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PRIMER

# TOR signaling in plants: conservation and innovation

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## ABSTRACT

Target of rapamycin (TOR) is an evolutionarily conserved protein kinase that plays a central role in both plants and animals, despite their distinct developmental programs and survival strategies. Indeed, TOR integrates nutrient, energy, hormone, growth factor and environmental inputs to control proliferation, growth and metabolism in diverse multicellular organisms. Here, we compare the molecular composition, upstream regulators and downstream signaling relays of TOR complexes in plants and animals. We also explore and discuss the pivotal functions of TOR signaling in basic cellular processes, such as translation, cell division and stem/progenitor cell regulation during plant development.


**KEY WORDS: Target of rapamycin protein kinase, Nutrient signaling, Metabolism reprogramming, Cell cycle regulation, Meristem, Stem cell niche**

## Introduction

Emerging evidence supports the notion that signaling and metabolic networks are intertwined and play instructive roles in developmental programs and responses to environmental changes and stresses (Krejci and Tennessen, 2017; Li and Sheen, 2016). Remarkably, the protein kinase target of rapamycin (TOR) has been shown to act in the center of such networks in all eukaryotes, from unicellular yeasts and algae to multicellular plants, animals and humans (Ben-Sahra and Manning, 2017; Dobrenel et al., 2016a; González and Hall, 2017; Saxton and Sabatini, 2017; Xiong et al., 2013; Xiong and Sheen, 2015). Since the discovery of rapamycin from a soil bacterium *Streptomyces hygroscopicus* on Easter Island (Sehgal et al., 1975), and the subsequent isolation of TOR genes in yeast (Heitman et al., 1991; Kunz et al., 1993), mammals (Sabatini et al., 1994) and plants (Menand et al., 2002), tremendous progress has been made in uncovering the molecular and cellular functions and mechanisms of TOR signaling.

In plants, as is the case in animals, null *tor* mutants are embryo lethal and rapamycin only partially impairs a broad spectrum of TOR activities (Gangloff et al., 2004; Kang et al., 2013; Menand et al., 2002; Ren et al., 2011; Xiong and Sheen, 2012). However, by coupling thoughtfully designed organismal experiments with inducible *tor* RNAi lines, quantitative assays for TOR phosphorylation targets, and specific chemical inhibitors (Box 1), it has been possible to connect the molecular, cellular and metabolic functions of TOR and its direct or indirect phosphorylation substrates to diverse developmental processes in plants (Caldana et al., 2013; Deprost et al., 2007; Montané and Menand, 2013; Ren et al., 2012; Xiong et al., 2013; Xiong and Sheen, 2012). In this Primer, we provide an overview of this progress. We first present an introduction to TOR complexes and their conservation. We then compare the conserved and unique roles of TOR signaling networks in different biological contexts. Finally, we highlight the impact of TOR signaling on plant development, discussing its role during various stages of the plant life cycle from embryogenesis and seedling growth, through to leaf expansion, flowering and senescence.

## The conservation of TOR complexes

TOR is a highly conserved but atypical Ser/Thr protein kinase that belongs to the phosphatidylinositol 3-kinase-related lipid kinase family (Heitman et al., 1991; Kunz et al., 1993; Menand et al., 2002; Sabatini et al., 1994). The TOR protein contains HEAT (Huntington, Elongation Factor 3 regulatory, subunit A of PP2A, TOR1) repeats and FAT (FRAP-ATM-TTRAP), FRB (FKBP-rapamycin-binding), kinase and FATC domains (Fig. 1). TOR proteins from diverse plant species share high sequence similarity with mTOR in mammals/humans, especially in the FRB and protein kinase domains. Early studies suggested that flowering plants were insensitive to rapamycin, and it was shown that the FRB domain of *Arabidopsis thaliana* TOR (AtTOR) does not interact with a complex consisting of rapamycin and FKBP12 (a rapamycin-binding protein) in yeast two-hybrid and *in vitro* pull-down analyses (Mahfouz et al., 2006; Menand et al., 2002). However, using a more sensitive split luciferase protein interaction assay in *Arabidopsis* mesophyll protoplasts, it was demonstrated that rapamycin specifically stimulates similar interactions between *Arabidopsis* and human FKBP12 with the FRB domain of AtTOR (Xiong and Sheen, 2012). Consistent with this, it was demonstrated that AtTOR-mediated phosphorylation of the ribosomal protein S6 kinases AtS6K1 (T449) and AtS6K2 (T455), which are conserved TOR targets, is inhibited by rapamycin in cell-based assays and in transgenic seedlings (Xiong and Sheen, 2012). *Arabidopsis* or human FKBP12 overexpression further enhances rapamycin sensitivity by more than 100-fold in plant cells and transgenic plants, a finding that greatly facilitated the elucidation of AtTOR functions in various cellular and developmental processes in plants (Deng et al., 2017; Li et al., 2015; Ren et al., 2012; Xiong et al., 2017, 2013; Xiong and Sheen, 2012).

