TOR Signaling and Nutrient Sensing

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Abstract

All living organisms rely on nutrients to sustain cell metabolism and energy production, which in turn need to be adjusted based on available resources. The evolutionarily conserved target of rapamycin (TOR) protein kinase is a central regulatory hub that connects environmental information about the quantity and quality of nutrients to developmental and metabolic processes in order to maintain cellular homeostasis. TOR is activated by both nitrogen and carbon metabolites and promotes energy-consuming processes such as cell division, mRNA translation, and anabolism in times of abundance while repressing nutrient remobilization through autophagy. In animals and yeasts, TOR acts antagonistically to the starvation-induced AMP-activated kinase (AMPK)/sucrose nonfermenting 1 (Snf1) kinase, called Snf1-related kinase 1 (SnRK1) in plants. This review summarizes the immense knowledge on the relationship between TOR signaling and nutrients in nonphotosynthetic organisms and presents recent findings in plants that illuminate the crucial role of this pathway in conveying nutrient-derived signals and regulating many aspects of metabolism and growth.

Contents

INTRODUCTION

When driving a car, the driver's ability to rapidly and accurately integrate both external (traffic lights, other cars) and internal (mechanical dysfunctions, fuel level, speed) information is essential for survival. Similarly, a living cell must perceive and respond to external nutritional information by quickly adapting its growth and metabolism. Such responses—e.g., determining when to grow, when to assimilate and store nutrients, and when to recycle reserves—are at the heart of life.

Unicellular organisms, such as yeasts and algae, are in direct contact with environmental nutritional changes. Multicellular organisms, such as plants and animals, must also sense and coordinate these cell-autonomous processes at the organism level via signals. Animal cells and organs are normally surrounded by a buffered supply of nutrients, and this organismal regulation of metabolic activity and cell growth is driven mainly by growth factors and hormones (26, 45, 75). Although hormonal signals are also important in plant life, several examples have illustrated the importance of nutrients as signals for the control of regulatory pathways and cellular processes in a cell- and non-cell-autonomous manner (84, 88, 106, 115). Moreover, plants have a highly plastic development and are autotrophic organisms that produce and store metabolites derived from carbon (C), nitrogen (N), and sulfur (S). But whereas inorganic N, S, phosphorus (P), and potassium (K)

ions are taken up from the soil in most plants, sugars are synthesized using light energy and CO_2. Therefore, unlike animals and yeasts, plants must additionally sense the quality and amount of light to produce C metabolites and decide whether to store sugars in source leaves or distribute these metabolites to sink organs such as young organs, roots, or seeds.

In eukaryotes, several interconnected signaling networks—such as those centered on the animal AMP-activated kinase (AMPK); the yeast equivalent, sucrose nonfermenting 1 (Snf1) kinase; or the target of rapamycin (TOR) kinase—perceive nutrient availability and direct growth and metabolic patterns (for general reviews on animals or yeasts, see 4, 18, 26, 87, 98, 165; for reviews on the plant TOR signaling pathway, see 37, 64, 77, 128, 129, 168). Rapamycin is an antibiotic produced by *Streptomyces hygroscopicus*, a bacterium found in a sample of soil from Easter Island (called *Rapa Nui* in the indigenous language). In yeasts, rapamycin stops division and produces cells with a N starvation phenotype. A search for mutations causing rapamycin resistance in yeast identified FK506-binding protein 12 (FKBP12) together with a large kinase, which was therefore named target of rapamycin (63). Because rapamycin is a very specific inhibitor of the TOR kinase, this pioneering work opened the way for a wealth of studies in both animals and yeasts (165). The TOR signaling pathway thus quickly emerged as a central regulatory hub connecting external signals, such as the availability of nutrients or the presence of hormones, to a myriad of biological outputs, including transcription of RNA, translation, ribosome biogenesis, translocation of regulatory proteins, autophagy, and storage of reserve compounds (35, 50, 100, 165).

In animals and yeasts, the TOR kinase is present in two high-molecular-mass complexes named TORC1 and TORC2. They differ by the presence of specific protein partners: kontroller of growth protein 1 (KOG1)/regulatory-associated protein of mTOR (RAPTOR) for TORC1 and adheres voraciously to TOR2 protein 1 (AVO1)/human stress activated MAP kinase interacting protein 1 (hSIN1) and AVO3/rapamycin-insensitive companion of mTOR (RICTOR) for TORC2, with the small lethal with SEC13 protein 8 (LST8) being found in both complexes (80, 87, 165) (**Figure 1**).

TOR: target of rapamycin

KOG1: kontroller of growth protein 1

RAPTOR: regulatory-associated protein of mTOR

AVO1: adheres voraciously to TOR2 protein 1

hSIN1: human stress activated MAP kinase interacting protein 1

RICTOR: rapamycin-insensitive companion of mTOR

LST8: lethal with SEC13 protein 8

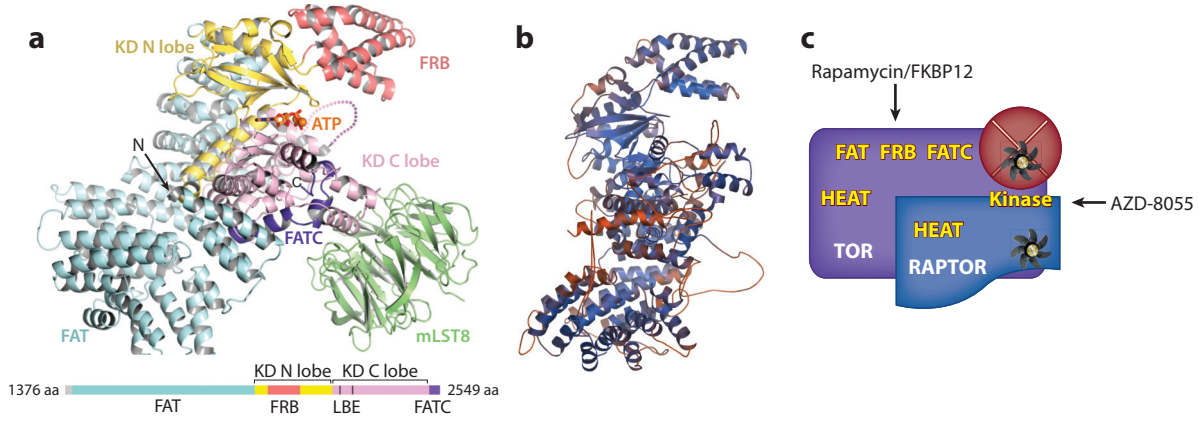

Figure 1

Structure of the TOR kinase domain and organization of the TORC1 complex. (*a*) Three-dimensional structure of the human TOR C-terminal region (FAT-FRB-kinase-FATC domains) associated with the LST8 protein. Abbreviations: aa, amino acids; KD, kinase domain; LBE, LST8-binding element. Adapted from Reference 170 with permission. (*b*) Prediction of the structure of the *Arabidopsis* TOR C-terminal region, showing its conservation with the animal model. The model is based on the three-dimensional structure of human TOR shown in panel *a* and was obtained using SWISS-MODEL (**http://swissmodel.expasy.org**). The quality of the model is indicated by colors from orange (poor quality) to blue (high quality). (*c*) Organization of the conserved TORC1 complex. The propeller WD40 structure is depicted in LST8 (*red disk*) and RAPTOR proteins. The domains affected by TOR inhibitors (rapamycin/FKBP12 and the active-site TOR inhibitor AZD-8055) are also shown. For TOR biological inputs and outputs, see **Figure 3**.

