Recent studies demonstrate that the mammalian target of rapamycin (mTOR) and its effector, S6 kinase 1 (S6K1), lie at the crossroads of a nutrient–hormonal signaling network that is involved in specific pathological responses, including obesity, diabetes and cancer. mTOR exists in two complexes: mTOR Complex1, which is rapamycin-sensitive and phosphorylates S6K1 and initiation factor 4E binding proteins (4E-BPs), and mTOR Complex2, which is rapamycin-insensitive and phosphorylates protein kinase B (PKB, also known as Akt). Both mTOR complexes are stimulated by mitogens, but only mTOR Complex1 is under the control of nutrient and energy inputs. Thus, to orchestrate the control of homeostatic responses, mTOR Complex1 must integrate signals from distinct cues. Here, we review recent findings concerning the regulation and pathophysiology associated with mTOR Complex1 and S6K1.

Introduction

The coordinated control of cell growth to produce a genetically predetermined cell size, organ shape or body plan is greatly influenced by mammalian target of rapamycin (mTOR) and its downstream effector S6 kinase 1 (S6K1), as first revealed by studies in mice and Drosophila [1]. In this context, S6K1 has emerged as a crucial effector of mTOR signaling. The ability of mTOR to phosphorylate downstream substrates, including S6K1, depends on three associated proteins, of mTOR signaling. The ability of mTOR to phosphorylate [1]. In this context, S6K1 has emerged as a crucial effector of mTOR Complex1–S6K1 signaling: at the crossroads of obesity, diabetes and cancer

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PtdIns(3,4,5) 

mTOR Complex1–S6K1 signaling in the absence of amino acids. The notion that amino acids are involved in mTOR Complex1 signaling first arose in a study of cultured hepatocytes in which amino acids inhibited the progression of macroautophagy [22]. In this study [22], it was shown that this inhibitory effect on macroautophagy is paralleled by increased phosphorylation of 40S ribosomal subunit protein S6. Subsequently, several research groups demonstrated that induction of S6K1 and 4E-BP1 phosphorylation by amino acids, especially the branched-chain amino acids and particularly leucine, depends on mTOR Complex1 [22]. Later studies, performed in several insulin-responsive cell lines, showed that amino-acid withdrawal results in the rapid dephosphorylation of S6K1 and 4E-BP1, whereas addition of amino acids rescues this response in a rapamycin-sensitive manner [23]. In contrast to initial findings [24], recent studies suggested that TSC1–TSC2 complex is not required to transduce the amino-acid signal to mTOR Complex1 [20,21]. Indeed, these studies demonstrated that S6K1 phosphorylation is elevated and completely resistant to insulin in cells in which either TSC1 or TSC2 levels had been reduced or completely depleted. By contrast, S6K1 activity is still regulated by amino acids in TSC1–TSC2-deficient cells that have lost the TSC1–TSC2 inhibitory signal.