Whereas yeast has two TOR genes, only one TOR gene is present and responsible for a large array of TOR kinase functions in plants, animals and humans (Ben-Sahra and Manning, 2017; Caldana et al., 2013; Deprost et al., 2007; Dobrenel et al., 2016a; González and Hall, 2017; Menand et al., 2002; Saxton and Sabatini, 2017; Xiong et al., 2013; Xiong and Sheen, 2015). In mammalian cells, TOR exists in two distinct protein complexes, mTORC1 and mTORC2, both of which have different signature components and distinct substrates and functions (Fig. 1). The core components of mTORC1 are mTOR, RAPTOR (regulatory-associated protein of mTOR; RPTOR) and mLST8 (small lethal with SEC13 protein 8) (González and Hall, 2017; Saxton and Sabatini, 2017). The 3D

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**Box 1. TOR kinase inhibitors**

Rapamycin represents the first generation of TOR kinase inhibitor, which promotes the interaction of FKBP12 with the FRB domain of the TOR protein and specifically inhibits TORC1 activity (Xiong and Sheen, 2012; Saxton and Sabatini, 2017). By developing more sensitive cell-based and seedling assays, it has been shown that the conserved TORC1 phosphorylation site in *Arabidopsis* S6K proteins is inhibited by rapamycin. Furthermore, overexpression of *Arabidopsis*, human or yeast FKBP12 increases the rapamycin sensitivity from 1 µM to 1 nM in leaf mesophyll cells and transgenic plants (Xiong and Sheen, 2012; Ren et al., 2012). More recent studies demonstrate that the next generation of ATP-competitive inhibitors of TOR kinase, including TORIN1, TORIN2, PP242, AZD8055, KU-63794, WYE-132, WYE-354, QL-IX-55 and INK-128, are more potent than rapamycin and can inhibit the kinase activity of both mTORC1 and mTORC2 based on specific phosphorylation substrates and sites (Schenone et al., 2011; Liu et al., 2012; Lamming et al., 2013). To date, AZD8055, TORIN1, TORIN2, WYE-132, WYE-354 and KU-63794 have been tested and found to be effective in blocking TORC1 activity in plants (Montane and Menand, 2013; Xiong et al., 2013; Deng et al., 2017; Li et al., 2017).

structure of mTORC1 has been resolved by high-resolution cryo-electron microscopy (Yip et al., 2010; Aylett et al., 2016) and suggests that two mTOR proteins dimerize to form a hollow lozenge-shaped structure with its binding partners, RAPTOR and mLST8, forming the peripheral parts of the complex at the longer and shorter axes, respectively (Fig. 2). The structure reveals the highly restricted catalytic center for substrate selectivity and explains how FKBP12-rapamycin limits access to the active site and the actions of the ATP-competitive inhibitors TORIN2 and PP242 (Aylett et al., 2016; Yang et al., 2013). Although mLST8 is also found in mTORC2, RAPTOR is not; instead, RICTOR (rapamycin-insensitive companion of mTOR) is a distinctive component of mTORC2 (Fig. 1). Notably, the FKBP12-rapamycin complex directly binds to and inhibits mTORC1, but not mTORC2, except in the case of prolonged rapamycin treatment (Jacinto et al., 2004; Sarbassov et al., 2004, 2006).

RAPTOR (*RAPTOR1A* and *RAPTOR1B*) and LST8 (*LST8-1* and *LST8-2*) genes have been identified in all sequenced plant species. In *Arabidopsis*, *RAPTOR1B* (At3g08850) and *LST8-1* (At3g18140) show predominant expression and viable mutant phenotypes (Anderson et al., 2005; Diaz-Troya et al., 2008; Kravchenko et al., 2015; Moreau et al., 2012; Salem et al., 2017; Tatebe and Shiozaki, 2017). By contrast, no plant RICTOR ortholog has been found, which suggests that TORC1, but not TORC2, is conserved in plants (Tatebe and Shiozaki, 2017). However, it has been suggested that plants may utilize RAPTOR-independent TOR complexes. For example, it has been demonstrated that *Arabidopsis raptor1a raptor1b* double mutant shows normal embryo development, although the mutant seedlings are arrested during development (Anderson et al., 2005).

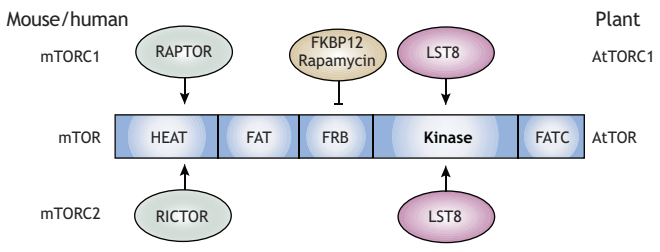


**Fig. 1. The domain structure of TOR and TOR-containing complexes.** The domain structure of TOR, highlighting the mTORC1/2 and AtTORC1 components that bind to each domain.

Many of the interactions between TOR complex components also appear to be conserved in plants and animals. The binding of *Arabidopsis* RAPTOR to the N-terminal HEAT domain of TOR is required for TOR-dependent phosphorylation of S6K (Mahfouz et al., 2006). *Arabidopsis* and mammalian LST8 proteins interact with the C-terminal kinase domain of TOR and may modulate TOR kinase activity toward selective substrates. The conserved FKBP12-rapamycin sensitivity and high similarity of TOR, RAPTOR and LST8 between plants and animals suggest that plant TORC1 may form a similar structure as TORC1 in animals and humans (Aylett et al., 2016; Yang et al., 2013). Importantly, comprehensive genetic, genomic, metabolic and phenotypic analyses of TORC1 functions suggest a significant overlap in the cellular and developmental processes that are regulated by TOR in plants, animals and humans (Fig. 2) (Ben-Sahra and Manning, 2017; Dobrenel et al., 2016a; González and Hall, 2017; Xiong and Sheen, 2015).

