The mTOR Pathway in the Control of Protein Synthesis

Signaling through mammalian target of rapamycin (mTOR) is activated by amino acids, insulin, and growth factors, and impaired by nutrient or energy deficiency. mTOR plays key roles in cell physiology. mTOR regulates numerous components involved in protein synthesis, including initiation and elongation factors, and the biogenesis of ribosomes themselves.

Overview of mTOR Signaling

Like its orthologs in lower eukaryotes, the mammalian target of rapamycin (mTOR) is a multidomain protein and a member of the family of phosphoinositide (PI) 3-kinase-related kinases [PIKKs; which also include ATM and ATR, proteins involved in DNA repair (17)]. Major features of mTOR are depicted in FIGURE 1A. Genetic knockouts of mTOR have revealed it to be an essential gene: mice lacking mTOR die in utero shortly after implantation (10, 36). Embryonic development appears to be arrested at E5.5, with evidence of multiple developmental aberrations.

Although mTOR is related to lipid kinases, it displays protein serine/threonine kinase activity in vitro (7), in common with other PIKKs. mTOR interacts with a number of protein partners, including proteins that probably act as adaptors or scaffolds and others that regulate mTOR. Immediately NH$_2$ terminal to the kinase domain of mTOR lies a region that binds the immunophilin FKBP12 when it is bound to rapamycin. The rapamycin:FKBP12 complex inhibits several functions of mTOR, although it is now very clear that it does not block all of them (see below). Rapamycin is an immunosuppressant and is used clinically to prevent kidney graft rejection, as well for other purposes (e.g., to treat restenosis after angioplasty) (8).

The other binding partners for mTOR include raptor and rictor, which respectively form complexes with mTOR termed mTORC1 and mTORC2 (FIGURE 1B). TORC2 mediates effects that are insensitive to rapamycin, whereas the best known actions of the TORC1 complex are sensitive to this drug (49). Raptor, a component of mTORC1, interacts with proteins that are regulated by mTOR in a rapamycin-sensitive manner. These mTOR targets contain short amino acid sequence motifs called TOS (mTOR-signaling) motifs. The best-characterized TOS motif-containing proteins are ones involved in regulating the translational machinery, as described below.

mTOR signaling is activated by hormones and growth factors. In the case of insulin, for example, this is believed to be mediated through the PI3-kinase pathway and PKB/Akt. PKB phosphorylates a protein called TSC2 (for tuberous sclerosis complex 2). Together with its partner TSC1, TSC2 acts as a GTPase-activator protein (GAP) for the small G-protein Rheb (Ras-homolog enriched in brain) (30). Phosphorylation of TSC2 is thought to inhibit its GAP activity, allowing Rheb to accumulate in its active GTP-bound form, although direct evidence is lacking for the alteration of the GAP activity of TSC2 in response to phosphorylation. Rheb interacts with mTOR complexes and Rheb. GTP stimulates the kinase activity of mTOR (measured in vitro (28)). Signaling from the classical MAP kinase pathway also activates mTOR signaling, although it is unclear whether this results from phosphorylation of TSC2 by Erk itself or by its downstream effector, ribosomal protein S6 kinase (RSK) (29, 45). These signaling connections are illustrated schematically in FIGURE 1C.

Many lines of evidence indicate that the hyperactivation of mTOR signaling favors cell and tissue growth (49). These include data from genetic studies in model organisms such as Drosophila and mice, and findings from investigations into human cell growth disorders such as tuberous sclerosis. This condition is caused by mutations in the genes for the tuberous sclerosis complex proteins TSC1 or TSC2. Since they are negative regulators of mTOR, loss of TSC1 or TSC2 leads to hyperactivation of mTOR signaling and increased cell growth, as manifested in the benign tumors (hamartomas), which are characterized by very large cell size. Regulating the rate of protein synthesis is an important mechanism for controlling cell growth. Disorders that involve enhanced rates of protein synthesis can lead to tissue hypertrophy (increased cell growth), as in the case of cardiac hypertrophy (14). Indeed, cardiac hypertrophy may be regarded as a useful model for studying the control of the growth of differentiated cells.

