# The Akt-mTOR tango and its relevance to cancer

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**The downstream effector of PI3K, Akt, is frequently hyperactivated in human cancers. A critical downstream effector of Akt, which contributes to tumorigenesis, is mTOR. In the PI3K/Akt/mTOR pathway, Akt is flanked by two tumor suppressors: PTEN, acting as a brake upstream of Akt, and TSC1/TSC2 heterodimer, acting as a brake downstream of Akt and upstream of mTOR. In the absence of the TSC1/TSC2 brake, mTOR activity is unleashed to inhibit Akt via an inhibitory feedback mechanism. Two recent studies used mouse genetics to assess the roles of PTEN and TSC2 in cancer, underscoring the importance of Akt-mTOR interplay for cancer progression and therapy.**

## Activation of Akt and the genesis of cancer

The evolutionarily conserved serine/threonine kinase Akt, also known as protein kinase B (PKB), is one of the most frequently activated protein kinases in human cancer. Hyperactivation of Akt is associated with resistance to apoptosis, increased cell growth, cell proliferation, and cellular energy metabolism. Mammalian cells express three highly homologous Akt isoforms (Akt1–3) that are encoded by separate genes and share over 80% amino acid sequence identity. The pathway leading to Akt activation is highly conserved across species. Upon activation, growth factor receptors activate the catalytic p110 subunit of phosphatidylinositol 3-kinase (PI3K) via recruitment of the corresponding p85 regulatory subunit or via Ras activation, which can directly activate p110. p110 then phosphorylates phosphoinositides (PI) at the D3-position of the inositol ring to generate PI (3,4,5) P3 (PIP3). The rate-limiting step in Akt-activation is the binding of PIP3 to the PH domain of Akt and subsequent translocation of Akt to the plasma membrane. Akt is then phosphorylated by PI3K-dependent kinase-1 (PDK1) at a threonine residue in the catalytic domain (Thr 308), and by another as yet incompletely defined PI3K-dependent kinase (PDK2) at a serine residue (Ser 473) in the carboxy-terminal hydrophobic motif (Figure 1). Phosphorylation at both sites is required for full activation of Akt (reviewed in Brazil and Hemmings, 2001; Lawlor and Alessi, 2001). Antagonizing PI3K activity negatively regulates Akt activity. Indeed, Akt activity is negatively regulated by the tumor suppressor PTEN (phosphatase and tensin homolog deleted on chromosome ten) (Cantley and Neel, 1999), a phospholipid phosphatase that antagonizes the activity of PI3K by dephosphorylating PIP3 (see Figure 1).

A number of nonexclusive mechanisms contribute to Akt hyperactivation in human cancer. Inactivating mutations or deletions of PTEN lead to Akt activation and occur frequently in human cancers, with a high incidence in prostate and endometrial cancers, glioblastoma, and melanoma (Cantley and Neel, 1999). PTEN haplodeficiency has also been associated with the development of a diverse array of tumors in mice. Although complete deficiency of PTEN is embryonic lethal, three different groups have reported a high incidence of tumors of the prostate, endometrium, thyroid, adrenal medulla, colon, and hematopoietic cells in *Pten* heterozygous mice of varying genetic background (Di Cristofano et al., 1998; Podsypanina et al., 1999; Suzuki et al., 1998a). Amplification and overexpression of the gene encoding the p110 catalytic subunit of PI3K is also observed in a subset of human cancers (Shayesteh et al., 1999). More recently, mutations in one of the genes encoding p110 have been observed in a large number of human cancers, which are likely to activate Akt (Kang et al., 2005). Activating Ras mutations can also potentially activate Akt and occur in nearly a third of epithelial tumors (Downward, 2003). Akt gene amplification has also been observed in a subset of human cancers. Lastly, the increased receptor tyrosine kinase activation observed in many human cancers can activate Akt. Perhaps the best example involves heterodimeric ErbB-2/ErbB-3 receptor activation, which frequently occurs in cancer cells and results in robust PI3K activation that can be attributed, in part, to the existence of six PI3K docking sites in ErbB-3. Thus, Akt appears to be hyperactivated in the majority of human cancers, implying that Akt activation plays a pivotal role in the genesis of cancer.

