 and mTORC2, respectively (2–5) and largely determine substrate specificity for the mTOR complexes. However, both complexes contain several other structural and regulatory components required for their function (1, 6).

mTORC1 phosphorylates several downstream targets to promote biosynthesis of proteins, lipids, and nucleotides while turning off autophagy, which is a major macromolecule degradation mechanism (7). Ribosomal protein S6 kinase (S6K) and eukaryotic initiation factor 4E (eIF4E) binding protein 1 (4E-BP1) are the best characterized mTORC1 targets (8–10). Phosphorylation of S6K by mTORC1 at Thr389 has been implicated in several important cellular processes, including transcription, translation, protein and lipid synthesis, all of which are critical for cell growth and proliferative metabolism (11). Sequential phosphorylation of 4E-BP1 at residues threonine 37/46 (Thr37/46), threonine 70 (Thr70), and serine 65 (Ser65) prevents its binding and sequestration of the eukaryotic translation initiation factor eIF4e, subsequently promoting cap-dependent translation (12, 13). Though far less is known about mTORC2 relative to mTORC1 (14), mTORC2 plays seminal functions in cell metabolism and survival through the phosphorylation of Akt at Ser473 (15). Akt is a critical kinase that promotes cell-cycle progression and survival, and is also important for activation of mTORC1 signaling (16).

Altered cell metabolism, uncontrolled cell-cycle progression, and enhanced survival through suppression of apoptotic programs are major hallmarks of cancer (17). As mTORC1 is a key regulator of such cellular functions, it is not surprising that mTORC1 activity is elevated in most human cancers (18, 19). This observation has promoted interest in selectively targeting cancer cells through inhibition of mTOR. As its name implies, mTOR is targeted by rapamycin, a macrolide antibiotic with critical antiproliferative properties (20). Much of what is currently known about mTOR came from studies trying to understand the mode of action of rapamycin (20). Rapamycin does not directly inhibit the kinase activity of mTOR. Instead, rapamycin binds to its intracellular receptor, FK506-binding protein 12 (FKBP12; ref. 21). The FKBP12–rapamycin complex binds to the FKBP12–rapamycin binding (FRB) domain of mTOR (amino acid residues 2025–2114), located immediately N-terminal to the kinase domain (22). The binding of rapamycin causes conformational changes in mTOR (23) that can interfere with functional mTOR complex assembly (2). mTORC1 is highly sensitive to rapamycin, whereas mTORC2 is relatively insensitive to the drug. Within one hour, rapamycin disrupts the association between mTOR and Raptor but not with Rictor (24). As Raptor plays a key role in mTORC1 substrate recognition, substrate binding is affected (10). Prolonged exposure (24 hours) to rapamycin inhibits mTORC2 activity in some, but not all cancer cell lines (25). It has also been reported that shorter exposures to rapamycin can reduce the association between mTOR and Raptor (26). As Raptor plays a key role in mTORC1 substrate recognition, substrate binding is affected (10). Prolonged exposure (24 hours) to rapamycin inhibits mTORC2 activity in some, but not all cancer cell lines (25). It has also been proposed that rapamycin-FKBP12 binds to nascent mTOR and prevents mTORC2 complex assembly (25, 27). These studies suggest a complex mode of action for the inhibition of mTOR by rapamycin that can vary with cell type and which mTOR complex is targeted.

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Another factor associated with the efficacy of rapamycin is that it shares the same binding site as phosphatidic acid (PA; refs. 28, 29). PA is a lipid metabolite produced by both the phospholipase D-catalyzed hydrolysis of phosphatidylcholine and during membrane phospholipid biogenesis (30, 31). PA binds mTOR in a manner that is competitive with and antagonistic to rapamycin (27, 28, 32) as it stabilizes, rather than destabilizes mTOR complexes. Rapamycin prevents the interaction between mTOR and PA. This competition between rapamycin and PA for the PA-binding site on mTOR represents the most plausible explanation for the inhibitory effects of rapamycin on mTORC1 and mTORC2. Importantly, the levels of PA in a cell can alter the concentration of rapamycin needed to suppress mTOR (27, 32). The competition between rapamycin and PA for mTOR could be an important factor in targeting cancer cells with rapamycin, as PLD activity is commonly elevated in cancer cells and can lead to rapamycin resistance (32).