In addition to the upstream control by hormones and growth factors, mTOR signaling is also regulated by amino acids and by cellular energy status. In most cell types, the effective amino acid is leucine (reviewed in Ref. 24). Omission of leucine from the medium causes the rapid inactivation of mTOR signaling, and
mTOR signaling becomes refractory to stimulation by extracellular factors such as insulin. The effects of leucine appear not to be a direct effect of the amino acid itself acting at an intracellular locus. They do not appear to require its metabolism or the mediation of a cell membrane receptor (2). Amino acids appear to regulate mTOR signaling via mechanisms that are independent of TSC2, although small changes in Rheb.GTP binding have been reported (44, 50). Recent data point to a role for the PI3-kinase-related protein Vps34 in the control of mTOR by amino acids (5, 37). The effect of amino acid deprivation on mTOR signaling varies greatly between cell types, perhaps reflecting differences in the availability of amino acids from intracellular sources, such as protein breakdown by autophagy or the proteasome.

Depletion of cellular ATP also causes an impairment of mTOR signaling, which involves the phosphorylation (and presumed activation) of TSC2 by the AMP-activated protein kinase (AMPK) (21), an important sensor of cellular energy status (21). By shutting down mTOR signaling, this effect likely serves to save valuable energy for the most essential cell functions, such as maintaining ionic gradients across the plasma membrane (e.g., the Na+/H+ exchanger).

The inhibition of mTOR signaling caused by lack of amino acids or energy clearly makes sense given that a major function of mTOR is to promote mRNA translation, a process that requires amino acids as precursors and consumes a high proportion of cellular energy. As described below, the elongation phase of translation (where almost all the energy is used) is also subject to control by an additional AMPK-mediated mechanism.

Overview of mRNA Translation

The process of protein synthesis (mRNA translation) involves the sequential decoding of the mRNA into protein, performed on the ribosome, which acts as an enzyme (a ribozyme) to catalyse the formation of the peptide bonds linking the amino acids of the new protein. Protein synthesis is conventionally divided into three main stages: initiation, elongation, and termination. Each involves a number of protein factors that are extrinsic to the ribosome. Their regulation generally involves alterations in their phosphorylation. mTOR controls a number of components involved in the initiation and elongation stages of translation. In a number of cases, the rapid activation of protein synthesis by insulin, growth factors, or other growth-promoting agonists is inhibited, at least partially, by rapamycin, implying that mTOR signaling is involved in stimulating the translational machinery. It is important to note that mTOR signaling likely contributes both to the short-term (minutes) activation of translation and to longer-term (hours) increases in the translational capacity of the cell through increased levels of ribosomes and other translational components.
Control of Translation Initiation Factors

These proteins are termed eukaryotic initiation factors (eIFs). They mediate key steps in translation initiation, such as the recruitment of the mRNA to the small (40S) ribosome subunit (eIF4 group of factors) (12) and the recruitment of the initiator methionyl-tRNA (Met-tRNA) that recognizes the start codon at the beginning of the coding region, after a process termed "scanning" during which the preinitiation complex (including the 40S subunit and Met-tRNA) inspects the 5'-untranslated region (5'-UTR) of the mRNA for a suitable start codon (FIGURE 2A).

eIF4E binds to the 5'-cap structure of the mRNA, which includes a 7-methyl guanosine triphosphate (m7GTP) moiety (12). eIF4E also binds protein partners such as eIF4G, a large scaffold protein that interacts with several other proteins (FIGURE 2B). These partners include the RNA helicase eIF4A and the poly(A)-binding protein PABP, which interacts with the tract of adenyl nucleotides at the 3' end of the mRNA. By binding eIF4E and PABP, eIF4G in effect circularizes the message. The eIF4A/E/G complex is often referred to as eIF4F. Such complexes are thought to be especially important for the translation of mRNAs whose 5'-UTRs contain secondary structure, since eIF4A can unwind such features, which otherwise impair the scanning process by which the ribosome is thought to locate the start codon in the mRNA. The helicase activity of eIF4A is enhanced by a further factor, eIF4B.