## The activation and repression of TORC1 signaling

### Glucose-TOR signaling

Extensive studies have demonstrated that TORC1 is activated by nutrients and growth factors, but inactivated by energy deprivation, starvation and stresses in both plants and animals (Fig. 3) (Dobrenel et al., 2016a; González and Hall, 2017; Saxton and Sabatini, 2017; Xiong and Sheen, 2015). In plants, glucose derived from photosynthesis is a major nutrient for cellular and organismal development (Li and Sheen, 2016; Xiong et al., 2013). By integrating chemical manipulations, estradiol-inducible *tor* RNAi mutants (*tor-es*), cell cycle labeling, S6K phosphorylation and transcriptome analyses, it has been shown that glucose-TOR signaling activates root growth via glycolysis-mitochondria-ETC (electron transport chain) relays. Furthermore, plant growth hormones, such as auxin, brassinosteroid (BR), cytokinin and gibberellin, cannot promote rapid root elongation or reactivate the quiescent root at the heterotrophic-to-photoautotrophic transition checkpoint without photosynthesis or exogenous sugars. Remarkably, glucose-TOR signaling dictates transcriptional reprogramming of broad gene sets involved in central and secondary metabolism, cell cycle, transcription, signaling, transport and protein folding (Xiong et al., 2013).

Although it is known that glucose metabolism is essential to fuel energy signaling and activate plant, as well as animal, TORC1, the underlying molecular mechanisms remain unclear. One possible shared mechanism for glucose-TOR signaling could be the promotion of TORC1 dimerization, which is a prerequisite for its translocation to the lysosome membrane and activation in mammalian cells (Kim et al., 2013), by the glucose/energy sensitive Tel2-Tti1-Tti2 (TTT)-RUVBL1/2 complex in flies and animals (David-Morrison et al., 2016; Kim et al., 2013). The assembly of the TTT-RUVBL1/2 complex and its interaction with TOR require the ATPase activity of RUVBL1/2, which is repressed by ETC inhibition or energy stresses. The *Arabidopsis* genome contains orthologous genes encoding putative Tti1, Tti2, Tel2 and RUVBLs that may form a TTT-RUVBL1/2 complex to regulate TORC1 dimerization and activation, although whether such a complex exists in plants requires further investigation. Defining the subcellular sites (i.e. the vacuole, endosome, mitochondria and/or nucleus) of TORC1 activation and of novel TOR signaling complexes also deserves future research efforts (Ren et al., 2011; Schepetilnikov et al., 2017).

Glucose activation of TOR signaling can also occur indirectly through inactivation of the conserved glucose/energy sensor protein

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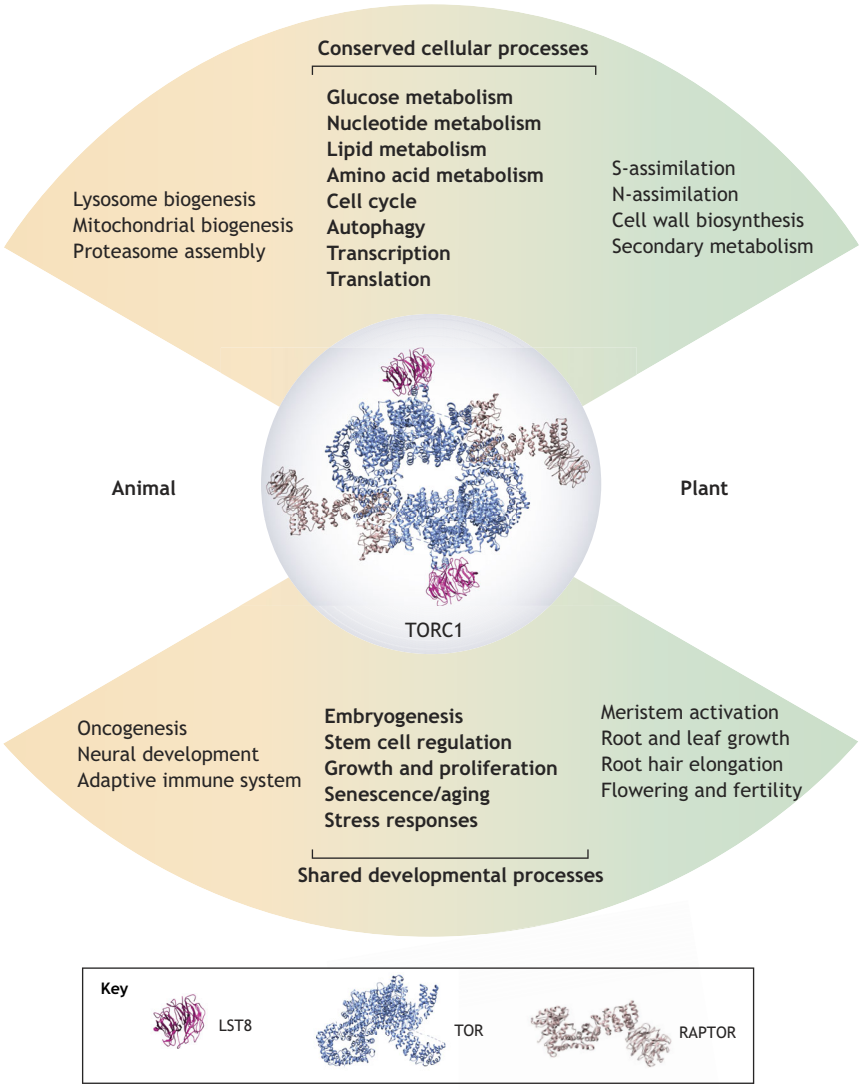