Akt can potentially phosphorylate over 9000 proteins in

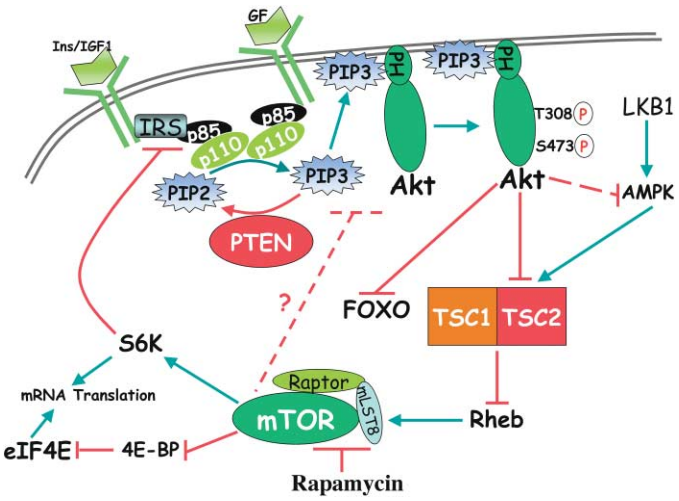


**Figure 1.** In the PI3K/Akt/mTOR pathway, Akt is flanked by two tumor suppressors: PTEN, which antagonizes PI3K and therefore inhibits Akt, and TSC1/TSC2 heterodimer, which inhibits mTOR by inhibiting the activity of Rheb

Akt activates mTOR via direct phosphorylation of TSC2 and by the inhibition of AMPK, thereby activating Rheb and mTOR-Raptor activity. Upon activation, mTOR-Raptor activates S6K and inhibits 4E-BP to accelerate mRNA translation, and also initiates feedback inhibition of Akt, which is at least in part mediated by S6K (for details see text).

mammalian cells (Lawlor and Alessi, 2001). However, it remains to be determined which downstream effectors of Akt are most critical for the genesis of cancer. Several lines of evidence point to the two most evolutionarily conserved downstream effectors, the forkhead family of transcription factors, FOXO, and the mammalian target of rapamycin, mTOR (Figure 1). FOXO transcription factors, which inhibit mammalian cell proliferation, are directly phosphorylated and inactivated by Akt (Tran et al., 2003), whereas mTOR, which is associated with increased cell proliferation, is indirectly activated by Akt.

**The interplay between Akt and mTOR**

One mechanism whereby Akt can activate mTOR is through direct phosphorylation of tuberous sclerosis complex 2 (TSC2), which otherwise inhibits mTOR activity (Figure 1; Hay and Sonenberg, 2004). Tuberous sclerosis complex 1 (TSC1) and TSC2 form a heterodimer with GTPase activity that inhibits the activity of Rheb, a small GTPase required for mTOR activation (Figure 1; Hay and Sonenberg, 2004). This mechanism of mTOR activation by Akt is conserved in *Drosophila*. In addition, TSC2 is directly phosphorylated and activated by AMPK (Inoki et al., 2003), and Akt inhibits AMPK activity, via its role in energy metabolism, to fully inhibit TSC2 and activate mTOR (Hahn-Windgassen et al., 2005). Thus, activation of Akt could also inhibit the tumor suppressor activity of AMPK kinase, LKB1 (Figure 1). Germline mutations in the genes encoding TSC1 and TSC2 are associated with the dominant genetic disorder, tuberous sclerosis (TSC), which is characterized by the development of benign tumors (hamartomas), and thus, TSC1 and TSC2 are considered tumor suppressors (Kwiatkowski, 2003). Therefore, in the PI3K/Akt/mTOR pathway, Akt is flanked by two tumor suppressors, which attenuate the pathway: PTEN, which acts upstream of Akt, and TSC1/TSC2 heterodimer, which acts downstream of Akt and upstream of mTOR.