THE PLANT TORC1 COMPLEX

S6K: ribosomal protein S6 kinase

Until recently, the deciphering of TOR functions in higher plants has been hampered by their relative but variable insensibility to rapamycin (108, 109). Indeed, in land plants, FKBP12 proteins show sequence differences in residues that are necessary for the formation of a TOR-rapamycin-FKBP12 ternary complex (102, 108, 142, 169). By contrast, algal FKBP12 is closer to human or yeast homologs, and residues critical for binding rapamycin are conserved in *Chlamydomonas*, which is consistently inhibited by rapamycin (27). Nevertheless, the expression of either human (102) or yeast (89, 127, 142) FKBP12 in *Arabidopsis* restores sensitivity to rapamycin. Therefore, in the presence of an FKBP12 protein with sufficient affinity for rapamycin, plant TOR can form a complex with FKBP12 and this inhibitor and is indeed a "target of rapamycin." One puzzling recent observation is that rapamycin added to liquid cultures of *Arabidopsis* can affect plant growth, possibly because it is more efficiently taken up or more available (167). Recent studies have also found that the specific TOR inhibitors developed in animal and medical research, such as Torin and AZD-8055, restrain plant growth in a highly efficient and TOR-specific manner (111, 134, 150).

Plant genomes encode orthologs of the known members of the mammalian and yeast TORC1 complex [RAPTOR (7, 31, 102) and LST8 (33, 39, 112)] as well as the direct TORC1 targets ribosomal protein S6 kinase (S6K) (153, 154, 175) and TAP46 (2, 3). Even though there is no evidence for the existence of a TORC2 complex in plants, the presence of a TORC1 complex in both land plants and algae is well documented (101, 129). Transient overexpression of tagged proteins in tobacco leaves demonstrated the interaction between the *Arabidopsis* RAPTOR protein and the TOR HEAT repeats (102). In *Chlamydomonas* and *Arabidopsis*, the LST8 protein interacts with the TOR kinase domain, as it does in other eukaryotes (33, 112). This suggests that a conserved TORC1 protein complex is formed in plants and algae with the TOR, RAPTOR, and LST8 partners (**Figure 1**).

The TOR Kinase

TOR is a member of the phosphatidylinositol 3-kinase (PI3K)–related kinase (PIKK) family, which also includes the homologous ataxia telangiectasia mutated (ATM) and ATM- and RAD3-related (ATR) kinases (147). Although they are serine/threonine protein kinases, PIKKs contain a lipid PI3K-like catalytic domain bordered on the N terminus by the FRAP, ATM, and TRRAP (FAT) and FKBP12/rapamycin-binding (FRB) domains and on the C terminus by the FATC domain (11, 165, 170) (**Figure 1**). The N-terminal part of TOR comprises several HEAT repeats that are involved in protein-protein interactions. So far, the TOR kinase has been found in all sequenced plant and algal genomes (66, 101, 128).

As in other eukaryotes, the TOR kinase in *Arabidopsis* is a very large protein (2,481 amino acids), and it is 39% identical to the human protein. The FAT kinase and FRB domains are the most conserved ones (109, 129).

The TOR Structure

Low-resolution electron microscopy models show that the TOR N-terminal region interacts with the RAPTOR WD40 repeats (1, 172). More recently, the crystal structure of a C-terminal part of mammalian TOR (mTOR) containing the FAT-FRB-kinase-FATC domains bound to LST8 was obtained (11, 170).

The mTOR kinase domain shows a two-lobe structure separating a cleft where ATP is bound that is characteristic of the PI3K kinase family. Specific domains found only in TOR include the

FRB domain, which is inserted within the kinase N-terminal part. There is also a smaller, 40-amino-acid-long insertion in the C lobe that defines a binding site for LST8. Interestingly, this site is conserved in plant TOR sequences (**Figure 1**) and may contribute to the stabilization of the kinase domain activation loop by the FATC region (170). The C-terminal conserved FATC domain is integrated into the kinase domain structure, and LST8 and the FRB domain protrude from this domain. This overall structural organization of this TOR region is well conserved in plants (**Figure 1**).

SnRK1: Snf1-related kinase 1

LST8 is thought to be required for TOR activation, and its interaction surface may influence the organization of the kinase active site. Indeed, the solubility of overexpressed TOR is dependent on the simultaneous expression of LST8 (170). This structure also suggests that TOR is basically active by nature and that its activity is regulated by protein partners or specific domains acting as gatekeepers for the kinase substrates. Substrate recruitment therefore may be a major mechanism controlling the kinase activity.

RAPTOR

All well-sequenced plant genomes encode RAPTOR/KOG1-like proteins that share a well-conserved domain organization, including the raptor N-terminal conserved (RNC) domain, three HEAT repeats, and WD40 repeats. *Arabidopsis* has two RAPTOR-encoding genes, which, owing to confusing nomenclature in previous reports, we here call *Raptor3g* and *Raptor5g* (for their localization on chromosomes 3 and 5, respectively). These genes code for proteins that show strong similarities to the yeast KOG1 protein and the human RAPTOR protein (approximately 40% identity). Lines homozygous for disruptions of *Raptor3g* often exhibit mild phenotypes similar to the ones observed after inhibition of TOR expression, including a reduced rate of vegetative growth, increased branching, and delayed flowering. Nevertheless, in some conditions, these mutants showed early embryo lethality with variable penetrance (31). By contrast, lines homozygous for disrupted forms of *Raptor5g* are indistinguishable from the wild type (7, 31). These differences can be attributed largely to the relatively low expression of *Raptor5g* in most vegetative tissues. Much stronger phenotypes occur in lines that are homozygous for disrupted forms of both genes (7). Interestingly, double-mutant lines retain some capacity for vegetative growth, suggesting that RAPTOR plays a major role in enabling vegetative growth but is not essential, as it is in animal and yeast cells.

In animal cells, the TORC1 complex is inactivated upon phosphorylation of the RAPTOR protein by AMPK on two conserved serine residues (Ser722 and Ser792) followed by binding of 14-3-3 proteins (58). This inactivation signals energy and nutrient stresses by repressing TORC1 activity. Because the region surrounding Ser792 is weakly conserved in the plant RAPTOR protein sequences, it is possible that Snf1-related kinase 1 (SnRK1), the plant homolog of AMPK, plays a similar role by directly inactivating the plant TORC1 complex. In addition, the animal RAPTOR residues Ser696 and Thr706 are phosphorylated in mitosis by the mitotic cyclin-dependent kinase 1 (cdc2/CDK1), and its partner, cyclin B, is immunoprecipitated with RAPTOR in mitotic cells (57).