Rapamycin derivatives, known collectively as rapalogs, are presently FDA-approved drugs for the treatment of certain cancers, most significantly renal cancers (20, 33). Results of clinical trials have not met the high expectations for rapamycin as an anticancer therapeutic agent. Intrinsic and acquired resistance to rapamycin have been widely observed in both preclinical and clinical studies (34). mTOR inhibition by rapamycin in clinical trials has traditionally been measured by examining the level of phosphorylation of S6K1 at Thr389 (35, 36). It is well appreciated that the dose of rapamycin needed to inhibit S6K1 phosphorylation can vary dramatically between different cancer cell lines (32, 37). Furthermore, the nanomolar doses of rapamycin sufficient for suppressing S6K1 phosphorylation do not suppress 4E-BP1 phosphorylation (38, 39). The suppression of 4E-BP1 phosphorylation requires micromolar doses (38), and there appears to be other kinases capable of phosphorylating 4E-BP1 (40). In this review, we address the differential doses of rapamycin needed to suppress mTOR in different cell lines; the different doses of rapamycin needed to suppress the phosphorylation of different mTORC1 substrates; and the differential sensitivity of mTORC1 and mTORC2 to rapamycin. These enigmatic properties of rapamycin dose can be explained largely by the competition between rapamycin and PA for mTOR.

**Differential Rapamycin Sensitivity in Cancer Cell Lines**

Studies with rapamycin or rapalogs in both cultured cancer cell lines (32, 37, 41) and mouse tumor xenografts (42) have shown a differential sensitivity to rapamycin. Some cancer cells show extreme sensitivity to rapamycin with IC_{50}s less than 1 nmol/L as indicated by inhibition of S6K1 phosphorylation at Thr389, while other cancer cell lines have IC_{50}s around 100 nmol/L for suppression of S6K1 phosphorylation (32). While it has been suggested that cancer cells with elevated PI3K are more sensitive to rapamycin (41, 43, 44), the correlations are not associated with the impact of rapamycin on mTOR kinase, but rather on the impact of mTOR inhibition on proliferation. It seems that rapamycin retards the proliferation of cells where the PI3K pathway is active. There does not appear to be a major difference in the concentrations of rapamycin needed to suppress mTOR in cells where PI3K activity is high.

Several factors have been associated with intrinsic resistance to rapamycin, including mutations in mTOR and FKBP12, mutations in proteins associated with DNA damage responses, reduced levels of 4E-BP, or other negative regulators of the cell cycle (45). Rapamycin treatment also reverses feedback suppression of growth factor–dependent phosphorylation of Akt at the mTORC2 site at Ser473 (46, 47). The activation of Akt in response to rapamycin can overcome the apoptotic effects of rapamycin (48). Elevated expression of ef4E has also been shown to confer resistance to mTOR inhibition (49), consistent with the observation that knockdown of ef4E is responsible for that apoptotic effect of rapamycin (38, 50). A lesser-appreciated mechanism for conferring rapamycin resistance is the competition between rapamycin and PA for mTOR (28, 29). There is a strong correlation between elevated PLD activity and the dose of rapamycin required for inhibition of S6K1 phosphorylation (27, 32), consistent with the competition between rapamycin and PA for mTOR (28, 29). PLD-generated PA is required for mTOR activity in response to both growth factors and nutrients (27, 51–53). In breast cancer cells, cell growth inhibition can be achieved at 20 nmol/L rapamycin in MCF-7 cells, whereas 20 μmol/L is required for MDA-MB-231 cells (32). The requirement for different doses in these breast cancer cell lines underscores differential sensitivities to rapamycin observed for different cell lines, even within the same tissue source. Importantly, PLD activity is consistently 10-fold higher in MDA-MB-231 cells than in MCF7 cells (54). The sensitivity of the MCF7 cells could be reduced if PLD levels were increased and the sensitivity of the MDA-MB-231 cells could be enhanced if PLD levels were reduced (27, 32). These findings demonstrate that PLD-generated PA is an important factor in determining the sensitivity to rapamycin by interacting with mTOR in a manner that is competitive with rapamycin (depicted schematically in Fig. 1). This competition between rapamycin and PA for mTOR opens the possibility of mTOR inhibition in rapamycin-resistant cells through combined therapy with agents that suppress PLD activity, and as a consequence, sensitize the cells to rapamycin.