Upon activation, mTOR, which forms a rapamycin-sensitive complex with Raptor (regulatory-associated protein of mTOR), increases mRNA translation via activation of S6-kinase and inhibition of eIF4E binding protein (4E-BP) (Figure 1; Hay and Sonenberg, 2004). TSC1 or TSC2 deletion constitutively activates rapamycin-sensitive functions of mTOR independently of Akt. In contrast, Akt activity is inhibited when mTOR is activated in TSC1 or TSC2 deficient cells via a negative feedback regulatory loop (Figure 1). This feedback inhibitory loop appears to be conserved in *Drosophila* (Radimerski et al., 2002) and has been attributed to the inhibitory effect of S6 Kinase (a downstream effector of mTOR) on insulin receptor substrate-1 (IRS-1), which mediates PI3K activation by insulin and IGF-1 (Harrington et al., 2005). However, this is unlikely to be the only mechanism that accounts for the negative feedback. A more general mechanism must exist, because Akt activity is not significantly elevated in TSC null cells, even when stimulated with serum or PDGF (platelet-derived growth factor) (Zhang et al., 2003). The relationship between Akt and mTOR is further complicated by the existence of mTOR-Rictor (rapamycin-insensitive companion of mTOR) complex, which possesses the rapamycin-insensitive mTOR activity. The mTOR-Rictor complex has a conserved activity that regulates the actin cytoskeleton (Jacinto et al., 2004; Sarbassov et al., 2004). Recent reports provide evidence that mTOR-Rictor possesses PDK2 activity, phosphorylating the serine residue in the C-terminal hydrophobic motif of Akt, and therefore essential for Akt activity (Sarbassov et al., 2005).

Despite the inhibition of Akt and the activation of FOXO (Manning et al., 2005), immortalized *Tsc2* null cells proliferate at the same rate or faster than wild-type cells and remain susceptible to oncogenic transformation to a comparable or greater extent relative to wild-type cells (Zhang et al., 2003; Ma et al., 2005a; C.C. Chen, J. Skeen, and N. Hay, unpublished data). This raises the possibility that mTOR may constitute the most critical downstream effector of Akt with respect to cell proliferation, tumorigenesis, and possibly cell survival. In cultured cells, mTOR inhibition by rapamycin attenuates cell cycle progression and, in some cases, elicits apoptosis (Hay and Sonenberg, 2004). The rapamycin analog CCI-779 attenuates tumor growth in *Pten*$^{+/-}$ mice predisposed to developing a diverse array of neoplasia (Podsypanina et al., 2001), as well as in cancer cells lacking functional PTEN (Neshat et al., 2001). Furthermore, transgenic mice expressing activated Akt in the prostate develop prostate intraepithelial neoplasia (PIN), which is antagonized by the rapamycin analog RAD001 (Majumder et al., 2004). Also, overexpression of eIF4E, a downstream effector of mTOR, in mouse B cell lymphoma accelerates tumorigenesis and mimics the neoplastic effect of activated Akt in these cells (Wendel et al., 2004). The critical role that mTOR and mRNA translation play in tumorigenesis is reinforced by the observation that the primary effects of oncogenic Ras or Akt on gene expression are via induction of mRNA translation (Rajasekhar et al., 2003).