Growth factors and hormones

Growth factors and hormones, such as insulin, regulate mTOR Complex1 through the generic class I phosphatidylinositol 3-kinase (PI3K) signaling pathway [1]. Stimulation of class I PI3K initiates several selective signaling cascades that lead to increased growth and proliferation, a phenomenon conserved throughout metazoans [16]. The interaction of insulin with its cognate tyrosine kinase receptor results in intermolecular phosphorylation of the receptor, creating docking sites for the recruitment of IRS1 and IRS2 to the cell membrane [1]. In turn, specific phosphorylated residues in IRS1 and/or IRS2 serve as recognition motifs for the binding of key signaling molecules, such as class I PI3K. At the membrane, class PI3K produces the second messenger phosphatidylinositol 3,4,5-trisphosphate [PtdIns(3,4,5)P_3] [1]. PtdIns(3,4,5)P_3 binds to the pleckstrin-homology (PH) domain of target proteins, including PKB/Akt [8] and phosphoinositide-dependent kinase 1 (PKD1) [1]. PtdIns(3,4,5)P_3 binding to the PH domain of PKD1 does not seem to be required for S6K1 T229 phosphorylation [17]. Binding of PtdIns(3,4,5)P_3 to the PH domain of PKB/Akt recruits this kinase to the cell membrane where it is activated through concerted phosphorylation by PKD1 at T389 and mTOR Complex2 at S473 [1]. The major negative regulator of this step in the signaling pathway seems to be the lipid phosphatase, phosphatase and tensin homolog (PTEN). PTEN converts PtdIns(3,4,5)P_3 into PtdIns(4,5)P_2, leading to a reduced recruitment of PKB/Akt to the cell membrane. In turn, activated PKB/Akt has several downstream substrates, including glycogen synthase kinase-3 (GSK3), forkhead box, sub-group O (FOXO) transcription factors and tuberous sclerosis protein 2 (TSC2) of the TSC1–TSC2 complex, which acts as a tumor suppressor complex. The phosphorylation of TSC2 results in its dissociation and degradation of TSC1–TSC2 complex, which releases the small GTPase RAS homologue enriched in brain (Rheb) from the inhibitory GTPase-activating protein activity of TSC2, driving Rheb into the GTP-bound active state [1]. It is believed that GTP-bound Rheb enables mTOR Complex1 signaling to downstream substrates, such as S6K1 (Box 1), by directly altering mTOR Complex1 activity or targeting it to a unique cellular compartment [1].

Nutrients

The insulin-induced class I PI3K–PKB signaling pathway is also activated by other growth factors, such as epidermal growth factor (EGF), insulin-like growth factor (IGF) and platelet-derived growth factor (PDGF) [18]. Once activated through these pathways, PKB/Akt can mediate the phosphorylation of several specific substrates, including those described above, in addition to caspase 9 and the BCL-2-antagonist of cell death (BAD), culminating in a prosurvival response [19]. Although the activation of mTOR Complex1 is involved in this response, the kinase activity of mTOR Complex1 cannot be triggered by class I PI3K in the absence of nutrients or cellular energy. Recent studies that analyzed the role of nutrients, specifically amino acids, revealed the existence of a novel signaling cascade that activates mTOR Complex1 [20,21]. The notion that amino acids are involved in mTOR Complex1 signaling first arose in a study of cultured hepatocytes in which amino acids inhibited the progression of macroautophagy [22]. In this study [22], it was shown that this inhibitory effect on macroautophagy is paralleled by increased phosphorylation of 40S ribosomal subunit protein S6. Subsequently, several research groups demonstrated that induction of S6K1 and 4E-BP1 phosphorylation by amino acids, especially the branched-chain amino acids and particularly leucine, depends on mTOR Complex1 [22]. Later studies, performed in several insulin-responsive cell lines, showed that amino-acid withdrawal results in the rapid dephosphorylation of S6K1 and 4E-BP1, whereas addition of amino acids rescues this response in a rapamycin-sensitive manner [23]. In contrast to initial findings [24], recent studies suggested that TSC1–TSC2 complex is not required to transduce the amino-acid signal to mTOR Complex1 [20,21]. Indeed, these studies demonstrated that S6K1 phosphorylation is elevated and completely resistant to insulin in cells in which either TSC1 or TSC2 levels had been reduced or completely depleted. By contrast, S6K1 activity is still regulated by amino acids in the absence of the TSC1–TSC2 complex inhibitory signal. Moreover, although amino-acid-induced mTOR Complex1 signaling requires Rheb, amino-acid withdrawal from either TSC1- or TSC2-deficient cells has no effect on high Rheb–GTP levels; however, such treatment leads to a rapid S6K1 dephosphorylation [20]. Thus, endogenous Rheb–GTP is required for this response, but is insufficient to activate mTOR Complex1 signaling in the absence of amino acids. These results indicate that amino-acid input to mTOR Complex1 might occur through a parallel signaling
pathway. Earlier studies from the late 1990s demonstrated that amino-acid stimulation of mTOR Complex1 signaling to S6K1 and 4E-BP1 is wortmannin-sensitive, despite the fact that amino acids do not induce PKB/Akt activation [22]. Indeed, small interfering (si)RNA-mediated depletion of class I PI3K almost completely blocks insulin-induced PKB/Akt S473 and S6K1 T389 phosphorylation, but has no effect on the ability of amino acids to induce S6K1 activation [20]. Thus, the wortmannin-sensitive target of amino-acid-induced mTOR Complex1 signaling might reside on a pathway that is distinct from the class I PI3K–PKB/Akt signaling pathway. By using several pharmacological, biochemical and molecular approaches, it was shown that the activity of the class III PI3K human vacuolar protein sorting-34 (hVps34) is modulated by amino-acid availability, and that the activation of S6K1 by amino-acid stimulation through mTOR Complex1 requires hVps34 [20,21] (Figure 1 and Box 2).