**Fig. 2. TOR signaling regulates conserved and specialized cellular and developmental processes.** The structure of an mTORC1 dimer is shown, highlighting the core components. Conserved (middle), plant-specific (right) and animal/human-specific (left) cellular and developmental processes that are regulated by TORC1 are listed.

kinase SnRK1 [SNF1-related kinase1, the ortholog of the α subunit of AMP-activated protein kinase (AMPK)] in plants, and via inactivation of AMPK in mammals; such a mechanism represents another evolutionarily conserved node for integrating responses to nutrient, energy and stresses (Baena-González et al., 2007; Broeckx et al., 2016; Herzig and Shaw, 2018; Li and Sheen, 2016; Wurzinger et al., 2018). In *Arabidopsis*, *KIN10* and *KIN11* encode the catalytic subunits of the heterotrimeric SnRK1 complex, which is suppressed by glucose but activated by starvation, energy deprivation and many abiotic stresses (Baena-González et al., 2007). Likewise, mammalian AMPK directly phosphorylates and activates TSC2 (tuberous sclerosis complex 2) or phosphorylates and inactivates RAPTOR to repress mTORC1 under energy deprivation and stresses (Gwinn et al., 2008; Herzig and Shaw, 2018). Although plants lack TSC genes, KIN10 interacts with and phosphorylates RAPTOR (Fig. 3) (Nukarinen et al., 2016). It may be possible that SnRK1 and TOR target more common phosphorylation substrates to sense nutrient and energy levels antagonistically and coordinate transcriptome, metabolism, cell growth and development, although further studies are required to assess this (Baena-González et al., 2007; Broeckx et al., 2016; Herzig and Shaw, 2018; Li and Sheen, 2016; Wurzinger et al., 2018).

### Alternative nutrient-TOR signaling

Beside glucose, other nutrients have been shown to be important regulators of TOR signaling in plants and animals. The mechanisms underlying TOR activation by essential amino acids has been extensively studied in mammalian cells. In brief, leucine and arginine activate mTORC1 through different sensors but converge on the activation of heterodimeric RAG GTPases to recruit mTORC1 to the lysosomal membrane, where RAG GTPases associate with the Ragulator complex and v-ATPase and RHEB (Ras homolog enriched in brain), which acts as a TOR activator (Bar-Peled et al., 2012; Kim et al., 2008; Zoncu et al., 2011). In addition, the lysosomal amino acid transporter SLC38A9 interacts with the RAG-Ragulator-v-ATPase complex and acts as a lysosomal arginine sensor for amino acid-TOR signaling activation (Fig. 3) (Rebsamen et al., 2015; Saxton and Sabatini, 2017; Wang et al., 2015). Although plants lack equivalents of these mammalian amino acid sensors and RAGs, it is known that other

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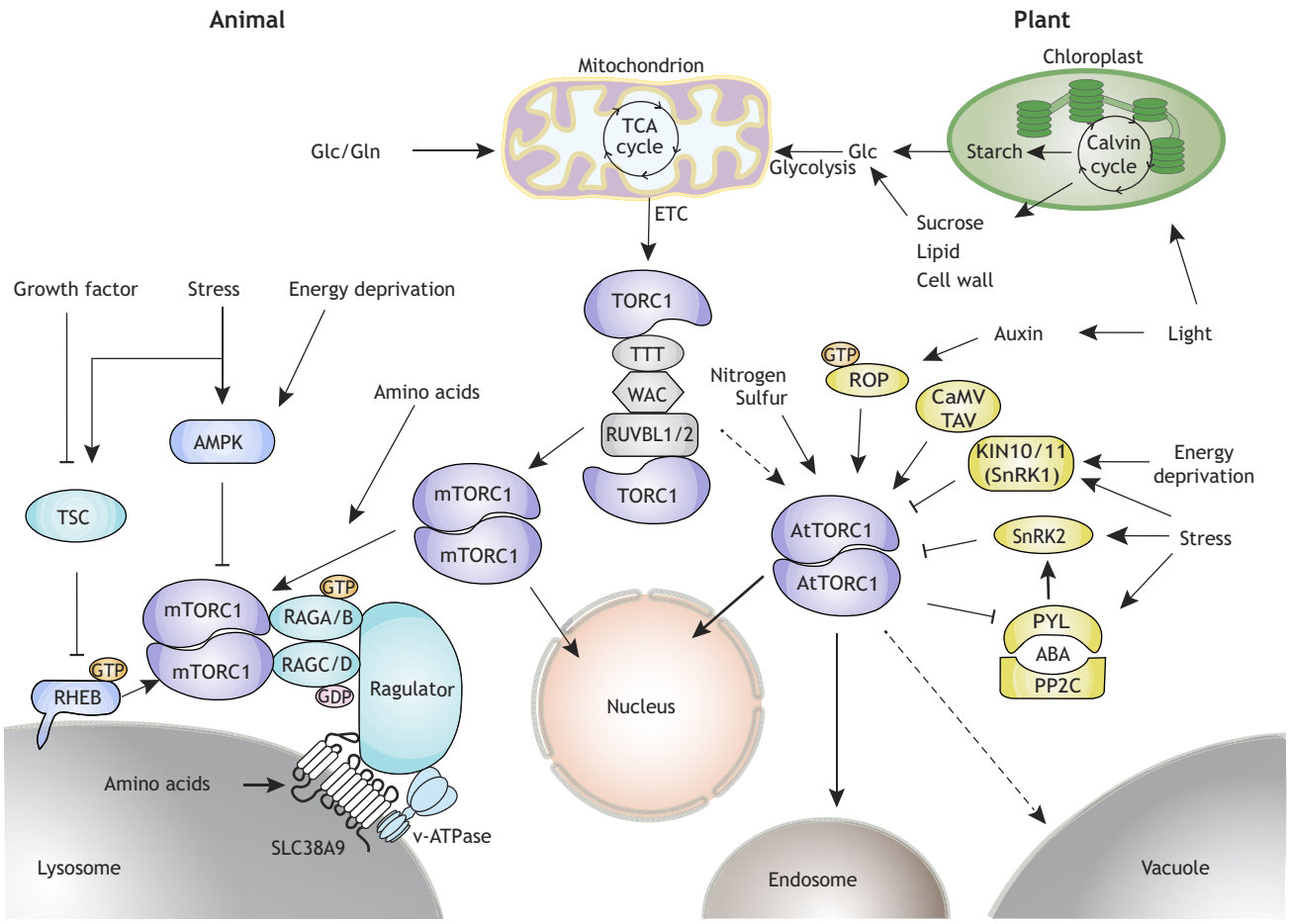