LST8

All plants and algae contain genes coding for the small LST8 protein (33, 39, 112). LST8 proteins are essentially made of seven WD40 repeats organized in a propeller-like structure (80). In *Arabidopsis*, *lst8* mutants display a retarded growth associated with an increased branching and delayed flowering together with a hypersensitivity to a shift from short to long days (112).

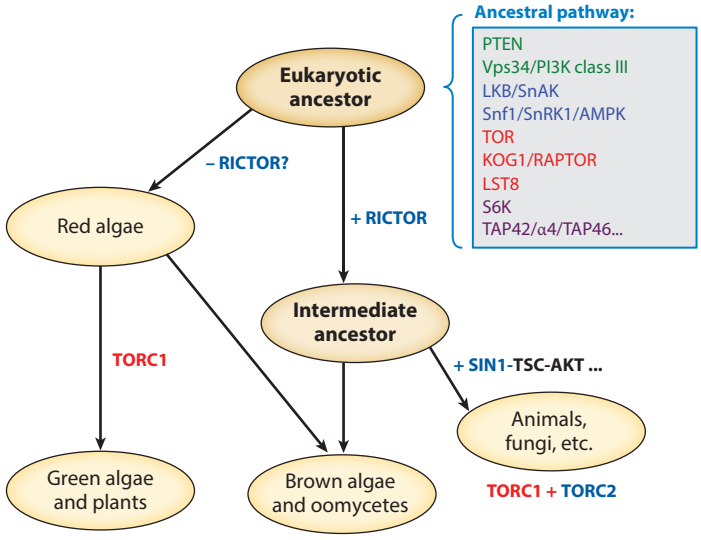

Figure 2

An evolutionary model of the eukaryotic TOR signaling pathway, showing the possible loss or acquisition of TOR signaling modules from the putative common eukaryote ancestor. The gray box lists the possible primitive eukaryotic core signaling components, with colors indicating different regulatory modules.

The Evolution of the TOR Complex

With the exception of some intracellular parasites, all eukaryotic cells characterized so far contain a presumably ancestral signaling pathway based on the TOR kinase that links growth to nutrient signaling and energy supply (22, 138, 158) (**Figure 2**). Therefore, *Arabidopsis*—like the rest of the Viridiplantae lineage, including the glaucophytes, the red and green algae, and land plants—contains this core signaling pathway (101, 138, 139). Interestingly, this signaling module is present even in the picoeukaryote *Ostreococcus tauri*, which has a highly reduced genome (66).

There is no evidence that plants have a TORC2 complex, and no homologs of the specific components AVO1/hSIN1 or AVO3/RICTOR have been detected in the green lineage (158). However, these proteins present a low degree of similarity, which could make it difficult to identify them in plants and algae. Interestingly, studies have found sequences potentially coding for RICTOR in oomycetes such as *Phytophthora* and brown algae such as *Ectocarpus*, which arose from a secondary symbiosis between a heterotrophic eukaryote cell and a red alga (138, 158). Serfontein et al. (138) have suggested that RICTOR was acquired rather than lost after the divergence between Archaeplastida (red algae to land plants) and other eukaryotes (**Figure 2**). The other components of the TORC2 complex could have developed later, during the evolution of animals and fungi. Nevertheless, the fact that RAPTOR and LST8 from rice, *Arabidopsis*, and *Chlamydomonas* complement yeast mutants shows that there is a good functional conservation of the TORC1 complex (33, 101, 112).

TAP42: type 2A phosphatase–associated protein 42

TOR Substrates in Plants

Important TOR substrates in animals and yeasts, such as S6K and the type 2A phosphatase–associated protein 42 (TAP42)/α4 subunit of protein phosphatase 2A (PP2A), are also present in plants, which suggests that TOR could act through conserved readouts (128, 165) (**Figure 3**). The ribosomal protein S6K is an evolutionarily conserved kinase in the AGC (PKA, PKG, PKC)

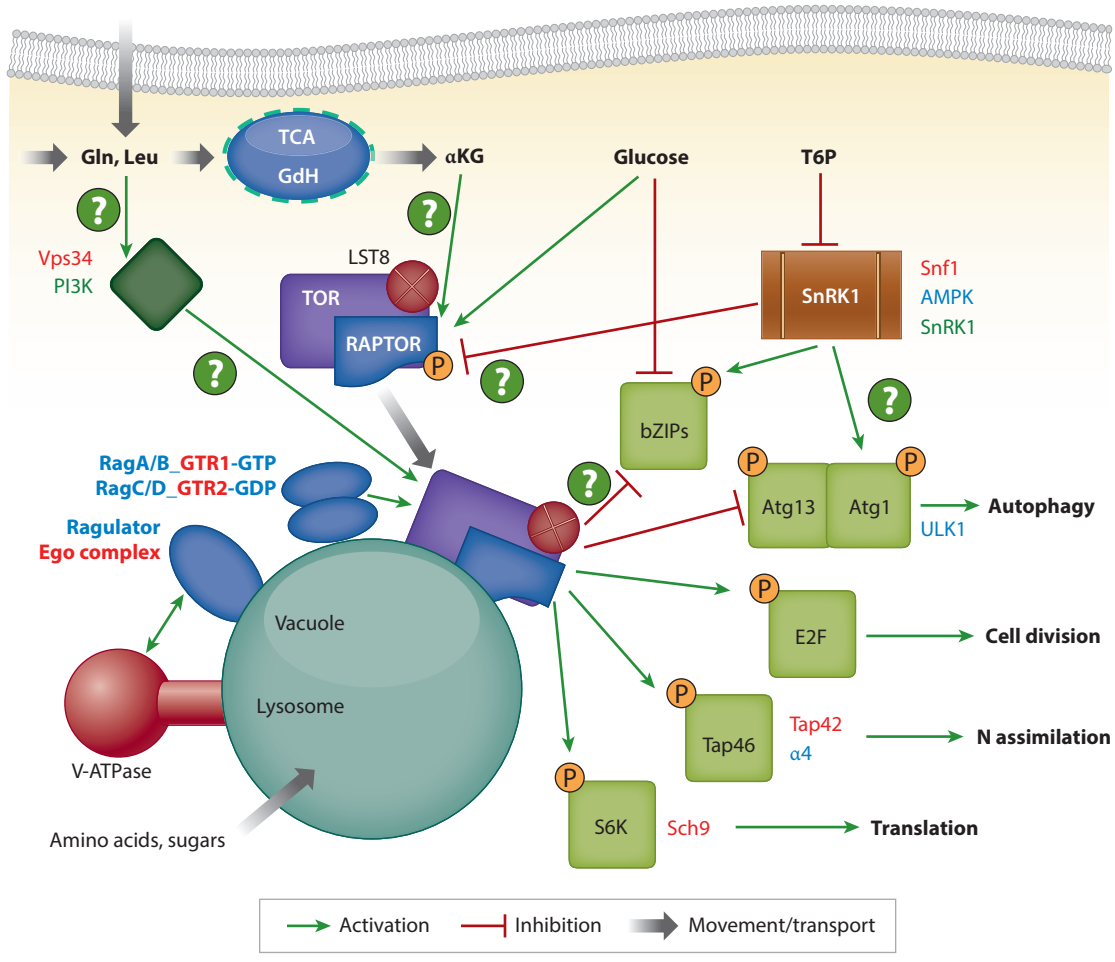

Figure 3

A simplified model of TOR regulation by nutrients, showing the various ways in which nutrients regulate the TOR kinase as well as the interactions between TOR and effector kinases and substrates in eukaryotes. The names of the regulatory or substrate proteins for animals, yeasts, and plants are shown in blue, red, and green, respectively.