Energy

The mechanisms regulating mTOR Complex1 signaling through cellular energy are not as well defined as those for growth factors and nutrients. Studies have largely relied on the role of either acute (minutes) or chronic (hours) energy depletion on mTOR Complex1 signaling. It was shown that mTOR Complex1 signaling to S6K1 is sensitive to small changes of intracellular ATP levels and does not depend on alterations of amino-acid levels [26]. Dennis et al. [26] showed that acute treatment with the mitochondrial Complex1 inhibitor rotenone results in a small reduction of intracellular ATP levels and insulin-induced S6K1 activation [26]. Consistent with the possibility that homeostatic levels of ATP directly regulate mTOR signaling [26], the apparent Kₐ of mTOR for ATP is similar to cellular ATP concentrations [27]. However, subsequent studies suggested that acute energy depletion by treatment with oligomycin, an inhibitor of oxidative phosphorylation and respiration, inhibits mTOR Complex1 signaling through AMP-activated kinase (AMPK) phosphorylation and activation of TSC2 [28–30] (Figure 1). In agreement with this finding, activated variants of AMPK inhibit mTOR signaling [28]. However, Smith et al. [25] have recently reported that acute treatment of TSC2-deficient cells with 2-deoxyglucose, an energy depleting agent, leads to inactivation of S6K1. The Drosophila ortholog of TSC2, dTSC2, does not have

Figure 1. mTOR Complex1–S6K1 pathway. mTOR exists in two structurally distinct complexes. mTOR Complex1, which contains raptor, is regulated by inputs including amino acids, ATP and insulin, which initiate diverse signaling cascades (broken arrows indicate the uncertainty of the mechanisms involved). Recent studies indicate that mTOR Complex2 is not upstream of mTOR Complex1 [5,10]. Phosphorylation of S6K1 by mTOR Complex1 enables PDK1 to phosphorylate and activate S6K1. Abbreviations: eEF2K, eukaryotic elongation factor 2K; eIF4B, eukaryotic initiation factor 4B; FYVE, Fab1/YOTB/2K632.12/Vac1/EEA1 domain; GEF, guanosine nucleotide exchange factor; PDCD4, programmed cell death protein 4; PX, Phox homology domain.
Box 2: Outstanding questions

- How does hVps34 signal as a positive effector of autophagy in the absence of nutrients and a positive effector of mTOR Complex1 in the presence of nutrients?
- What is the target of AMPK in mTOR Complex1–S6K1 signaling, in the absence of TSC1 and TSC2?
- Does the activation of AMPK by metformin result in inhibition of mTOR and S6K1?
- Are the effects of EGF-receptor inhibition on fasting glucose levels due to reduced PKB/Akt activity, leaving it more sensitive to the effects of circulating insulin?
- Would combination of current diabetic therapies with an inhibitor of mTOR result in a more dramatic affects on insulin resistance?
- Can dietary or lifestyle modifications increase the efficacy of current cancer therapeutics?