**Differential Rapamycin Sensitivity of mTORC1 Substrates**

Historically, mTOR inhibition has been signified by inhibition of phosphorylated S6K at Thr389. There is a fundamental reason for the examination of phosphorylated S6K—researchers were not comfortable with results achieved by examination of phosphorylated 4E-BP1. Several factors were responsible for this uncertainty. 4E-BP1 has four sites that are phosphorylated by mTORC1 that show differential sensitivity to nanomolar doses of rapamycin (38). Data generated for phosphorylated 4E-BP1 were difficult to interpret and therefore frequently excluded. In fact, there was uncertainty as to whether 4E-BP1 was actually an mTORC1 substrate (10). Consistent with this concept, 4E-BP1 can apparently be phosphorylated when mTOR is suppressed (40). It is now widely accepted that low nanomolar doses of rapamycin often lead to complete inhibition of S6K, yet only partial inhibition of 4E-BP1. Two lines of research, one with mTOR catalytic inhibitors (39, 55, 56), and another using higher doses of rapamycin (38), helped establish the idea of partial inhibition of 4E-BP1 by low-dose rapamycin treatment. The development of ATP–competitive catalytic inhibitors of mTOR (57) demonstrated clearly that 4E-BP1 is indeed an mTORC1 substrate (39). However, there are some cell lines where 4E-BP1 is insensitive to the catalytic inhibitors (40), indicating that other kinases are able to phosphorylate...
4E-BP1. While 4E-BP1 phosphorylation is clearly less sensitive to rapamycin than is S6K, higher micromolar doses of rapamycin are able to suppress the phosphorylation of 4E-BP1 (38).

Catalytic inhibitors of mTOR result in profound inhibition of cell growth, targeting both mTORC1 (effectively inhibiting both S6K1 and 4E-BP1) and mTORC2. Although the concern is that the inactivation of mTORC2 contributed to inhibition of proliferation, identical kinetics were observed in wild-type mouse embryo fibroblasts (MEF) and MEFs lacking either of the mTORC2 components Rictor (39) or Sin1 (55), indicating that the inhibition of 4E-BP1 phosphorylation was responsible for inhibition of proliferation. Importantly, studies using micromolar (high-dose) concentrations of rapamycin lead to the same conclusions. Data from Yellen and colleagues (38) indicated that low-dose rapamycin induces a partial dissociation of mTOR and Raptor as the presence of a protein cross-linker recovered the mTOR–Raptor interaction. This partial dissociation of mTOR and Raptor interaction. This partial dissociation of mTOR and Raptor is enough to prevent S6K, but not 4E-BP1, phosphorylation (Fig. 2). Significantly, at micromolar doses, rapamycin caused the complete dissociation of mTOR and Raptor, which could not be recovered by protein crosslinking. Blenis and colleagues have suggested that there is a weaker interaction between Raptor and S6K than with Raptor and with 4E-BP1 (10, 58). This supports the idea that low doses of rapamycin weakly affect mTORC1, only enough to prevent binding to S6K, whereas 4E-BP1 requires a more profound destabilization of mTORC1 to completely

Figure 1.
Model for the impact of PA on the dose of rapamycin needed to inhibit mTOR. PA and rapamycin compete to bind mTOR. Cell lines with high levels of PA generated by PLD or by other pathways will be more resistant to rapamycin because high levels of PA favor the formation of mTORC1 and mTORC2 complexes by shifting the equilibrium to the right. Low levels of PA shift the equilibrium to the left, allowing free mTOR to bind to rapamycin–FKBP12. With low levels of PA, lower doses of rapamycin are needed to bind and thus prevent the formation of mTOR complexes. The dissociation constant (K_D) for the dissociation of mTORC1 to PA and mTOR is much greater than the dissociation constant (K_D2) for the dissociation of mTORC2 to PA and mTOR. Therefore, there are far fewer dissociations of PA from mTORC2 relative to mTORC1. The ability of rapamycin–FKBP12 to suppress mTORC1 and mTORC2 depends on the availability of free mTOR to bind rapamycin–FKBP12. However, given the greater stability of mTORC2, generating free mTOR from mTORC2 is a very rare event and explains the relative insensitivity of mTORC2 to rapamycin.