**Fig. 3. Upstream regulators of TORC.** In mammalian cells, the assembly of a TORC1 dimer is fueled by nutrient/energy-dependent TCA-ETC activities in the mitochondria in a TTT-WAC-RUVBLs complex-dependent manner, which may be conserved in plants. mTORC1 is activated by the small GTPase RHEB at the lysosomal membrane, whereas plant small GTPase ROPs act as AtTORC1 activators downstream of auxin. In both mammals and plants, stresses commonly suppress TORC1 functions through AMPK/SnRK1. The plant stress hormone ABA couples with SnRK2 to regulate AtTORC1 in a reciprocal manner, which balances growth and stress responses. Differences in the localization of TOR-containing complexes in plant and animal cells are also evident; plant AtTORC1-ROP2 is localized to the endosome during auxin activation, whereas nuclear TOR functions have been reported in both plant and mammalian cells. CaMV, *Cauliflower mosaic virus*; Glc, glucose; Gln, glutamine; PP2C, Protein Phosphatase 2C; PYL, Pyrabactin Resistance 1 Like; RAG, Rag GTPase; RUVBL, RuvB Like AAA ATPase; TCA cycle, tricarboxylic acid cycle; WAC, WW domain containing adaptor with coiled-coil.

nutrients such as nitrogen (N), phosphate (Pi) and sulfur (S) play crucial roles in promoting plant growth and development, and recent studies suggest that these may function via a TOR-based pathway. For example, a recent study showed that S availability coordinates glucose signaling to activate TOR (Dong et al., 2017). In addition, nitrate is a major N source and acts as a nutrient signal to promote system-wide shoot growth and root establishment in *Arabidopsis* (Liu et al., 2017). Of note, *Arabidopsis* seedlings overexpressing TOR are hyposensitive to high nitrate inhibition of roots (Deprost et al., 2007). Amino acids also activate plant TOR signaling, based on enhanced S6K phosphorylation (Xiong and Sheen, 2015), and future research may thus identify plant-specific amino acid transporter-sensors involved in TOR regulation.

### Phytohormone-mediated regulation of TOR signaling

Although the regulation of mTORC1 by growth factors has been well characterized in animal and human cells, the roles of plant growth factors and hormones in regulating TOR are less clear. Recent advances, however, have uncovered how the coordinated actions of auxin and ROPs (Rho-like small GTPases) can activate TOR signaling at the endosome to regulate the translation of mRNAs that contain upstream open reading frames (uORFs) within their 5′ untranslated regions (Schepetilnikov et al., 2017). Importantly, it was shown that auxin could activate TOR kinase via TOR phosphorylation at S2424 to enhance phosphorylation of the TOR substrate S6K1. Furthermore, it was demonstrated that GTP is required for ROP2-mediated activation of TOR, resembling the mechanism of mTOR activation by the small GTPase RHEB in animal and human cells (Schepetilnikov et al., 2017). Interestingly, recent findings have also revealed a crucial role for glucose-TOR signaling in the shoot apex, which is synergistically activated by light and glucose. Mediated by red light photoreceptor phytochromes and blue light photoreceptor cryptochromes, light activates auxin biosynthesis genes and ROP2 (Fig. 3) to enable TOR signaling by glucose during leaf primordia proliferation. In the root meristem, however, light activation of auxin synthesis is not required to promote glucose-TOR signaling in cell cycle activation (Xiong et al., 2013; Li et al., 2017). In contrast to the light-auxin and glucose synergism in activating plant TOR signaling, the plant stress hormone abscisic acid (ABA) has been reported to repress TOR signaling via ABA-mediated activation of SnRK2s, which phosphorylate RAPTOR1 to dissociate it from AtTORC1.

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This in turn enhances ABA-PYL receptor signaling in stress responses by reducing TOR phosphorylation and inhibiting ABA receptors (Fig. 3) (Wang et al., 2018).