mTOR Complex1–S6K1 signaling in obesity and diabetes

As discussed before, mTOR Complex1–S6K1 integrates various extrinsic signals that regulate cell growth and metabolism. Activation of mTOR Complex1–S6K1 signaling by nutrients has received broad attention because of its implication in obesity and insulin resistance [1,34]. Nutrient overload by increased carbohydrate, fat and/or protein intake leads to obesity, which is characterized by increased adipocyte mass and number. Early experiments with rapamycin provided a link between mTOR Complex1–S6K1 and adipogenesis. In these studies, rapamycin inhibited both clonal expansion and adipocyte differentiation [1]. Recent studies have shown that S6K1-deficient mice exhibit increased lipolysis and reduced adipose tissue mass (Figure 2). They also demonstrated that S6K1-deficient mice are protected from diet- and age-induced obesity [15]. The decreased level of adipogenesis in these mice might be due to a cell-autonomous defect—that is, the failure in transduction of signals induced by adipogenic stimuli such as insulin or by amino acid availability. Another possibility, however, is that the adipogenesis defect in S6K1-deficient mice is not cell autonomous but caused by impaired humoral effects or secondary effects due to loss of S6K1 in early development. These possibilities might be addressed in vitro by using S6K1-deficient mouse embryonic fibroblasts (MEFs) and testing their potential to differentiate into adipocytes and in vivo by using adipocyte-conditional S6K1 knockout mice.

Interestingly, Cota et al. [35] recently demonstrated that leptin is involved in the control of feeding behavior in rats by activating mTOR Complex1 in the hypothalamus. These authors showed that intracerebroventricular administration of leucine results in an increase of mTOR activity and a subsequent decrease in food intake and body weight. Administration of leptin leads to a similar anorectic response, which is blunted by rapamycin [35]. However, it is still not known whether lack of S6K1 in the hypothalamus can elicit similar effects and whether this would affect adipogenesis.

It is well-known that morbidly obese patients are often affected by increased insulin resistance, resulting in the development of type 2 diabetes. Recent studies have shown that insulin resistance can be regulated by mTOR Complex1 activation of S6K1 through a negative-feedback loop. Initial observations found that amino-acid stimulation inhibits insulin-induced class I PI3K signaling, whereas subsequent studies showed that this inhibition is reversed by rapamycin treatment [36]. Studies in Drosophila revealed that the S6K1 and S6K2 ortholog, dS6K, is a negative effector of dPKB/dAkt activation, suggesting for the first time that S6K1 or S6K2 regulates PKB/Akt [37,38]. In agreement with these findings, insulin receptors desensitize in S6K1-deficient mice maintained on a HFD, but the mice remain exquisitely insulin-sensitive, as does PKB/Akt activation [29]. This suggests that S6K1 elicits a selective inhibitory effect on PKB/Akt activation at a point that is downstream of the insulin receptor (IR). Phosphorylation of IRS1 at sites S307 and S632, which is known...
mTOR Complex1–S6K1 signaling contributes to the negative-feedback loop that downregulates PKB/Akt through IRS1 alone or multiple targets. Shah et al. [43] have shown that IRS2 protein levels are also reduced in TSC2−/− cells. Thus, in understanding the role of S6K1 in the regulation of insulin signaling, it is necessary to establish the extent to which IRS1 and IRS2 contribute to this response.

mTOR Complex1–S6K1 signaling and cancer

Because of the key role of mTOR Complex1 and S6K1 in cell growth and metabolism, it is reasonable to predict an association between mTOR Complex1 activity and aberrant forms of growth, including cancer. In fact, several of the upstream and downstream components of the mTOR Complex1 pathway are altered in cancer (Table 1 and Table 2). Upregulation and/or mutation of class I PI3K and PKB/Akt, loss of PTEN, mutation of the TSC genes, and upregulation of S6K1 and eIF4E have all been identified in specific cancers [44]. Not surprisingly, rapamycin and its derivatives have been developed and are being pursued in several clinical settings, either as monotherapies or in combination with other anti-cancer agents, with promising results reported in Phase II trials for breast cancer [45] and renal cell carcinoma [46]. In specific settings, such as tuberous sclerosis complex, rapamycin and its derivatives have a pronounced effect [47]. However, given that in nutrient-replete conditions rapamycin and its derivatives are largely cytostatic and not cytotoxic, the highest clinical potential for rapamycin derivatives might be in combination therapy. Consistent with this hypothesis, in a preclinical cell-based assay, the Novartis rapamycin derivative, RAD001, sensitized tumor cells to DNA-damage-induced apoptosis through inhibition of p21 translation [48], providing the basis for testing this combination in upcoming Phase II clinical trials. Similarly, the recent completion of a Phase II clinical trial in which breast-cancer patients were treated with either the aromatase inhibitor letrozole alone or in combination with rapamycin revealed a better progression-free survival rate in the combination therapy [49]. A recent study reported that resistance to the tyrosine kinase inhibitor imatinib (Gleevec, Novartis), which is caused by secondary mutations in proteins that affect the mTOR Complex1–S6K1 pathway