family. The *Arabidopsis* genome contains two S6K-encoding genes with very similar sequences. In budding yeast, the homolog of S6K, Sch9, regulates cell size as well as nutrient signaling and aging (143, 156). A recent study by González et al. (53) suggested that yeast Ypk3 is the S6K ortholog that regulates ribosomal protein S6 (RPS6) phosphorylation in a nutrient-dependent manner. Even if the N- and C-terminal regions of the plant S6Ks are divergent from the animal sequences, the kinase domain is highly conserved. Moreover, the major and regulatory phosphorylation sites identified in human S6K are conserved in the *Arabidopsis* S6K (128, 154). Phosphorylation of Thr388/389 in animal S6K is widely used as a TOR activity readout. Antibodies specific for phosphorylated human Thr389 are able to recognize phosphorylated Thr449 and Thr455 in *Arabidopsis* S6K1 and S6K2, respectively (2, 134, 135, 167). In *Arabidopsis*, the S6K activity is also activated by auxin, which seems to augment the amount of TOR protein (109, 134). The *Arabidopsis* S6K can be activated by insulin in human cells after induction of TOR activity (153). Consistently,

the *Arabidopsis* S6K interacts with RAPTOR and phosphorylates RPS6 (102). Henriques et al. (65) proposed that S6K limits cell division and growth in sugar-starved cells in *Arabidopsis*.

The *Arabidopsis* TAP46 protein, a regulatory subunit of PP2A (61), is an ortholog of yeast TAP42, which is phosphorylated by TORC1 (18, 98). *Arabidopsis* TOR consistently phosphorylates TAP46 in vitro (3) (**Figure 3**). In yeast, when nutrients are abundant, TOR phosphorylates TAP42, which then binds PP2A and presumably inactivates it (18, 28). Under nutrient starvation, PP2A is released from TAP42 and dephosphorylates cognate substrates. *Arabidopsis* plants deficient in TAP46 activity resemble TOR-inactivated plants, exhibiting a global repression of translation and induction of autophagy (3). Overexpression of TAP46 resulted in larger plants, increased phosphorylation of S6K (probably as a result of TOR activation), and stimulated nitrate assimilation (2). Conversely, silencing of TAP46 resulted in lowered activity of nitrate assimilation enzymes such as nitrate reductase. Interestingly, in another experiment, plants overexpressing TAP46 were more sensitive to abscisic acid, probably owing to a modulation of abscisic acid insensitive 5 (ABI5) phosphorylation (70).

TOR inhibition by rapamycin in *Chlamydomonas* also induced phosphorylation of the endoplasmic reticulum chaperone luminal-binding protein 2 (BiP2), which is linked to endoplasmic reticulum stress (34). Recent work in *Arabidopsis* has suggested that E2F transcription factors, which are well known from animal models for their role in controlling cellular proliferation, constitute a previously unrecognized target for TORC1-mediated phosphorylation (166). The expression of E2Fa targets, many of which relate to cell cycle control, correlates with TOR activity and is repressed by TOR inhibitors.

A novel class of TOR substrate that is present in plants and many fungi but not in animals was recently confirmed by an analysis of its founding member, Mei2p, in *Schizosaccharomyces pombe* (163). In response to cues related to N limitation and mating pheromones, Mei2p acts through an RNA-binding activity to switch cells from mitotic growth to a more determinate meiotic development. A relationship with TOR was later revealed with the recognition that a Mei2-interacting protein (MIP1), recovered as a suppressor of Mei2p, is the fission yeast ortholog of RAPTOR (140). More recent work has shown that TOR activity suppresses meiotic development by phosphorylating Mei2p in a MIP1-dependent manner, thereby targeting Mei2p for ubiquitination-mediated turnover (117).

In contrast to the single *Mei2*-like gene in *S. pombe*, higher plants contain a structured family of *Mei2*-like genes (5, 6, 74) that are defined by an unusual RNA recognition motif shared with Mei2p. Some degree of functional conservation is suggested by the recovery of *Arabidopsis* Mei2-like 1 (AML1) in screens for cDNAs that complement meiotic mutants of *S. pombe* (68) as well as the interaction with *Arabidopsis* RAPTOR in yeast two-hybrid assays (6). The members of a second clade of *Mei2*-like genes, *TERMINAL EAR-LIKE* (*TEL*), have a domain organization similar to those of the *AML* and *Mei2* genes but are distinguished by a well-conserved insertion in the *Mei2* RNA recognition motif (25, 74). The focused expression of TELs in meristematic tissues of the shoot and root, together with precocious differentiation of tissues in loss-of-function mutants in maize and rice (120, 159), suggests that TELs may promote indeterminate growth.

REGULATION OF TOR BY NUTRIENTS IN ANIMAL AND YEAST CELLS

Mechanisms of Nutrient-Dependent TOR Regulation

Many studies in animals and yeasts have demonstrated the central role of the TOR signaling pathway in connecting nutrient sensing to the global and specific regulation of cell metabolism.

Indeed, exposing yeast cells to rapamycin results in the same phenotype as nutrient (C, N, or S) starvation does: an inhibition of translation together with the induction of autophagy and pathways, allowing the use of alternative, less favored sources of nutrients (18, 28, 98). For instance, upon N starvation, the decrease in TOR activity seems to trigger the endocytosis and degradation of specific high-affinity transporters, which are then replaced by more general transporters that are able to acquire a wider diversity of nutrients (17, 18). TOR inactivation is also involved in the onset of transcriptional programs in response to starvation. In yeast, for example, TOR promotes the cytoplasmic retention of the GATA transcription factor Gln3 by activation of TAP42, which inhibits PP2A activity (13). Following starvation, TOR is inactivated, which subsequently releases TAP42 from PP2A complexes. Gln3 is then translocated to the nucleus, where it induces the transcription of genes needed for the assimilation of alternative N sources (such as proline or urea).