eIF4E also binds small phosphoproteins termed 4E binding proteins (4E-BPs). There are three 4E-BPs in mammals, with 4E-BP1 being by far the best characterized (FIGURE 2C). These proteins bind to the same region of eIF4E as eIF4G does, so binding of 4E-BPs to eIF4E prevents eIF4E from binding eIF4G and engaging in active translation initiation complexes (12). The association of 4E-BP1 with eIF4E is regulated by phosphorylation of 4E-BP1, although the situation is complicated. Although some phosphorylation sites in 4E-BP1 directly impair eIF4E binding, others do not, but these sites may influence the ability of the regulatory sites to undergo phosphorylation. For example, phosphorylation at the NH2-terminal sites (Thr37/46 in human 4E-BP1) is required for subsequent modification of the sites adjacent to the eIF4E-binding site (Ser65/Thr70) but does not itself affect eIF4E binding (11, 40). It remains unclear for several reasons (see Ref. 55) whether mTOR directly phosphorylates all the regulated sites in 4E-BP1. Some may be targets for other kinases that are associated with and/or controlled by mTOR. Although much attention has focused on the regulation of 4E-BPs and their role (as targets for mTOR signaling) in the control of mRNA translation, their importance for the regulation of overall protein synthesis remains unclear. For example, knockouts of 4E-BP1 or 4E-BP2 do not

FIGURE 2. Eukaryotic mRNA
A: schematic illustration of eukaryotic mRNA showing the 5'-cap (m7GTP) and the start codon (AUG). Most of the coding region (dashed line) and the 3'-UTR/poly(A) tail are not shown. B: by binding the 5' cap, eIF4E allows formation of translation initiation factor complexes at the 5' end of the mRNA. The scaffold protein eIF4G, which binds eIF4E, also interacts with several other proteins, including the helicase eIF4A and the poly(A)-binding protein PABP. The latter interaction results in the circularization of the mRNA. The diagram is not intended to reflect relative sizes of components; not all components are shown. C: schematic diagram of 4E-BP1, showing all the known phosphorylation sites (P), the eIF4E binding motif, and the regulatory RAIP and TOS motifs. The RAIP motif mediates inputs from mTOR that are promoted by amino acids but insensitive to rapamycin. D: control of eEF2 kinase by mTOR involves its phosphorylation at three or more sites, one of which (Ser366) is a direct target for the S6 kinases. The kinases acting at Ser78 and Ser359 have still to be identified. Phosphorylation at each of these sites inhibits eEF2 kinase. In contrast, phosphorylation at Ser398 by AMPK appears to activate it, serving to slow elongation when ATP levels fall. Other important features of eEF2 kinase are shown: the calmodulin (CaM) binding site; the catalytic domain (large shaded block), and the probable substrate (eEF2) binding site at the extreme COOH terminus.
have general phenotypes, with the reported effects being in specific tissues such as fat and brain, respectively, in which these proteins are expressed at relatively high levels (1, 51). This could, of course, reflect the fact that many tissues express both proteins, leading to redundancy in function.

eIF4B also interacts with the eIF4F complex (12). It contains two RNA-binding domains, interacts with eIF4A, and stimulates its RNA helicase activity (26). eIF4B is a substrate for phosphorylation by S6 kinase (42). It is suggested that the phosphorylation of eIF4B by S6 kinases (which are regulated by mTOR; see Control of Translation Elongation) stimulates its function. Indeed, this phosphorylation event favors recruitment of eIF4B into complexes with eIF3, which promotes the recruitment of ribosomes to the 5' end of the message (19). This likely serves to bring eIF4B to complexes containing eIF4G/4A and enhance RNA unwinding during active translation initiation.

Control of Translation Elongation

In mammalian cells, translation elongation requires two factors: eEF1 and eEF2. eEF2 is regulated by mTOR signaling. Its role is to promote the translocation step of elongation, in which the ribosome moves by the equivalent of one codon relative to the mRNA, and the peptidyl-tRNA migrates from the ribosomal A site into the P site, following formation of the new peptidyl bond. eEF2 undergoes phosphorylation at Thr56 in its GTP-binding domain (41). This inhibits the binding of eEF2 to ribosomes and thereby impairs its activity (6). The phosphorylation of eEF2 is catalysed by a highly specific protein kinase, eEF2 kinase (FIGURE 2D). This calcium/calmodulin (CaM)-dependent enzyme is an unusual kinase that does not belong to the main protein kinase superfamily (48) but to another small group of enzymes whose primary sequences show no similarity to other protein kinases.

Insulin and a number of other agents that activate protein synthesis (41) induce the rapid dephosphorylation of eEF2. This results in increased eEF2 activity and accelerated elongation (43). The dephosphorylation of eEF2 appears to be due to the inhibition of eEF2 kinase, which is also brought about by insulin. Both these effects are blocked by rapamycin (43).