<table>
<thead>
<tr>
<th>Gene</th>
<th>Syndrome</th>
<th>Molecular function</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI3K</td>
<td>Ovarian and gastrointestinal cancer</td>
<td>Activates PKB/Akt via PI3</td>
</tr>
<tr>
<td>PKB/Akt</td>
<td>Breast and ovarian cancer</td>
<td>Activates mTOR Complex1</td>
</tr>
<tr>
<td>RAS</td>
<td>Pancreatic and colon cancer</td>
<td>Activates PI3K</td>
</tr>
</tbody>
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Table 2. Proto-oncogenes that affect the mTOR Complex1–S6K1 pathway

<table>
<thead>
<tr>
<th>Gene</th>
<th>Syndrome</th>
<th>Molecular function</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSC1 and TSC2</td>
<td>Tuberous sclerosis complex and lymphangioleiomyomatosis</td>
<td>Negative regulator of Rheb</td>
</tr>
<tr>
<td>PTEN</td>
<td>Cowden syndrome and prostate carcinoma</td>
<td>Negative regulator of class I PI3K</td>
</tr>
<tr>
<td>LKB1</td>
<td>Peutz–Jeghers syndrome</td>
<td>Negative regulator of mTOR Complex1 via AMPK</td>
</tr>
<tr>
<td>NF1</td>
<td>Neurofibromatosis 1</td>
<td>Negative regulator of IRS1 via IRS1 phosphorylation</td>
</tr>
<tr>
<td>PML</td>
<td>Promyelocytic leukemia</td>
<td>Negative regulator of mTOR Complex1</td>
</tr>
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the breakpoint cluster region/Abelson proto-oncogene (BCR/ABL) fusion kinase in chronic myelogenous leukemia (CML) patients, seems to be in part mediated by activation of PI3K and mTOR [50]. Therefore, rapamycin treatment of such patients might be useful in helping to resolve tyrosine-kinase-inhibitor resistance.

Consistent with these results, OSI Pharmaceuticals, the developer of the EGF-receptor inhibitor Erlotinib (Tarceva), recently published a synergistic effect of Erlotinib and rapamycin on the activation of PKB/Akt and S6K1 in various tumor-derived cell lines [51]. Similarly, Wang et al. [52] have shown synergism between rapamycin and herceptin in slowing the growth of breast cancer cells with high expression of ERBB2 and in reducing tumorigenicity in xenograft models. Recently, Shokat’s group [53] has developed a panel of PI3K and PI3K-like inhibitors with dual class I PI3K and mTOR inhibitor, arrests growth of glioma-xenografted tumors with little-to-no toxic effects [54].

A commonly overlooked aspect of tumor development is the ability of malignant cells to survive in nutrient-deprived settings. Amino-acid and glucose transporters are commonly upregulated in specific tumors [55]. In many primary tumors, the mRNA for the amino-acid transporter large neutral amino acids transporter 1 [LAT1, also known as solute carrier family 7, member 5 (SLC7A5)] is overexpressed [56]. LAT1 represents the light chain of a heterodimer, together with the heavy chain solute carrier family A3, member 2 (SLC3A2, commonly known as CD98), and is selectively involved in the transport of the bulky branched-chain amino acids [57]. Although SLC3A2 forms heterodimers with other proteins that are implicated in cancer, such as integrins, Shishido et al. [58] reported that transformation and tumorigenicity of BALB/c3T3 cells requires overexpression of both SLC3A2 and LAT1. Moreover, Campbell and Thompson [59] have correlated the overexpression of LAT1, observed in hepatocarcinogenesis, with the ability of exogenous LAT1 alone to increase amino-acid transport in primary mouse hepatocytes, but not in fibroblasts. Recently, LAT1 expression has been correlated with poor survival in patients with glioblastomas, and expression of LAT1 was a strong predictor of outcome, independent of other variables [60]. It was also demonstrated in glioma C6 cells and in a xenograft model that the LAT1 inhibitor and leucine analog, 2-amino-cyclohexane-2-carboxylic acid (BCH), dose-dependently reduced cell growth. The increased intracellular flux of nutrients in a tumor cell would serve as fuel for the mTOR Complex1–S6K1 pathway, which would drive ribosome biogenesis, cell growth and suppress autophagy [22].