Vps34: vacuolar protein sorting–associated protein 34

In animal cells, several elegant studies have shown that the TORC1 complex is activated by amino acids through recruitment to the lysosomal surface (46, 132, 133, 178). Amino acids, especially leucine, modify the lysosomal vacuolar-type ATPase (V-ATPase), which allows the release of the multimeric so-called Ragulator complex followed by the activation of Rag-type GTPases and the recruitment of TOR activity by their binding to RAPTOR (81, 35, 42, 45, 75) (**Figure 3**). Interestingly, a meta-analysis of metabolite and transcript changes in *Arabidopsis* plants subjected to various stresses also identified leucine as a mediator of coordinated responses (59). These results suggest the involvement of the plant TOR pathway in this link, which could thus be evolutionarily conserved.

Other studies also indicated that a specific lysosomal amino acid transporter (SLC38A9) is involved in the specific activation of TOR by arginine and glutamine at the lysosomal surface (125, 161). This transporter could act as a transceptor (rather than a transporter) that mediates TOR recruitment and activation by a specific amino acid. Moreover, glutamine has a prominent role in the regulation of TOR activity (75, 76). For example, glutaminolysis has recently emerged as an important process stimulating TOR activity, presumably through alpha-ketoglutarate (αKG) production in mitochondria by glutamate dehydrogenase (43). The strong activation of the TOR pathway in cancer cells could be due in part to an active glutamine metabolism (26, 75). αKG is thought to activate the TOR pathway by the intermediate of the Rag complex at the lysosomal membrane. Similarly, glucose seems to activate TOR by the same mechanism (46). Moreover, TOR can be tethered to other membranes by small GTPases such as Rab1A, which recruits TOR at the Golgi surface (149). In yeasts, the Gtr1/2 GTPases perform the same function and recruit TOR to the vacuolar membrane, thereby transmitting the amino acid sufficiency signal to this signaling pathway (98, 119). In plants, the vacuole also serves as a nutrient reservoir, and the degradation of proteins by autophagy results in an increase in vacuolar amino acids, which in turn could activate TOR to control autophagy through a feedback mechanism. The involvement of plant V-ATPase in the same process remains to be determined, but this complex is already known to be important for several nutrient-related processes (137). Indeed, V-ATPase deficiency results in the stimulation of nitrate assimilation and the accumulation of glutamine, which is also observed in *lst8* and TOR-deficient plants or after TAP46 overexpression (2, 86, 112, 127).

Regulation Through Phosphatidylinositol 3-Kinase

Plants, animals, and yeasts all contain PI3K activity, but plants and yeasts have only type III PI3K [also called vacuolar protein sorting–associated protein 34 (Vps34)] (22), which phosphorylates phosphoinositides at position 3 of the inositol ring to produce phosphatidylinositol 3-phosphate (PI3P) (9, 113). PI3P is essential for endosomal trafficking, and Vps34 is recruited by membrane-bound Rab GTPases (9, 124). The produced PI3P binds to FYVE or PX protein domains, which

contributes, for example, to phospholipase D activation and production of phosphatidic acid (148). Phosphatidic acid directly activates TOR in animals (42, 151). Amino acids consistently stimulate PI3K activity, which in turn activates the TORC1 complex (56). However, studies in *Drosophila* have produced conflicting results (79). Ongoing studies also suggest that such a link may exist in plants between PI3K/Vps34 and the TOR kinases (91; A.S. Leprince & C. Meyer, unpublished results).

Autophagy

Because nutrient levels can fluctuate in plants (for example, when starved for N or when light is limiting for photosynthesis), they have efficient ways of storing resources in the form of starch, proteins, lipids, or amino acids. To ensure homeostasis within the cell or the plant, these reserves and other cell components must be remobilized during starvation. Plants use different strategies to produce energy and nutrients in times of scarcity, and autophagy is an important part of this process (8, 12, 55, 105). In mammals, energy and nutrient limitation activates AMPK, which phosphorylates autophagy-related 1 (Atg1)/Unc51-like kinase 1 (ULK1), the main switch initiating the autophagic process (47, 62, 82). By contrast, the antagonist TORC1 complex represses autophagy in part through the inhibitory phosphorylation of Atg1/ULK1 and of its protein partner Atg13 (41, 62, 82) (**Figure 3**). Thus, a close crosstalk exists between AMPK/Snf1 and TOR that fine tunes the inception and repression of autophagy in cells. Indeed, because autophagy results in the degradation of cellular components such as ribosomes or organelles, this process must be used only when necessary to avoid cell death. In plants and algae, studies have shown that the TORC1 complex regulates autophagy (8, 12, 95, 122) and that Atg1 is a phosphorylated protein (146), but the role of the SnRK1/TOR crosstalk in the initiation of autophagy remains to be established. Autophagy has also been implicated in the pathogen-induced plant hypersensitive response that limits the spread of cell death (69, 110, 173), and it would be of interest to determine the role of the SnRK1/TOR balance in regulating this process.

In mammals, ULK1 induces phosphorylation of RAPTOR on Ser855 and Ser859, which contributes to TOR inhibition (40). This could build a positive feedback loop that increases autophagy. However, to maintain homeostasis within the cell, amino acids that are later excreted from the lysosome or vacuole as a result of protein degradation may then restart TOR activity. Moreover, ULK1 also inhibits AMPK, which contributes to another feedback loop that moderates autophagy.

The PI3K/Vps34 kinase is also known to activate autophagy, which appears to be contradictory to its role in promoting TOR activity. In fact, studies have suggested that Vps34 may act in two different complexes, one linked to autophagy initiation and one to TOR activation. AMPK plays a key role in regulating the different Vps34 complexes: AMPK activates the autophagy-linked Vps34 complex and inhibits the other complex by phosphorylating Thr163/Ser165 in Vps34 and lowering PI3P production (41, 56, 79). Interestingly, inhibition of Vps34 by AMPK in response to starvation was shown to be important for survival (41).

REGULATION OF TOR IN PLANTS

Upstream Metabolic Regulators of the TOR Pathway in Plants

Unlike the well-described molecular mechanisms linking TOR to nutrients in mammals and yeasts, little information on such mechanisms is available in plants. Indeed, it seems that some components of the upstream TOR regulatory pathway are not shared with plants, as some important regulators are missing, such as tuberous sclerosis complex 1/2 (TSC1/2), Ras homolog

enhanced in brain (Rheb), class I–II PI3Ks, and phosphokinase B (138, 158). Plants are likely to rely, at least in part, on specific signaling mechanisms involving auxin, cytokinin, abscisic acid, and other hormones. Hormones play significant roles in tissue patterning and in adaptive qualitative and quantitative growth responses by regulating cellular growth, division, and determination processes. Moreover, hormonal signaling is influenced by levels of C, N, and other nutrients (96, 131), but the relationship between the hormones and TOR regulation is not well defined. The lack of conservation of these upstream regulators suggests that plants may have evolved their own regulation pathway of the TOR activity to better adapt to their sessile and photoautotrophic features. The absence of conserved key players upstream of the TOR pathway and the lack (so far) of a reliable TOR kinase activity assay have complicated the elucidation of signals implicated in the regulation of TOR in plants.