The mTOR-dependent control of eEF2 kinase involves its phosphorylation at several sites. Ser366 (in human eEF2 kinase) is phosphorylated by S6K1, and this leads to inhibition of eEF2 kinase activity, at least at submaximal Ca^{2+} ion concentrations (57). This site is also phosphorylated by the RSKs, which lie downstream of the Erk pathway. A second input is provided by phosphorylation at Ser78, which is induced by insulin and tightly controlled by mTOR. This phosphorylation impairs the binding of CaM to eEF2 kinase, thus inhibiting its activity (4). Ser359 is a further mTOR-regulated site. Phosphorylation here inhibits eEF2 kinase activity. These regulatory inputs into eEF2 kinase are summarized in FIGURE 2D.

Stimuli that activate mTOR, such as insulin and amino acids, can thus activate translation elongation, and this complements their abilities to enhance the loading of ribosomes onto mRNAs through their effects on translation elongation. Most of the large amount of energy used by protein synthesis is used in elongation, and the inhibition of mTOR by AMPK would serve to slow elongation and save energy, while preserving polysomes. In fact, a second AMPK-dependent input also serves to slow elongation: this is the direct phosphorylation and apparent activation of eEF2 kinase by AMPK (3, 20) (FIGURE 2D).

Two recent studies have highlighted the importance of inhibition of mTOR and eEF2 for cell survival during hypoxia, a condition that is associated with potential depletion of cellular energy, although other responses are clearly also involved (25, 27).

The RSKs

The ribosomal protein (rp) S6 kinases first came to attention as enzymes that phosphorylate rpS6, a component of the small (40S) ribosomal subunit. rpS6 lies in a region of the ribosome close to the interface between the large and small subunits that also contacts mRNA and tRNA, as well as certain translation factors (reviewed in Ref. 9). Phosphorylation of S6 increases under a variety of conditions linked to cell growth and/or proliferation, such as stimulation of quiescent cells with serum or mitogens, insulin treatment, in the regenerating liver, or in vivo on refeeding. Phosphorylation of S6 is strongly inhibited by rapamycin, implying a role for mTOR. The activation of the S6 kinases is likewise blocked by rapamycin. [Other kinases have also been termed or RSKs (46), but their regulation is not sensitive to rapamycin, and they likely play, at most, a minor role in phosphorylating S6 physiologically.]

There are two S6 kinase genes in mammals (S6K1, S6K2). The control of the S6K1 and S6K2 proteins appears to be similar. Their substrate specificities are not identical, and data from knockout mice suggest that S6K2, rather than S6K1, may be the major physiological kinase for S6 (39). Mice in which S6K1 has been knocked out show a small cell-size phenotype, but this is not seen for S6K2 knockouts (39). The knockout of the single S6K gene in Drosophila also yields a small cell-size phenotype (35), but the fact that S6K2 seems to be the main S6 kinase in mammals indicates that it is not phosphorylation of S6 that is responsible for the effect on cell size. S6K1−/− mice show decreased circulating insulin levels, smaller pancreatic β-cells, and mild glucose intolerance (38).

S6K1 and S6K2 each exist as two splice variants, one of which has a nuclear localization signal (FIGURE 3A). The regulation of S6K1 has been the subject of intensive study: its activity is controlled by amino
acids and insulin, such that they have a low basal activity that is maintained by amino acids and can be elevated further in response to insulin, provided that amino acids are available (see, e.g., Refs. 15, 56).

Despite many years of study, the physiological function of S6 phosphorylation remains unclear. One idea was that it might be related to the control of the translation of the mRNAs that encode ribosomal proteins (see below; Ref. 9). However, data from mice in which both S6K1 and S6K2 are knocked out have disproved this (39), as has use of mice in which the phosphorylation sites in rpS6 have been converted to alanines (47). The role of S6 phosphorylation still remains obscure; some interesting phenotypes are seen in the mice lacking phosphorylatable rpS6, such as a selective decrease in the size of pancreatic β-cells and hypoinsulinemia. Cells (embryonic fibroblasts) from these animals actually show an enhanced rate of protein synthesis, faster proliferation, and reduced size (47), but it is unclear how these effects are causally connected to the phosphorylation of rpS6.

As mentioned already, S6Ks have been shown to phosphorylate other components of the translational machinery such as eIF4B (42) and eEF2 kinase (57). It will be informative to use cells from S6K1/2 knockout animals to explore their importance in controlling specific stages in mRNA translation. Recent data have shown that S6K1 associates with the translation initiation factor eIF3 in a regulated manner. mTOR also associates with eIF3 (19). As discussed above, the association of S6K1 with eIF3 likely targets it to its substrate eIF4B. Interestingly, cell activation results in recruitment of the upstream regulator of S6K1, mTOR/raptor (TORC1) to eIF3, where it can presumably phosphorylate eIF4B (19).