## Downstream targets of TORC1

### Multiple TORC1 substrates modulate the cell cycle

Rapamycin was first discovered as an antifungal antibiotic, and was later used as an anticancer drug and as an immunosuppressant during organ transplantation (Sehgal et al., 1975; Martel et al., 1977; Eng et al., 1984). The convergent mechanism for these three rapamycin activities appears to be blockade of TORC1-activated cell proliferation (Heitman et al., 1991; Saxton and Sabatini, 2017), although precisely how rapamycin did this remained unknown for decades. It has now been shown that, in mammalian cells, the G1-S transition of the cell cycle is regulated by both S6K and 4EBP1 [eukaryotic initiation factor 4E (eIF4E)-binding protein 1], which are directly phosphorylated and activated (S6K) or inactivated (4EBP1) by mTORC1, to stimulate *de novo* pyrimidine synthesis by S6K (Ben-Sahra et al., 2013) and enhance the translation of proteins during cell cycle progression by elF4E (Fig. 4) (Dowling et al., 2010; Fingar et al., 2004). A recent study has also demonstrated that mTOR regulates B-cell proliferation by controlling the transcription and translation of the BACH2 transcription factor, which targets cyclin D3 to initiate the cell cycle (Tamahara et al., 2017).

In plants, TOR is highly expressed in rapidly growing tissues such as the embryo, shoot meristem, root meristem and lateral root primordia, implicating the involvement of TOR signaling in cell proliferation (Menand et al., 2002). However, the regulation of the

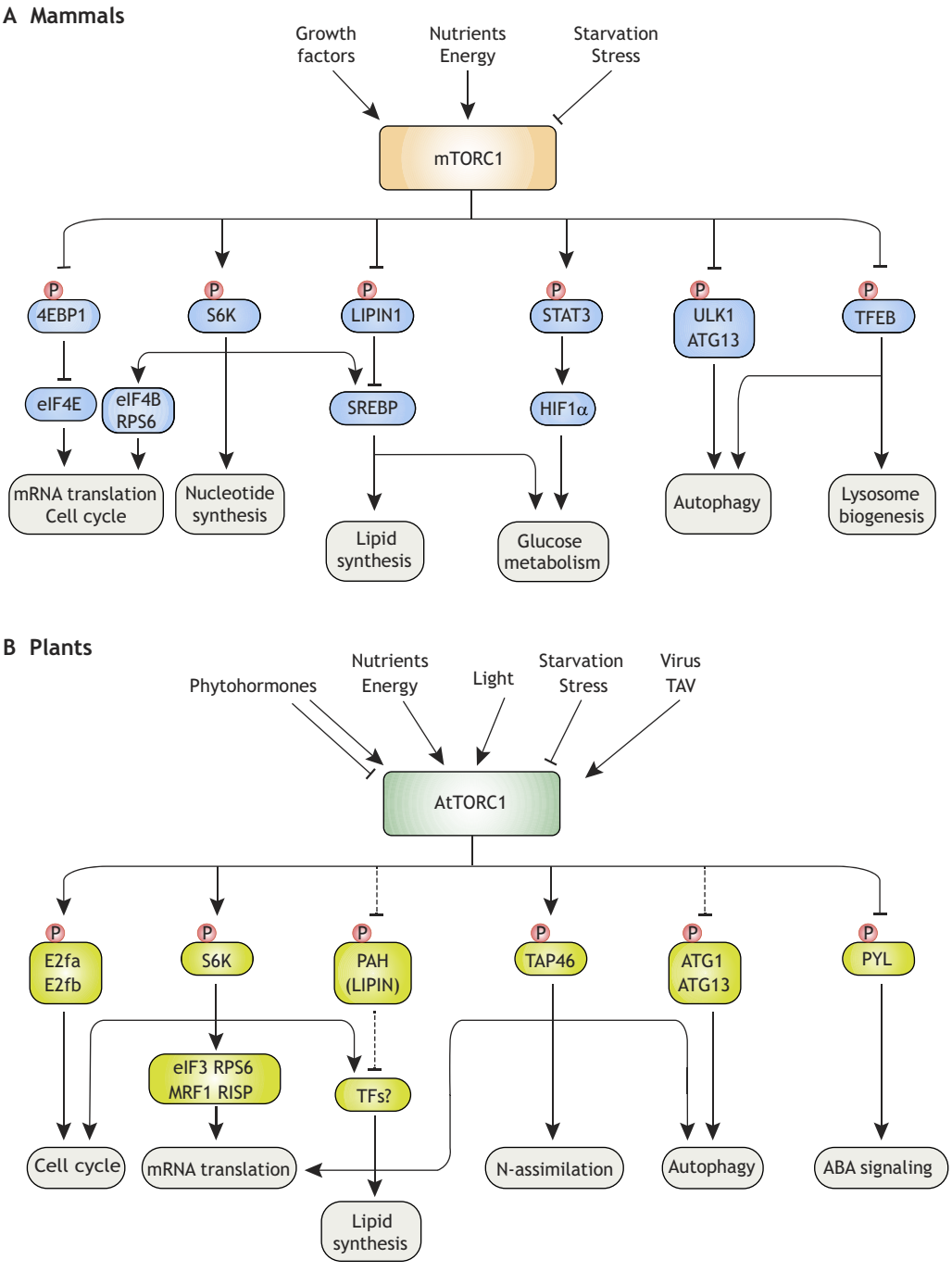


**Fig. 4. TOR kinase directly phosphorylates and modulates downstream signaling components.** (A,B) Comparison of direct TORC1 substrates and their downstream key signaling components and functions in mammals (A) and plants (B). TFs, transcription factors.

cell cycle by plant S6K is complex because osmotic and salt stresses, as well as 3-phosphoinositide-dependent protein kinase1 (PDK1), also regulate S6K to exert a negative role in cell cycle regulation in response to stress, but not TOR or nutrients (Mahfouz et al., 2006). Furthermore, S6K can act as either a positive or negative regulator of the plant cell cycle with diverse partners in different subcellular compartments in a context-dependent manner. For instance, S6Ks bind to and activate RBR1 (RETINOBLASTOMA-RELATED 1) to suppress E2Fs, resulting in abnormal cell division (Henriques et al., 2010). It will thus be interesting to determine whether TOR-mediated phosphorylation of S6Ks modulates the cell cycle and underlies TOR function in controlling cell proliferation in plants (Xiong et al., 2013; Xiong and Sheen, 2012).