Despite the above difficulties, studies have shown that the presence of glucose induces TOR activity in four-day-old seedlings (166, 167) and that TOR is necessary for the glucose-dependent exit from mitotic quiescence in young seedlings at both the cellular and transcript levels (166). Moreover, anoxia, which is known to affect C catabolism, largely reduces the phosphorylation level of RPS6, which is presumably also TOR dependent in plants (102, 164; T. Dobrenel & C. Meyer, unpublished results). Plants harvested during the night exhibit a similar reduction of RPS6 phosphorylation when compared with plants harvested during the day (15, 155). Finally, TOR RNA interference (RNAi) and *lst8* mutants are severely affected by high concentrations of sucrose, and the *lst8* mutants have a more severe phenotype under long-day conditions than under short-day conditions, which may be related to a deregulation of the starch, raffinose, and trehalose content (112). Together, these results suggest that the TOR activity is regulated by intracellular sugar availability (36, 168) (**Figures 3** and **4**).

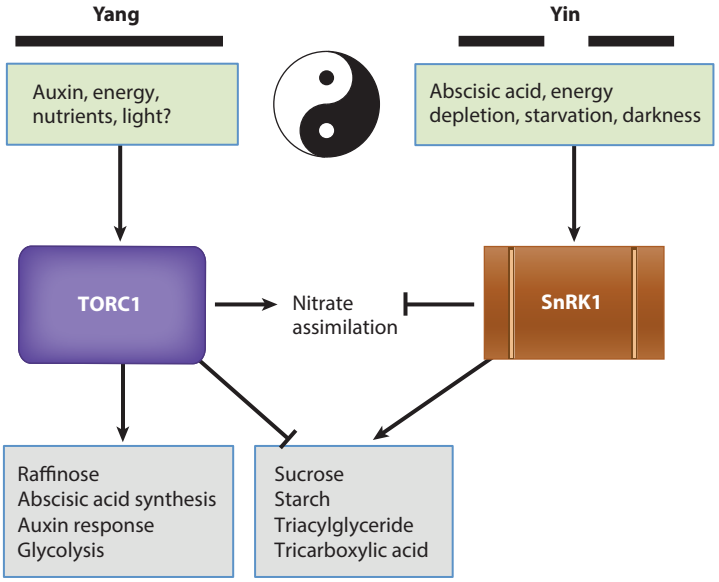

Figure 4

Summary of metabolites and biological processes regulated by the TOR and SnRK1 kinases in response to different stimuli and signals. The conserved and crucial SnRK1 and TOR kinases can be seen as the yin and yang, respectively, of cell metabolism and growth. Indeed, both kinases represent contrary and vital forces that are interconnected and in reciprocal and constant increase and decrease.

The most compelling examples of a coupling of hormonal and TOR signaling have been provided by analyses that show not only the activation of TOR by auxin, but also the contribution of TOR activity to downstream auxin signaling–mediated processes (16, 109, 134). Schepetilnikov et al. (134) showed that the link between TOR and the translation reinitiation after an upstream-translated micro–open reading frame (μORF) in mRNA leader regions is promoted by the application of exogenous auxin, suggesting that the TOR pathway overlaps at least partially with some phytohormone responses. A transcriptomic analysis of seedlings treated with the TOR inhibitor AZD-8055 confirmed this result, demonstrating an induction of some genes involved in the abscisic acid, ethylene, jasmonate, and salicylic acid pathways together with a repression of the auxin, cytokinin, brassinosteroid, and gibberellin pathways (38). Conversely, long-term inhibition of the TORC1 complex results in the downregulation of both abscisic acid synthesis and response (85).

Crosstalk with the Starvation- and Stress-Activated SnRK1 Kinase

SnRK1 is a plant multisubunit kinase, with the catalytic α subunit encoded by three genes in *Arabidopsis*; of these, *KIN10* and *KIN11* are believed to be the most important (10, 29, 123, 129). In plants, SnRK1 is activated by stress conditions that limit energy availability in the cell, such as hypoxia, flooding, and reduced photosynthetic capacity. In this situation, SnRK1 represses energy-demanding processes such as anabolism or cell division (10, 60), which are often positively regulated by TOR, and activates stress-dependent energy-generating processes such as starch reallocation and gluconeogenesis (10, 78). On a general level, it seems that, as in animals for AMPK and yeasts for Snf1, the processes controlled by TOR are regulated by SnRK1 in an opposite manner (29, 47, 60, 67) (**Figures 3** and **4**).

SnRK1 activity is regulated by a plethora of factors, ranging from phytohormones to metabolites (10, 78, 123). In nonplant organisms, AMPK and Snf1 are specifically regulated by AMP/ADP levels, providing direct energy-dependent control of the kinase activity, but the plant kinase seems to lack this regulatory response (48). High sugar levels inhibit SnRK1 (114), and trehalose 6-phosphate, a probable readout for sugar availability (99), could be a direct negative regulator of SnRK1 activity (121, 176) (**Figure 3**). Mair et al. (103) recently showed that SnRK1 phosphorylates and thereby regulates the activity of the transcription factor basic leucine zipper 63 (bZIP63) in order to trigger global adaptation to low energy.

BIOLOGICAL PROCESSES CONTROLLED BY TOR IN PLANTS

In contrast to the results obtained in mammals or yeast, very little is known about the key physiological mechanisms regulated by the TOR pathway in plants. This lack of information is due mainly to the embryo lethality of *tor* null mutants (32, 108, 126) and the varying levels of insensitivity to rapamycin. To circumvent these difficulties, several groups have used constitutive or inducible methods to inactivate TOR through either overexpression of FKBP12 or TOR silencing by RNAi or microRNAs (20, 32, 126, 166). Over the last decade, these strategies have enabled investigators to connect the TOR pathway with a large number of mechanisms of major importance for plant growth and development.

Control of mRNA Translation

In plants, as in other eukaryotes, mRNA translation (from ribosome biogenesis to protein production) requires a large amount of energy (162). A specific feature of plants is that

ribosome-constitutive proteins are encoded by gene families comprising two to seven members (19, 130, 72); this large variety of combinations is thought to permit a plasticity in the translation of specific mRNA clients during development or in responses to the environment, and may be part of the adaptive response to stress conditions or energy availability (71, 141). Whether the TOR activity level acts on this plasticity remains unclear, and dedicated experiments will be necessary to answer this question. Nevertheless, studies so far have shown that, as in yeasts, inactivation of TOR results in a significant decrease in polysome accumulation (32, 50, 142). As mentioned above, the TOR-S6K signaling axis is implicated in translation reinitiation after a μORF (135), and the fact that approximately 35% of the mRNA from *Arabidopsis* presents a μORF upstream of the initiating ATG codon (160) suggests that this mechanism may play an important role in TOR-dependent translation reprogramming and control of growth and development (177).