S6K1 can phosphorylate insulin receptor substrate (IRS) 1 and impair the activation by insulin of PI3-kinase and PKB/Akt (16, 52) (indicated as a dashed line in FIGURE 1C). This effect would interfere with the ability of insulin to exert many of its effects, which are mediated through these signaling connections. Since S6K is activated in response to nutrients, it has been suggested that this may contribute to the insulin resistance observed in obesity.

**Control of Ribosome Biogenesis**

The above mechanisms function to control the activity of components of the translational machinery acutely over periods of minutes to a few hours. In the

FIGURE 3. S6 kinase 1
A: schematic diagram of S6 kinase 1 showing the catalytic domain and the nuclear localization signal found only in the longer splice variant. Phosphorylation at several sites is required for full activation, and these are shown in cartoon form. As indicated, phosphorylation of a site COOH-terminal to the catalytic domain by mTOR (mTORC1) allows phosphorylation within the catalytic domain. This results in kinase activation. B: 5′-TOP mRNAs contain an inhibitory element (‘TOP’; red) that acts to repress their translation under unstimulated conditions. Stimulation of cells, e.g., with serum, causes the 5′-TOP mRNAs to more efficiently bind ribosomes and become translated. This is blocked by rapamycin, although the mTOR-linked mechanism by which these mRNAs are controlled is unknown. Although the figure depicts 5′-TOP mRNAs as bound to a single ribosome in unstimulated cells, this is purely schematic, and many may be in non-ribosomal complexes. C: mTOR regulates by the transcription of rRNA (in the nucleolus) and the translation of r-protein (5′-TOP) mRNAs in the cytoplasm. This coordinated control ultimately leads to the assembly of functional ribosomes in the nucleolus.
longer term, the cellular capacity for protein synthesis is also regulated, such that anabolic stimuli increase the numbers of ribosomes and other translational components (e.g., elongation factors). mTOR signaling also seems to play an important role in this.

Mammalian ribosomes are composed of four different ribosomal RNAs (rRNAs) and around 85–90 distinct proteins (r proteins). The mRNAs for r proteins are subject to translational control (34). In serum-starved cells, they are translated inefficiently and are found mainly in the non-polysomal region of a sucrose density gradient. In response to stimulation of the cells (e.g., addition of fresh serum to serum-deprived cells), these mRNAs shift markedly into polysomes and are thus translated more efficiently (23) (FIGURE 3A). This control is mediated via a tract of pyrimidines at the extreme 5’ end of these mRNAs (5’-TOP), which acts to suppress their translation under basal conditions (FIGURE 3B). Importantly, the shift into polysomes is inhibited, at least partially, by rapamycin. This finding indicates that mTOR provides an input into the translational control of the 5’-TOP mRNAs. This makes excellent “sense” since mTOR signaling is activated by amino acids (precursors for ribosome biogenesis and protein synthesis) and by anabolic and hypertrophic stimuli.

How does mTOR control 5’-TOP mRNA translation? Earlier data were interpreted as suggesting that this involved the S6 kinases and were interpreted in terms of a role for the S6 kinases in promoting 5’-TOP mRNA translation (22). However, more recent findings have disproved this idea. For example, rapamycin-sensitive 5’-TOP mRNA translation is still observed in cells lacking both isoforms of S6 kinase (39). Furthermore, in cells in which the five phosphorylation sites in S6 have all been altered to alanines, 5’-TOP mRNA translation is still observed in polysomes and is thus translated more efficiently (23) (FIGURE 3A). This control is mediated via a tract of pyrimidines at the extreme 5’ end of these mRNAs (5’-TOP), which acts to suppress their translation under basal conditions (FIGURE 3B). Importantly, the shift into polysomes is inhibited, at least partially, by rapamycin. This finding indicates that mTOR provides an input into the translational control of the 5’-TOP mRNAs. This makes excellent “sense” since mTOR signaling is activated by amino acids (precursors for ribosome biogenesis and protein synthesis) and by anabolic and hypertrophic stimuli.