The contention that mTOR executes the most critical functions of Akt with regards to cell growth and proliferation is supported by genetic studies in *Drosophila*. In *Drosophila*, both *pten* deletion and the loss of either *tsc1* or *tsc2* result in similar phenotypes characterized by increased cell size and cell proliferation. Genetic epistasis analyses in *Drosophila* have shown that cells doubly deficient for *akt* (or overexpressing PTEN) and either *tsc1* or *tsc2* mimic the phenotype induced by *tsc1* or *tsc2* inactivation (Potter et al., 2001). Similarly, cells doubly deficient for *pten* and *tor* are indistinguishable from cells lacking *tor* alone, which are characterized by reduced cell size and impaired proliferation (Zhang et al., 2000). Thus, in *Drosophila*, TSC1/TSC2 and TOR are epistatic to PTEN and Akt. Based on these observations, one might expect that mutations in the genes encoding the tumor suppressors TSC1 and TSC2 should be frequently observed in a wide spectrum of human cancers, as is observed for PTEN. However, unlike mutations in the *pten* gene, mutations in either *tsc1* or *tsc2* gene have not yet been identified in sporadic human cancers (Kwiatkowski, 2003). Moreover, tuberous sclerosis patients with inherited mutations in either *Tsc1* or *Tsc2* develop hamartomas in multiple organs, but rarely develop malignant cancers (Kwiatkowski, 2003). In contrast, patients with Cowden disease that harbor *Pten* gene mutations develop similar lesions but are predisposed to malignant cancer development (Eng, 2003). Also, when tuberous sclerosis patients do develop malignant cancer, it is generally restricted to certain types of tumors such as renal cell carcinoma or angiomyolipomas (Kwiatkowski, 2003). Finally, unlike *Pten*$^{+/-}$ mice that are predisposed to multiple neoplasia, *Tsc2*$^{+/-}$ mice develop mainly kidney tumors and hepatic hemangioma and, depending on the genetic background, also lung adenoma and angiosarcoma (Kobayashi et al., 1999; Onda et al., 1999). Taken together, these observations raise the question of why TSC1/TSC2 deficiency does not recapitulate the PTEN deficiency in respect to cancer. One possibility is that in vivo, the Akt inhibition mediated by mTOR activation impedes the tumor progression promoted by TSC1/TSC2 deficiency. Independent studies by two different groups have attempted to address this

issue in vivo in the mouse. Since complete loss of either PTEN or TSC2 leads to embryonic lethality, both groups employed *Pten*$^{+/-}$, *Tsc2*$^{+/-}$, and *Pten*$^{+/-}$*Tsc2*$^{+/-}$ mice to address this question (Ma et al., 2005b; Manning et al., 2005). Although the source of *Pten*$^{+/-}$ mice utilized in both studies was the same, the source of *Tsc2*$^{+/-}$ mice was different. The *Tsc2*$^{+/-}$ mice used by Ma et al. predominantly develop renal carcinoma and, after a long latent period, hepatic hemangiomas (Kobayashi et al., 1999), whereas the *Tsc2*$^{+/-}$ mice used by Manning et al. develop hepatic hemangiomas and angiosarcomas in addition to kidney tumors (Onda et al., 1999).

Based on the epistasis analyses in *Drosophila*, the deficiency in TSC2 is expected to increase the phenotype of PTEN deficiency, whereas the deficiency in PTEN is not expected to enhance the phenotype of TSC2 deficiency. Indeed, both groups found that *Pten*$^{+/-}$*Tsc2*$^{+/-}$ mice display enhanced lymph node hyperplasia, which is observed in *Pten*$^{+/-}$ mice and is the main cause of death of these mice, and therefore there is a significant decrease in the life span of *Pten*$^{+/-}$*Tcs2*$^{+/-}$ mice in comparison with *Pten*$^{+/-}$ mice. However, Manning et al. did not find that TSC2 haplodeficiency enhances the endometrium and prostate neoplasia, gastrointestinal polyps, or thyroid and adrenal medulla tumors, which are typically found in *Pten*$^{+/-}$ mice. In contrast, Ma et al. found that haplodeficiency of TSC2 accelerates the development of prostatic neoplasia in *Pten*$^{+/-}$ mice, since PIN rarely progresses to carcinoma in *Pten*$^{+/-}$ mice, whereas progression to carcinoma is frequently observed in *Pten*$^{+/-}$*Tsc2*$^{+/-}$ mice. In addition, they found that a small percentage of the doubly heterozygous mice developed skin cancer, which was not observed in either of the singly heterozygous mice. Consistent with what could be extrapolated from the epistasis analyses in *Drosophila*, Ma et al. found that PTEN haplodeficiency did not enhance renal carcinoma development in their *Tsc2*$^{+/-}$ mice. Manning et al., however, found that haplodeficiency of PTEN, which only modestly accelerated kidney adenomas, dramatically decreased the latency and increased the penentrance of liver hemangiomas and angiosarcomas in *Tsc2*$^{+/-}$ mice. Both groups attributed the differences in their results to the different genetic background of the mice used in these studies. Interestingly, both groups found that the feedback inhibition of Akt induced by TSC2 deficiency is alleviated by PTEN haplodeficiency.