Auxin treatment of *Arabidopsis* seedlings leads to the phosphorylation and activation of TOR by an unknown mechanism and promotes the association of TOR with polysomes, where it phosphorylates S6K (16, 134). Schepetilnikov et al. (134) showed that inhibition of TOR by RNAi or chemical inhibitors blocks gravitropism, a classic auxin-mediated growth response. Molecular analyses suggest that the dependence of gravitropism on TOR activity is tied to a novel form of translational regulation in which activated S6K phosphorylates the translation initiation factor eIF3, thereby stabilizing the association of ribosomes with mRNAs after transiting short μORFs. Variations on this theme also appear to be key to the translation of polycistronic messages of cauliflower mosaic virus (135). Furthermore, TOR inhibition decreased potyvirus replication in *Arabidopsis*, which depends heavily on the availability of eiF4E (118). Interestingly, eiF4E-binding protein (4EBP) is a major target of TOR in animal cells, in which TOR promotes translation initiation by phosphorylation and inactivation of 4EBP (50). So far, there is no evidence for a 4EBP function in plants.

The TOR Pathway Influences Both Nutrient Transcriptional and Metabolic Programs

A key question concerning the interface between TOR and nutrient-related signaling is how outputs are coordinated with programs for multicellular development. In contrast to animals, plants and many fungi feature remarkably plastic patterns of development, many of which support growth-based foraging strategies for nutrients (e.g., pseudohyphal growth in yeasts and root growth in plants) (52, 90).

During the last decade, investigators have used large-scale analysis, including transcriptomic and metabolomic experiments, to attempt to better understand the pathways regulated by the TOR complex. The different approaches they have used (mainly to inactivate the TOR complex), as well as the variety of developmental stages and the length of the inactivation treatments, have revealed a poor overlap between the experiments, suggesting that the result of the TOR inactivation triggers a dynamic response depending on the length of the TOR inactivation, the growth conditions, or the developmental stage (20, 32, 38, 166). This is consistent with some physiological observations showing that repression of TOR expression has a much more dramatic effect during germination than it does later in development (32, 111, 126). However, a large number of the pathways affected by the TOR complex inactivation are related to energy (at the level of either energy sensing or production) or to growth processes. It is interesting that genes implicated in photosynthesis are often present in the anabolic pathways that are mainly downregulated after TOR inactivation (20, 38, 127, 166), which is consistent with the yellowing phenotype observed in both the TOR RNAi and *lst8* mutants (32, 112). Similarly, a combination of transcriptional and metabolic analyses in

response to rapamycin identified cysteine and methionine metabolisms as the most affected in *Chlamydomonas* (83).

The Role of the TOR Pathway in the Regulation of Starch Metabolism

In all eukaryotes, several pieces of evidence point to a role of TOR in modulating C metabolism (20, 21, 44, 98, 128, 165). A common phenotype of *Arabidopsis* mutants with repressed TORC1 components (i.e., TOR and LST8) is an increase in starch content (36). Remarkably, in animals and yeasts, disruption of TORC1 results in the accumulation of glycogen, a starch analog polymer. Many efforts have been made to elucidate the precise mode of action of TOR in this regulation. In yeasts, the transcription factor MSN2, which regulates the expression of enzymes involved in glycogen synthesis, is phosphorylated only under TORC1 repression (51, 136). Similarly, in RAPTOR-deficient muscles, enhanced glycogen content is triggered by a hyperphosphorylation of protein kinase B (PKB/Akt), which increases the phosphorylation and activates glycogen synthase kinase 3β (GSK3β) concomitantly with the downregulation of glycogen phosphorylase (14). This suggests that TOR could conceivably have an evolutionarily conserved role in plant starch metabolism.

Starch, a widespread short- and long-term storage compound in plants, is negatively correlated with biomass (144, 145). It is synthesized in the chloroplast during the day and broken down at night to support metabolism and growth (144). In this context, it remains to be elucidated whether the starch excess phenotypes observed in *Arabidopsis* TORC1 mutants are due to stimulation of starch synthesis and/or impairment of its degradation (36). Although the pattern of C assimilation, storage, and usage during the diurnal cycle seems relatively simple, there is a complex regulatory network that is crucial to maintain the proper C balance (144, 174). Starch metabolism involves the coordinated action of several enzymes and their isoforms, and many of them are subjected to phosphorylation and redox regulation (97, 144, 174).

Because the TOR signaling pathway mediates the phosphorylation of a vast number of substrates and effectors in mammals and yeasts (17, 98), it is possible that TOR directly or indirectly phosphorylates enzymes involved in starch metabolism. One possible partner would be the plant energy sensor SnRK1, because it regulates enzymes involved in sucrose-starch metabolism (10, 60, 78). Another question to be addressed is whether starch accumulates as a result of changes in C partitioning between starch and sucrose, the two main C sinks.

The Role of the TOR Pathway in the Regulation of *myo*-Inositol and Raffinose Metabolism

The expression of *myo*-inositol 1-phosphate synthase 1 (MIPS1) is closely connected with biomass and genes involved in responses to changes in the C network (145). MIPS1 catalyzes the rate-limiting step in the synthesis of *myo*-inositol, which is then incorporated into lipid-dependent (e.g., phosphatidylinositol and inositol phosphates as well as sphingolipid signaling molecules) and lipid-independent pathways (e.g., raffinose, galactinol, and UDP-glucuronate) (157). Raffinose is a trisaccharide synthesized from galactinol and sucrose using *myo*-inositol as a cofactor. Interestingly, levels of raffinose and galactinol as well as of MIPS1 and galactinol synthase transcripts were reduced in *lst8* mutants, in ethanol-inducible TOR RNAi lines, and in rapamycin-treated *Arabidopsis* plants (32, 112, 127). Similarly, genes differentially expressed in *Arabidopsis lst8* and *mips1* mutants exposed to long-day conditions showed a significant overlap (68%), suggesting a role for the TOR kinase complex in linking environmental cues, growth, and C metabolism (112). It is also likely that a significant part of the observed phenotypic and metabolic variations in *lst8* mutants is due to a defect in the synthesis of *myo*-inositol (36, 128).

The Role of the TOR Pathway in the Regulation of Lipid Metabolism

A long-term reduction of TOR expression in *Arabidopsis* seedlings also led to an increase in triacylglycerides (TAGs), especially those with long-chain polyunsaturated fatty acids (20). The highly reduced state of these neutral lipids enables them to provide energy and C storage (94) not only in seeds but also in other tissues, such as senescing leaves or floral tissues, and they are involved in a wide range of biological processes (e.g., stress response, senescence, and N deprivation) (23, 24, 94). In eukaryotes, the committed acylation step in TAG biosynthesis can be catalyzed by one of three classes of diacylglycerol acyltransferases—DGAT1, DGAT2, and a phospholipid:diacylglycerol acyltransferase (PDAT)—depending on the tissue and species. Although studies have shown that DGAT1 is involved in the conversion of galactolipids to TGAs in response to senescence or N starvation (152, 171), transgenic lines with conditional silencing of *Arabidopsis* TOR showed neither changes in the levels of DGAT1 transcripts nor a significant breakdown of galactolipids (20). Similarly, the transcript level of PDAT, which has a role in inducing and directing fatty acids from the membrane to TAG synthesis in *Arabidopsis* leaves (49), was also not affected by TOR inhibition. In the unicellular algae *Cyanidioschyzon merolae* and *Chlamydomonas*, rapamycin-mediated TOR inhibition led to the accumulation of TAG derived from newly synthesized fatty acids (73, 83).