Figure 2.
Model for the differential sensitivity of mTORC1 to rapamycin for different mTORC1 substrates. Low (nanomolar) doses of rapamycin cause a partial dissociation of mTOR and Raptor, which suppresses phosphorylation of S6K, but not 4E-BP1. In contrast, high (micromolar) doses of rapamycin cause the complete dissociation of mTOR and Raptor such that neither S6K nor 4E-BP1 is phosphorylated.
prevent binding to Raptor. An important aspect of the study of Yellen and colleagues (38), is that complete inhibition of 4E-BP1 phosphorylation leads to a complete cell-cycle arrest in the presence of serum (59) and apoptotic cell death in the absence of serum (38, 60), underscoring the importance of 4E-BP1 phosphorylation for both cell-cycle progression and survival. The apoptotic effect of rapamycin was due to complete suppression of eIF4E by 4E-BP1, as apoptosis could be achieved by knockdown of eIF4E (50). Importantly, knockdown of 4E-BP1 was able to overcome the effect of high-dose rapamycin, alleviating concerns regarding possible off-target effects of high-dose rapamycin. The fact that high dose rapamycin can kill cancer cells in the absence of serum has important implications for therapeutic use. The factor in serum that protects cancer cells from the apoptotic effects of rapamycin is TGF-β (50, 60). Thus, cancer cells with defective TGFβ-signaling such as pancreatic cancers (61) could be attractive targets for targeting mTOR. It has been reported that pancreatic cancer cells with defective TGFβ-signaling can be killed in the presence of serum/TGFβ by complete suppression of mTORC1 (62), although the feedback activation of mTORC2 and the phosphorylation of Akt at Ser473 (46, 47), had to be suppressed as well (62). While these results suggest promise for the targeting of mTOR in cancer therapeutically, they also reveal important problems—first, the high micromolar doses of rapamycin needed to suppress the critical mTORC1 target, 4E-BP1, are toxic in the clinic; and second, the feedback activation of mTORC2, which activates the survival kinase Akt, also needs to be suppressed. These limitations likely explain, in part, why rapamycin treatment of human cancer has had very limited success (34). Therefore, finding a way to achieve complete mTORC1 inhibition at tolerated nanomolar doses of rapamycin is a major concern. This could potentially be achieved through the combination of low-dose rapamycin with compounds that suppress PLD activity, which lowers the levels of rapamycin needed to suppress both mTORC1 and mTORC2, which has been shown to work in the laboratory (27, 32). In addition, it was reported that activating AMP-activated protein kinase with AICAR (5-aminoimidazole-4-carboxamide-1-β-4-ribofuranside) suppresses PLD activity (63) and that AICAR makes mTORC2 highly sensitive to nanomolar doses of rapamycin (64). Thus, suppressing PLD activity makes rapamycin cytotoxic at tolerated doses of rapamycin.

Differential Rapamycin Sensitivity of mTORC1 and mTORC2

Another intriguing aspect of rapamycin sensitivity is the differential sensitivity of mTORC1 and mTORC2. mTORC2 is generally resistant to rapamycin even at micromolar doses. However, prolonged treatment with nanomolar doses of rapamycin can lead to suppression of mTORC2 in several human cancer cell lines (25). The effect of prolonged treatment with rapamycin was attributed to rapamycin–FKBP12 binding to newly synthesized mTOR, before it could bind to Rictor and other components of the mTORC2 complex (25). The implication is that mTORC2 is a very stable complex and that once assembled, prevents rapamycin from accessing the FRB domain of mTOR. Subsequently, we demonstrated that if the level of PLD-generated PA was suppressed, mTORC2 could be inhibited by nanomolar doses of rapamycin without prolonged treatment (27). The implication was that PA bound to mTOR facilitated the formation of a very stable mTORC2 complex that is resistant to dissociation, thwarting access of rapamycin to the FRB domain of mTOR. However, reduction of PA levels weakened the complex, sensitizing mTORC2 to rapamycin at doses that ordinarily only inhibit mTORC1. This is shown schematically in Fig. 1 where it is speculated that the dissociation constant (KD) for mTORC2 going to PA and free mTOR is much lower than the dissociation constant (KD1) for mTORC1 going to PA and free mTOR. Critically, PA binds to mTOR in a competitive manner with rapamycin. Thus, the differential sensitivity of mTORC1 and mTORC2 to rapamycin is explained by the differential affinity of mTORC1 and mTORC2 to PA. The higher sensitivity of mTORC1 to rapamycin is consistent with the lower affinity of PA for mTORC1, which allows access to rapamycin upon dissociation. Similarly, a higher affinity of PA to mTORC2 is consistent with lower sensitivity to rapamycin, as PA will rarely dissociate from mTORC2 and allow access to rapamycin. This model is clearly an oversimplification in that the association of PA with the mTOR complexes is combined with the association of mTOR with other components of the mTOR complexes. But it makes clear that rapamycin cannot bind to mTOR unless PA dissociates from the FRB domain of mTOR (25). A PA-based model for the differential sensitivity of mTORC1 and mTORC2 to rapamycin may trigger new routes of cancer therapy with drugs that significantly lower the levels of PA in combination with rapamycin at clinically tolerable, nanomolar doses.