**Diabetes, obesity and cancer**

Although the link between obesity and diabetes is well established, that of metabolic disease and aberrant cell growth has received less attention. However, recent studies have suggested that obesity is not only a risk factor for diabetes, but also for many cancers [61,62]. In particular, endometrial and colon cancer risk have been positively correlated to the body mass index (BMI) [61]. Similarly, an inverse relationship exists between physical activity and incidence of endometrial, colon and breast cancer [61]. Using a cohort of 900 000 subjects from the USA, Calle et al. [63] showed that the heaviest individuals (those with a BMI >40) had cancer death rates 52% (men) and 62% (women) higher than their healthy weight counterparts. Furthermore, the same study attributed up to 14% and 20% of all cancer deaths in man and women, respectively, in the USA to the overweight and obese state. Similar trends have been recorded for large cohorts in Europe and Japan [64,65]. Diabetes itself has been shown to be a risk factor for hepatocellular carcinoma, endometrial, colorectal and breast cancer [66–69]. It is also well-known that, in insulin-resistant states of obesity, there is not only a rise in plasma concentrations of insulin and glucose but also in amino acids, particularly branched-chain amino acids [70–72]. These latter findings are associated with the increased consumption of processed meat over the past 50 years and with high-protein diets with glucose intolerance, insulin resistance and increased incidence of type 2 diabetes [1]. Thus, the diabetic tissues that express insulin receptors and glucose and amino-acid transporters might exist in a proto-oncogenic state. Therefore, a cell predisposed to malignancy in a diabetic would have access to a saturating growth-factor signal (e.g. insulin) and a saturating nutrient environment (e.g. glucose and amino acids). Although insulin receptors might desensitize over time, leading to insulin resistance, glucose and amino acids would still be taken up by peripheral tissues expressing passive nutrient transporters. In addition, in insulin-responsive tissues, the uptake of amino acids, especially the branched-chained amino acids, and glucose are stimulated by insulin [73].

If obesity and diabetes are linked to cancer through the PKB/Akt–mTOR pathway, is it possible to treat one condition using a drug that has been produced for the other? Recently, Shaw et al. [74] showed that the common therapeutic agent for diabetes, metformin, activates AMPK through an LKB1-dependent mechanism. Similarly, Zakhani et al. [75] showed that the common thera-

also experienced improvement in her diabetic condition [80]. It will be of interest to follow future clinical trials that target this pathway in cancer, also focusing on metabolic parameters.

**Concluding remarks**

It has become clear that the mTOR–S6K1 signaling pathway has a major role in cell growth by integrating growth factor and nutrient cascades. Using various model systems, it was shown that this pathway is essential for cellular homeostasis and that aberrant modulation of this pathway can contribute to obesity, diabetes and cancer. Strong epidemiological links exist between metabolic disorders and cancer, and these links are recapitulated by drug activity observed in *vivo* and *in vitro*. How does the activation of AMPK by metformin result in inhibition of mTOR and S6K1? Are the effects of EGF-receptor inhibition on fasting glucose levels due to reduced PKB/Akt activity, thereby making glucose levels more sensitive to the effects of circulating insulin? Would combination therapy with an inhibitor of mTOR have more dramatic effects on insulin resistance? Further clinical and biochemical investigation is needed to provide answers to these questions (Box 2). Considering the circumstantial biochemical and epidemiological links among obesity, diabetes and cancer, and the mTOR Complex1–S6K1 pathway, these questions will require careful consideration in the future.

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