Collectively, the results of these studies do not provide a conclusive explanation for the lack of mutations in *Tsc* genes in sporadic cancers, or for the limited spectrum of tumors induced by TSC2 deficiency. Nevertheless, based on their results, Manning et al. suggested that the feedback inhibition of Akt induced by the deletion of TSC2 impedes the progression of cancer, and that when PTEN level is also reduced, the restored Akt activity enables faster tumor progression. How does restoration of Akt activity in *Tsc2*$^{+/-}$ mice contribute to tumorigenesis? As tumorigenesis is a multistep process, which requires multiple genetic lesions, it is conceivable that Akt activation accelerates the mutation rate, including the loss of heterozygosity (LOH) of *Tsc2* observed in tumors of *Tsc2*$^{+/-}$ mice. Notably, activation of Akt or deletion of PTEN could overcome a G2 cell cycle checkpoint and accelerate mutagenesis (Kandel et al., 2002; King et al., 2004; Puc et al., 2005). In addition, accelerated mRNA translation and ribosomal biogenesis induced by the deficiency of TSC2 consume high levels of cellular energy. Since Akt is required to maintain cellular energy metabolism (Hahn-Windgassen et al., 2005), the limited intracellular ATP in *Tsc2* null cells could inhibit their survival and proliferation, in particular within a neoplastic lesion, an environment where nutrients and oxygen have more restricted availability, unless Akt activity is restored. Other prooncogenic activities of Akt, particularly its antiapoptotic activities, are also likely to contribute.

Based upon their results, Ma et al. have provided an alternate explanation for the discrepancy between *Pten* and *Tsc2* mutational frequencies in cancer. These authors found that while tumors initiated by *Tsc2* heterozygosity develop only after LOH, tumors initiated by *Pten* heterozygosity can develop in the absence of LOH. This raised the possibility that PTEN is a haploinsufficient tumor suppressor. Because they also found that tumors initiated by *Pten* heterozygosity are accelerated by *Tsc2* heterozygosity but do not exhibit LOH at either of the two genes, they concluded that TSC2 also constitutes a haploinsufficient tumor suppressor for certain types of cancer.

**Are PTEN and TSC2 haploinsufficient tumor suppressors?**

According to the classic tumor suppressor two-hit paradigm defined by Knudson, a germline mutation in a tumor suppressor gene is followed by the loss of function of the other allele during tumor development via genetic or epigenetic mechanisms. However, whether PTEN follows that rule is controversial. Although biallelic *PTEN* inactivation is frequently observed in several types of cancer, the loss of a single allele, with the preservation of the other allele, is also common. For instance, LOH at 10q23, the chromosomal localization of *PTEN*, was reported to occur in over half of human metastatic prostate cancers, but only a third of these cases display biallelic *PTEN* intragenic mutations (Suzuki et al., 1998b). This, however, does not completely rule out the possibility that the expression of or the activity of PTEN is either reduced or lost by other documented epigenetic mechanisms (Kurose et al., 2001). Likewise, despite the absence of *Pten* LOH in neoplastic lesions described by Ma et al., reduced PTEN function by inactivating mutations in the preserved allele cannot be fully excluded, as this was not exhaustively examined. Furthermore, these results seemingly contradict those reported by others demonstrating *Pten* LOH in lymphoma, endometrial carcinoma, adrenal tumors, and prostatic neoplasia in *Pten*$^{+/-}$ mice (Podsypanina et al., 1999; Podsypanina et al., 2001; Suzuki et al., 1998b). Clearly, the long latency period required for neoplasia development in *Pten*$^{+/-}$ mice, which is markedly shortened in the complete absence of PTEN (Trotman et al., 2003; Wang et al., 2003), suggests that the expression and/or activity of the remaining wild-type *Pten* allele is somehow affected in this process in *Pten*$^{+/-}$ mice. Nevertheless, the absence of LOH at the *Pten* locus in the lymph node hyperplasia of *Pten*$^{+/-}$ mice suggests that haplodeficiency of PTEN is sufficient to confer some cell survival and possibly proliferative advantage to cause preneoplastic lesions. The transition to high-grade neoplasia requires additional modifying mutations, including those affecting the wild-type *Pten* allele. The list of candidate modifier genes would ostensibly include regulators of mTOR activity, given the fact that tumorigenesis is enhanced in *Pten*$^{+/-}$*Tsc2*$^{+/-}$ mice.