By establishing an experimental platform using quiescent seedlings that are synchronized at the time point of endogenous glucose depletion, it has been shown that AtTORC1 senses and transduces glucose signals to activate the cell cycle in the root meristem by orchestrating global transcriptional reprogramming (Xiong et al., 2013). The identification of target genes of the E2Fa transcription factor in glucose-TOR signaling led to the unexpected finding that AtTOR directly phosphorylates E2Fa to activate transcription of S-phase genes and promote root meristem activation and rapid root growth (Xiong et al., 2013). Recent studies have also revealed that AtTOR directly phosphorylates E2Fb, and that activated E2Fa and E2Fb are required for leaf primordia proliferation and embryogenesis (Li et al., 2017). It would be interesting to investigate whether the mammalian E2F transcription factors are phosphorylated and regulated by mTOR signaling.

#### TOR mediates dynamic translational control

In addition to regulating the cell cycle, TOR acts as a master regulator of gene expression by coordinating rRNA transcription, ribosomal protein (RP) gene activation, ribosome assembly, and dynamic translational control (Dobrenel et al., 2016b; Gingras et al., 1999; Holz et al., 2005; Ren et al., 2011, 2012; Schepetilnikov and Ryabova, 2018; Xiong et al., 2013). In mammals, a key function of mTORC1 signaling in translational control is to phosphorylate 4EBP1, which acts as a negative regulator of eIF4E and releases it for 5′ cap-dependent mRNA translation initiation (Fig. 4) (Burnett et al., 1998; Gingras et al., 1999). Intriguingly, mTOR phosphorylates 4EBP1 at multiple sites in both rapamycin-sensitive and rapamycin-insensitive manners, although the physiological functions of this differential 4EBP1 phosphorylation remains enigmatic (Kang et al., 2013). However, no plant 4EBP1 ortholog has been identified to date, suggesting that the effects of TOR on translational control are mediated by other effector proteins in plants.

One possible effector is S6K, which is phosphorylated by TORC1 at a conserved site in plants and animals, is sensitive to rapamycin, and is crucial for translational regulation (Brown et al., 1995; Burnett et al., 1998; Xiong and Sheen, 2012). Mammalian S6K1 regulates mRNA translation in several dynamic ways, including via the phosphorylation of eIF4B to activate mRNA translation initiation (Holz et al., 2005) and by the phosphorylation and degradation of PDCD4 (programmed cell death protein 4), an eIF4B inhibitor (Dorrello et al., 2006). Ribosomal protein S6 (RPS6) is the first identified S6K substrate to control protein synthesis, although the detailed mechanism is still debated (Ruvinsky and Meyuhas, 2006; Roux and Topisirovic, 2012). Likewise, S6K1 in *Arabidopsis* is associated with TORC1 via RAPTOR1, and its phosphorylation and activation lead to RPS6 phosphorylation (Mahfouz et al., 2006; Xiong et al., 2013). The TOR-S6K signaling relay phosphorylates RPS6 at S240; this phosphorylation event is induced by auxin or sucrose but repressed by the TOR inhibitor AZD8055 or in ethanol-inducible *tor* RNAi transgenic lines (Dobrenel et al., 2016b). Unexpectedly, RPS6 can bind to HISTONE DEACETYLASE 2B (AtHD2B) to regulate rDNA expression via epigenetic perturbation (Kim et al., 2014).

Although the specific functions of the plant TOR-S6K1-RPS6 relay in controlling translation require further investigation, comprehensive evidence supports a novel role for TOR-S6K1 signaling in regulating mRNA translation re-initiation (Fig. 4) (Schepetilnikov and Ryabova, 2018). More than 30% of eukaryotic mRNAs possess one or multiple uORFs within their 5′ UTR, and these have been shown to suppress downstream translation (Calvo et al., 2009; Rahmani et al., 2009; Johnstone et al., 2016). In *Arabidopsis*, translation re-initiation after uORF-dependent repression depends on the phosphorylation of eIF3h, which is a subunit of eukaryotic initiation factor 3 (eIF3) and a putative target of S6K1. Upon auxin simulation, TOR phosphorylates S6K1, which leads to eIF3h phosphorylation and activates uORF-mRNA translation re-initiation of auxin response factors (ARFs) (Schepetilnikov et al., 2013). Moreover, the *Cauliflower mosaic virus* re-initiation factor TAV (transactivator-viroplasmin) can bind to and activate host TOR to translate polycistronic mRNAs. After activation by TAV, TOR activates S6K1 and thus phosphorylates eIF3h and RISP (re-initiation-supporting protein) to recruit re-initiation factors and polysomes to re-initiate mRNA translation (Schepetilnikov et al., 2011; Thiébeauld et al., 2009). Furthermore, MRF1 (MA3 DOMAIN-CONTAINING TRANSLATION REGULATORY FACTOR 1) was recently reported to be an S6K substrate, which regulates mRNA translation especially in energy deficient conditions (Lee et al., 2017).