In contrast to long-term TOR inhibition in algae, evidence has emerged that TOR plays a role in repressing genes encoding TAG lipase and acyl–coenzyme A (acyl-CoA) oxidase involved in β-oxidation of lipids during the heterotrophic-photoautotrophic transition in *Arabidopsis* (166, 168). Moreover, Li et al. (93) recently reported that a *ribosomal large subunit 4* (*rpl4d*) mutant shows reduced lipid accumulation only in meristems. The authors also found that lipid metabolism integrates auxin-regulated tissue differentiation and endomembrane trafficking by regulating ribosomal proteins. Taking into account the possible involvement of TOR in lipid, auxin, and translational regulation, it is tempting to speculate that this kinase links lipid metabolism, auxin, and ribosome-mediated translational controls (93, 134).

Apart from being the largest C sink in plants, the cell wall regulates plant growth through a constant remodeling of its components. Notably, studies have demonstrated a link between the TOR kinase pathway and cell wall structure in yeast and *Arabidopsis* (89, 92). The *repressor of LRR-extensin 1* (*rol5*) mutant was found in a suppressor screen of the *lrx1* mutant, which develops aberrant root hairs. The *ROL5* gene is an ortholog of *Ncs6* in yeast, which acts as a downstream target of TORC1 (89). Rapamycin treatment of *lrx1* mutants overexpressing yeast FKBP12 rescued the *lrx1* root phenotype by modifying its pectin content and arabinogalactan proteins (11). Furthermore, studies have identified a deregulation of the expression of genes encoding expansins in loss-of-function TOR and *lst8* mutant lines (20, 112).

TOR and the Regulation of Nitrogen Metabolism

In yeasts, TOR is rapidly inactivated by N starvation, and it appears that AMPK represses the TORC1 complex (presumably by phosphorylating the RAPTOR protein) in response to N stress in mammals (30). Nitrate, the main source of N for many plants, is an important nutrient but also serves as a signaling molecule that specifically and rapidly induces the expression of hundreds of genes (for recent reviews, see 84, 107). In addition to genes involved in nitrate and nitrite uptake and assimilation, nitrate supply rapidly induces not only genes involved in amino acid and nucleotide biosynthesis but also those involved in ribosome biogenesis and trehalose metabolism (104, 107).

Interestingly, the addition of sucrose to starved seedlings also leads to an induction of genes for amino acid and ribosome synthesis (116). These results imply that the availability of C or N stimulates protein synthesis, possibly through TOR activation in plants. Plants have evolved sophisticated mechanisms to integrate C and N assimilation and transport (115). Indeed, processes

such as amino acid synthesis need a stoichiometric amount of C and N skeletons. In plants, αKG serves as the entry point for the synthesis of organic N molecules through the activity of the glutamine synthetase (GS)–glutamate oxoglutarate aminotransferase (GOGAT) cycle. C and N metabolism could be coordinated by sensing the C/N balance and regulating several processes (such as photosynthesis, the tricarboxylic acid cycle, and N assimilation) through the crosstalk between the TOR and SnRK1 kinases in order to adapt protein synthesis and metabolism to the available resources (84, 115, 128) (**Figures 3** and **4**).

CONCLUSION AND PERSPECTIVES

The TOR signaling pathway integrates information about the nutrient environment of cells and tissues to mount the necessary physiological and developmental responses. Great progress has been made in understanding TORC1 signaling in animals and yeasts, but knowledge about this regulatory pathway in plants has lagged behind. Nevertheless, in the last few years, the plant TOR field has been booming, and mounting evidence clearly indicates that, in photosynthetic organisms as well, the TOR signaling pathway has a conserved role as a central regulatory node in conjunction with SnRK1, adapting growth and metabolism to nutrient and hormone signals. Indeed, it has been proposed that TOR is activated in favorable conditions when nutrients are present, which results in the stimulation of growth and anabolic metabolism, whereas nutrient or energy limitation activates the antagonist SnRK1 kinase to promote energy saving and nutrient remobilization. Compared with animals and yeasts, these signaling pathways may be even more critical in multicellular plants and algae, which cannot escape from harsh environmental conditions or nutrient scarcity.

Crosstalk between TOR and SnRK1 in plants may rely on as yet undocumented phosphorylation of RAPTOR by SnRK1 or may be based on evolutionary developments in the plant lineage. It is tempting to speculate that these plant-specific mechanisms involve metabolic control of protein activity based on carbohydrate levels, by analogy with the importance of the amino acid and adenylate levels in mammalian and yeast systems (4, 18, 75, 98). The specific relationships among the plant SnRK1, PI3K, TOR, and Atg1 kinases in autophagy induction and in responses to variations in nutrient or energy levels remain unknown. It will be of particular interest to determine whether the crosstalk in plants between these regulatory kinases and hormone signals operates via evolutionarily conserved or plant-specific mechanisms that were developed after the divergence of photosynthetic organisms from other eukaryotes. It is possible that, under the range of fluctuations of nutrient and energy levels that occur physiologically, some of these signaling pathways act in parallel or independently in a time- and tissue-specific manner.

Taken together, those studies indicate that the plant TOR signaling pathway has a different mode of action in stimulating photosynthesis and C and N assimilatory metabolisms and in inhibiting C storage into different compounds (starch, TAG, etc.). A better understanding of those mechanisms is now needed and might offer a novel route for the manipulation of C partitioning and conversion of plant energy content to increase biomass yield.

SUMMARY POINTS

1. The TOR kinase complex TORC1 is present in all eukaryotic photosynthetic organisms, including land plants.
2. The TORC1 organization is similar to that found in animals and yeasts with the TOR, RAPTOR, and LST8 proteins.

3. Several conserved TOR substrates are present in plants, including the S6 kinase and the PP2A phosphatase-associated protein TAP46.
4. TOR activity seems to control many growth-related processes as well as N and C assimilation.
5. TOR inactivation stops growth and triggers the accumulation of starch and lipids.
6. TOR controls many aspects of mRNA translation, including translation reinitiation after a μORF, and is needed for stress adaptation.
7. The activity of TOR appears to be regulated directly by glucose to stimulate growth.

FUTURE ISSUES

1. Is there more than one TOR complex in plants? If one accepts the dictum that TORC2 is important for polarized growth in eukaryotes, how do plants manage without it?
2. What is the relationship between the antagonist TOR and SnRK1 kinases in plants in terms of common substrates and regulatory cross-phosphorylations?
3. Is the proposed stimulation of TOR by nutrients regulated through the action of conserved small GTPases and V-ATPase?
4. How was the TORC1 complex recruited in plants during evolution to regulate specific processes, such as auxin signaling, N assimilation, photosynthesis, starch synthesis, and plastid functioning?
5. Could the TOR signaling pathway be harnessed to improve biomass production, increase crop yield, or enhance pathogen resistance?

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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