Unlike PTEN, both TSC1 and TSC2 follow the classical tumor suppressor two-hit paradigm in human tumors (Kwiatkowski, 2003), and LOH is usually observed in tumors developed in *Tsc2*$^{+/-}$ mice (Kobayashi et al., 1999; Onda et al., 1999). However, Ma et al. found that in the prostate neoplasia of *Pten*$^{+/-}$*Tsc2*$^{+/-}$ mice, there is no *Tsc2* LOH, suggesting that when

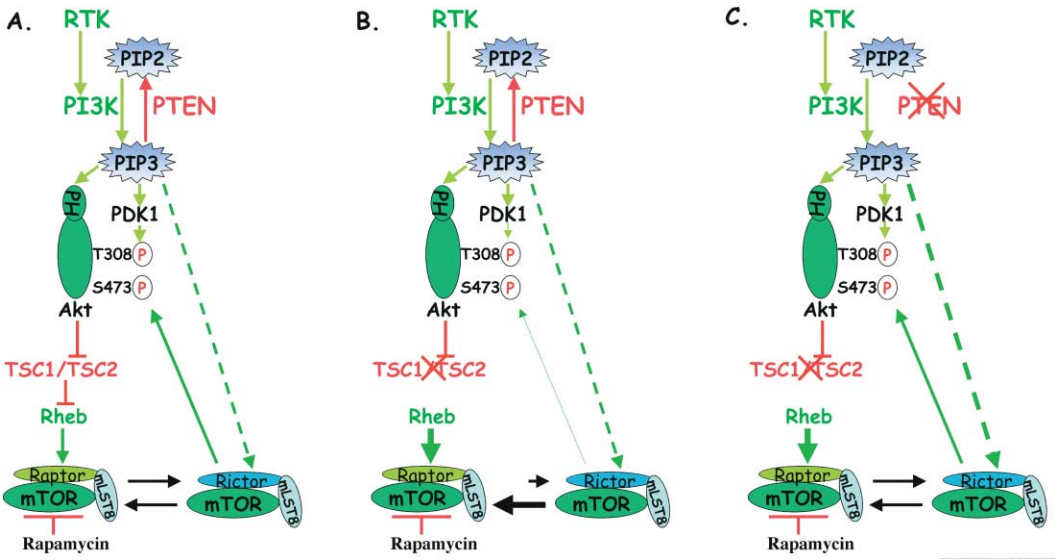


**Figure 2.** An equilibrium between mTOR-Raptor and mTOR-Rictor complexes could provide an alternative mechanism for the feedback inhibition of Akt by mTOR

**A:** In wild-type cells, the activation of receptor tyrosine kinase (RTK) leads the activation of PI3K. PI3K then leads to the activation of Akt by inducing its translocation to the plasma membrane and its phosphorylation by PDK1 and by mTOR-Rictor (PDK2). Upon activation, Akt induces the assembly of the active mTOR-Raptor complex. The assembly of mTOR-Raptor active complex inhibits the assembly of the mTOR-Rictor active complex, and thereby inhibits Akt. However, in wild-type cells, this inhibition is transient, because the inhibition of Akt would eventually inhibit mTOR-Raptor.
**B:** In TSC-deficient cells, mTOR-Raptor active complex is constitutively active, thereby reducing mTOR-Rictor activity and therefore also Akt activity.
**C:** In cells doubly deficient for PTEN and TSC, PI3K is hyperactivated, leading to the hyperactivation of mTOR-Rictor and thereby restoring Akt activity.