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Of course, making a functional ribosome requires rRNAs as well as proteins. rDNA transcription, which occurs in the nucleolar compartment and is largely catalysed by RNA polymerase I (Pol I), is also under the control of mTOR signaling. mTOR is required for the activation of rDNA transcription (13) and positively regulates the phosphorylation and function of UBF (upstream binding factor), an rDNA transcription factor (FIGURE 3C). The data from this study indicated a key role for eIF4K in linking mTOR to the control of UBF and rDNA transcription. However, although UBF seems to play a key role in the hypertrophic growth of cardiomyocytes, data from mice in which both S6K genes have been knocked out indicate that they are dispensable for pathological or physiological cardiac hypertrophy in mice (33).

Further work is clearly needed to explore the control of rRNA transcription in systems such as this model of cell size control.

mTOR also regulates Pol I transcription through controlling the activity of TIF-IA (FIGURE 3B) (31). TIF-IA is a regulatory factor that senses nutrient and growth-factor availability. Treatment of cells with rapamycin causes the translocation of TIF-IA into the cytoplasm and consequently inhibits transcription-initiation complex formation.

The coordinated control of the synthesis of ribosomal proteins and rRNA is logical (FIGURE 3B), as is the involvement of mTOR in this, since it coordinates responses to nutrients and hormones/growth factors. Identification of the molecular events involved in these effects is a high priority, as is information on the control of r-protein mRNA transcription.

FIGURE 4. Sensitivity of protein synthesis in selected cell types to inhibition of mTOR signaling by rapamycin

The figure depicts the effects of the phorbol ester TPA (tetradeconyl phorbol acetate, 1 μM, 45 min), insulin (100 nM, 45 min in A, 90 min in B), or the hypertrophic agonist PE (phenylephrine, 10 μM, 90 min) on rates of protein synthesis in HEK293 cells (A) or in primary adult rat ventricular cardiomyocytes (B). Protein synthesis was determined by incorporation of [35S]methionine into total protein. Cells were treated with rapamycin (typically 50 nM for 30 min) before addition of agonist. These data are taken from Refs. 18, 53, 54.
mTOR Signaling and the Control of Protein Synthesis

Rapamycin substantially inhibits the short-term (1–2 h) activation of protein synthesis by a variety of agents in certain cell types, as shown in FIGURE 4. In the widely used cell line HEK (human embryonic kidney) 293, the activation of protein synthesis either by phorbol ester (TPA; which activates ERK signaling) or by insulin (via PI3-kinase/PKB; Ref. 18) was decreased by 50% or more by pretreatment of cells with rapamycin. In cardiomyocytes, the activation of protein synthesis induced by either insulin or the hypertrophic agonist phenylephrine was inhibited >50% by rapamycin (53, 54). In each case, the rapamycin-insensitive component of activation is modest (which amounts to around 40% of the overall increase in cardiomyocytes) but statistically significant. This component may be entirely independent of mTOR (e.g., through control of regulatory translational components that are not downstream of mTOR, such as eIF2B), or it may involve rapamycin-insensitive outputs from mTOR.

Increased rates of protein synthesis are a key feature of hypertrophy driving myocyte growth. Certain types of hypertrophy (which involve, e.g., structural and functional remodeling of the heart) constitute a major risk factor for heart failure and mortality. It is important to note in this context that in vivo hypertrophy is prevented, or even reversed, by treatment of rats with rapamycin (32), implying a key role for mTOR signaling in this process. It is likely that mTOR also plays a role in other types of physiological and developmental growth of the myocardium too.

Perspectives and Future Directions

There is currently a very high level of interest in mTOR signaling. In mammalian cells, the best understood targets for control by mTOR remain the components of the translational machinery (initiation and elongation factors) described in this article. Nevertheless, key questions remain. It is still not clear how mTOR controls several of its targets, such as eEF2 kinase, 4E-BP1, and the translation of the 5′-TOP mRNAs. Our understanding of the control of ribosome RNA transcription and its coordination with ribosomal protein production is incomplete. The quantitative contributions of the regulation of the 4E-BPs, eIF4B, eEF2 kinase, and eEF2 in cell physiology remain to be established, as do the physiological functions of the much-studied S6 kinases. Indeed, although several components of the translational are controlled by the mTOR pathway, it is still not yet clear what quantitative contributions these various regulatory events make to the overall activation of protein synthesis, or the control of the translation of specific mRNAs, under physiologically relevant conditions. The availability of transgenic mice in which these regulatory components have been deleted or otherwise modified will be crucial to unraveling how mTOR signaling contributes to the control of protein synthesis and amino acid metabolism in whole tissues and animals.

References