Conclusions

mTOR plays a central role in the regulation of G1–S-phase cell-cycle progression and survival. Consistent with these important roles for mTOR in cell proliferation, many of the signals that are dysregulated in human cancer are those that ensure mTOR is active (18, 19). Thus, there has been substantial interest in targeting mTOR as an anticancer therapeutic strategy (34, 65). Rapamycin is a natural product that suppresses mTOR with high specificity. The high specificity of rapamycin for mTOR is likely due to the nature of the mTOR–rapamycin interaction. Rapamycin interacts with the FRB domain of mTOR in a manner that is competitive with PA (27–29, 32). In the absence of PA, or in the presence of rapamycin, mTOR complexes do not form or are destabilized (2, 27). This unusual mechanism for interfering with mTOR signals undoubtedly contributes to the high degree of specificity of rapamycin, as the interaction between PA, mTOR, and mTORC1 and mTORC2 subunits involves very complex associations that are not likely replicated in the cell. The highly specific and complex interaction between mTOR, PA, and mTOR subunits is also likely responsible for much of the observed enigmatic dosing issues associated with rapamycin treatment because rapamycin competes with the PA–mTOR interaction, which varies with cellular PA levels and the differential stabilities of the mTORC1 and mTORC2 complexes (Fig. 1). The key point is the opposing effects of rapamycin and PA. If rapamycin binds mTOR, the mTOR complexes do not form. If PA binds mTOR, then mTOR combines with Raptor or Rictor and other components to form mTORC1 and mTORC2 complexes, respectively (27, 66). Thus, PA and rapamycin have opposing effects on mTOR complex formation and activity.

In this review, we have addressed three enigmatic aspects of rapamycin sensitivity that have caused confusion in both laboratory and clinical settings. The three problematic areas are the different doses of rapamycin required to: (i) achieve the same effect in different cell lines; (ii) suppress the phosphorylation of
different mTORC1 substrates; and (iii) suppress mTORC1 and mTORC2. All three effects can be attributed, at least in part, to the interaction between mTOR and PA. For the differential rapamycin sensitivity in cell types, it was shown that altering the level of PLD expression in cells, and hence the level of PA, altered the dose of rapamycin required to suppress mTORC1 (32). With regard to the differential rapamycin dose requirements for different mTORC1 substrates, the higher doses needed to suppress the phosphorylation of 4E-BP1 involved complete versus partial dissociation of Raptor from mTOR (38), again implicating PA-dependent complex stability. Finally, the differential effect of rapamycin on mTORC1 and mTORC2 is contingent upon the differential stability of the two mTOR complexes, which is also dependent on PA.

The complexities of cell type, mTORC1 substrates, and the mTOR complexes themselves compel a calculated strategy for rapamycin dosage. However, they also present opportunities to achieve different specificities using different dosages and conditions. Low nanomolar doses of rapamycin suppress the phosphorylation of 4E-BP1 by mTORC1; micromolar doses suppress the phosphorylation of both 4E-BP1 and 4E-BP1. mTOR catalytic inhibitors suppress both mTORC1 and mTORC2, preventing phosphorylation of both 4E-BP1 and 4E-BP1 and the mTORC2-mediated feedback phosphorylation of Akt at Ser473 (46, 47). While there have been reports of mTORC2-independent phosphorylation Akt at Ser473 (67), cells from knockout mice for Rictor (68) and Sin1, another component of mTORC2 (69) lack Akt phosphorylation at Ser473. Thus, while there may be mTORC2-independent mechanisms for phosphorylating Akt at Ser473, novel strategies for targeting mTORC2 with rapamycin remain an attractive therapeutic option, in that the catalytic inhibitors are ATP analogues with an inherent lack of specificity. Suppressing PA levels can sensitize mTORC2 to nanomolar doses of rapamycin (27), substituting for the potent yet nonspecific, toxic effects of mTOR catalytic inhibitors. The ability to differentially suppress mTOR complexes using rapamycin and PLD suppression is characterized in Fig. 3. In this regard, we just reported that reducing PLD activity by activating AMP-activated protein kinase can make mTORC2 sensitive to clinically tolerable nanomolar doses of rapamycin (64). Thus, while there are problems associated with the use of rapamycin or rapamycin analogues, the role that mTOR plays in promoting the survival of what is likely most human cancers (1, 18, 19), the high degree of specificity of rapamycin and the versatility of differentially inhibiting different downstream targets of mTOR make rapamycin a valuable reagent in the laboratory and the clinic.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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