PTEN levels are reduced, TSC2 is haploinsufficient to suppress tumorigenesis. Indeed, they found that, at least ex vivo, mouse embryonic fibroblasts doubly heterozygous for *Pten* and *Tsc2* exhibit elevated mTOR activity when compared with their singly heterozygous counterparts. This is consistent with the results of Manning et al. showing that $Pten^{+/-}Tsc2^{+/-}$ hyperplastic lymph nodes display elevated mTOR activity in the absence of LOH. Thus, it is not immediately clear why there is a loss of TSC2 in kidney tumors and hepatic hemangiomas derived from $Pten^{+/-}$ $Tsc2^{+/-}$ mice (Kwiatkowski, 2003). Also, if indeed TSC2 is haploinsufficient to suppress tumor development on the background of other mutations, which enhance PI3K activity, it is not clear why TSC patients rarely develop malignant cancer, which is restricted only to certain cell types. Obviously, more studies are required to resolve this issue.

**The implication of Akt-mTOR interactions for cancer therapy**

The studies by Ma et al. and Manning et al. underscore the importance of Akt-mTOR interrelationships for the progression and therapy of cancer. Akt and mTOR are linked to each other via positive and negative regulatory circuits, which restrain their simultaneous hyperactivation (Figure 2). This might have been evolved as a protection mechanism to inhibit uncontrolled cell survival and proliferation. As indicated above, the feedback inhibition of Akt induced by hyperactivation of mTOR rapamycin-sensitive activity was attributed to the inhibitory effect of S6 kinase on IRS-1 downstream of IGF-1 and insulin receptors. However, the inability of serum or PDGF to overcome this inhibition, together with the finding by Ma et al. and Manning et al. that the feedback inhibition also occurs in vivo in mouse tissues that are exposed to a variety of growth factors, which activate their cognate receptors and PI3K, points to a more general mechanism. Since haplodeficiency of PTEN is sufficient to alleviate the feedback inhibition, one possibility is that hyperactivation of the rapamycin-sensitive activity mTOR could elevate PTEN activity. Alternatively, the existence of two mTOR complexes may explain the inhibitory feedback. As indicated above, mTOR exists in two separate complexes, the mTOR-Raptor, a rapamycin-sensitive complex, which is activated by Akt, and the mTOR-Rictor, a rapamycin-insensitive complex, which is activated by growth factors and possesses PDK2 activity (Sarbassov et al., 2005). If mTOR-Rictor is indeed the principal PDK2, following growth factor stimulation, the mTOR-Rictor complex activates Akt. When activated, AKT inhibits the activity of TSC1/TSC2 heterodimer to activate Rheb, which in turn promotes the formation of mTOR-Raptor complex to activate the rapamycin-sensitive activity of mTOR. Assuming that an equilibrium exists between these two complexes within the cell, when the mTOR-Raptor complex is formed, it could antagonize the formation of mTOR-Rictor complex and therefore reduce Akt activity (Figure 2). Although speculative, this could provide, in addition to the documented specific mechanisms (Harrington et al., 2005; Zhang et al., 2003), a simple general mechanism for the feedback inhibitory loop. Thus, when mTOR-Raptor is activated independently of Akt, via the deletion of TSC1/TSC2, it may inhibit the formation of mTOR-Rictor complex and therefore also Akt activation (Figure 2). This is also compatible with the observation that knockdown of Raptor increases Akt activity (Sarbassov et al., 2005). Because PDK2 activity is dependent on PI3K, it is conceivable that reduced activity of PTEN would enhance mTOR-Rictor activity and therefore alleviate the inhibition of Akt by the hyperactive mTOR-Raptor complex in TSC-deficient cells.

The rapamycin derivatives CCI-779, RAD001, and AP23573

are currently being investigated in clinical trials for cancer therapy (Vignot et al., 2005). However, because the primary activity of rapamycin is to attenuate cell cycle progression and cell growth, it is not presently clear whether these agents are simply cytostatic or can also eliminate tumor cells by inducing cell death. Moreover, because of the negative regulatory loop, rapamycin can elevate Akt activity (Harrington et al., 2005), this could pose a significant strategic dilemma when designing cancer therapies using these compounds, unless prolonged rapamycin treatment also impairs mTOR-Rictor complex activity and consequently Akt activity. In principle, therefore, therapeutic approaches that simultaneously target both Akt and mTOR-Raptor may ultimately prove more efficacious.

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