Plant TAP46, an ortholog of TAP42 in yeast and α4 (a regulatory subunit of protein phosphatase 2A; the human α4 protein is also known as IGBP1) in animals, also plays a role downstream of TOR in regulating translation (Fig. 4). TAP46 is a conserved regulatory subunit of PP2A (protein phosphatase 2A) and a direct TOR phosphorylation substrate. Disruption of *TAP46* expression results in global translation defects with decreased polysome accumulation and methionine incorporation (Ahn et al., 2011). Although plant TAP46 protein levels are dependent on TOR activity, whether TAP46 functions in protein translation through S6K1, or whether it exerts similar functions in animals is unknown (Ahn et al., 2015).

#### Metabolic pathway control by TOR signaling

Besides regulating the cell cycle and translation, TOR acts as a central organizer that senses and transduces nutrient/energy signals to orchestrate cellular anabolic and catabolic processes. In mammalian cells, the S6K1-SREBP (sterol responsive element binding protein) and STAT3-HIF1α (signal transducer and activator of transcription 3-hypoxia-inducible factor 1) cascades modulate glucose metabolism through direct mTOR phosphorylation (Dodd et al., 2015). Mammalian S6K1 is also responsible for the TOR-dependent nucleotide synthesis that supports DNA replication and ribosome biogenesis (Ben-Sahra et al., 2013). However, whereas S6K is present, SREBP, HIF1α and STAT3 orthologs are missing in plants, raising the question of how TOR mediates its effects on metabolic pathways in plants. As glucose-TOR signaling clearly activates genes involved in nucleotide synthesis in *Arabidopsis* (Xiong et al., 2013), it is likely that the regulation of common enzymes is involved.

In mammalian cells, mTOR-S6K1 regulates lipid biosynthesis and the pentose phosphate pathway by stabilizing the active form of SREBP (Düvel et al., 2010). Moreover, mTOR directly

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phosphorylates LPIN1, a suppressor of SREBP, to prevent LPIN1 nuclear translocation and SREBP inactivation (Peterson et al., 2011). Although plants lack SREBP orthologs, two *Arabidopsis* LPIN1 homologs, *AtPAH1* and *AtPAH2*, which encode phosphatidate phosphatases, have been identified (Nakamura et al., 2009). Whether PAH1 and PAH2 are the substrates of plant TOR and act as regulators requires further experimental investigation. Studies in various inducible *tor* RNAi and *amiR-tor* (artificial microRNA) transgenic plants indicate that plant TOR does indeed regulate lipid metabolism. For instance, glucose-activated TOR induces lipid synthesis genes and downregulates lipid degradation genes (Xiong et al., 2013). *Arabidopsis raptor* mutants also exhibit altered lipid composition (Salem et al., 2017), and defective TOR/RAPTOR-S6K1 signaling in rice results in decreased galactolipid content in chloroplast membrane biogenesis (Sun et al., 2016). Significantly, transcriptome and metabolomics analyses in conditional *tor-es*, *amiR-tor* and *lst8* mutants (Xiong et al., 2013; Caldana et al., 2013; Moreau et al., 2012) have revealed broad regulation of diverse plant metabolic pathways modulating myo-inositol, raffinose, galactinol, trehalose, sucrose, starch, nitrate- and S-assimilation, glucosinolate synthesis, membrane and storage lipids, phytohormones, and cell walls (Fig. 2). Further dissection of the glucose-TOR signaling network may, therefore, yield new insights into the dynamic regulatory programs coordinating plant-specific sugar and cell wall metabolism, phytohormone metabolism, lipid synthesis and storage, and secondary metabolic pathways (Caldana et al., 2013; Dobrenel et al., 2016a; Dong et al., 2015; Leiber et al., 2010; Moreau et al., 2012; Salem et al., 2017; Xiong et al., 2013).

### TOR-based regulation of autophagy

Autophagy is a conserved process in eukaryotic cells that is used to degrade and recycle proteins, cytoplasmic organelles and macromolecules to maintain development and growth in response to nutrient and energy deprivation, as well as many biotic and abiotic stresses. AMPK and mTOR are the main regulators of autophagy in response to nutrient and energy levels. In nutrient-restricted conditions, mammalian AMPK activates autophagy by phosphorylating ULK1 (UNC-51-like kinase 1, a homolog of yeast ATG1) to promote the formation of a complex with ULK1, FIP200 (ATG17; also known as RBC1CC1), ATG13 and ATG101 for autophagosome initiation. In nutrient-rich conditions, mTOR phosphorylates ULK1 and ATG13 to prevent complex formation (Kim et al., 2011; Russell et al., 2014; Puente et al., 2016). Another mTOR substrate, TFEB (transcription factor EB), is also involved in autophagy regulation and lysosomal biogenesis (Fig. 4) (Settembre et al., 2012). In plants, the regulation of autophagy by TOR and SnRK1 is conserved; *tor* RNAi, *raptor1b* and *tap46* mutants, as well as inactivation of TOR by the inhibitor AZD8055, induce autophagy, as indicated by increased numbers of autophagosomes and ATG8e expression levels (Ahn et al., 2011; Liu and Bassham, 2010; Pu et al., 2017). In addition, the *tor-es* mutant blocks autophagy gene suppression by glucose (Xiong et al., 2013). Furthermore, in the S deficiency condition, suppressed TOR activity causes ATG8 lipidation, which is indicative of the activation of autophagy (Dong et al., 2017). *Arabidopsis* ATG1 and ATG13 form a complex that regulates autophagy, suggesting a conserved function for ATG1/13 in plants and animals. Interestingly, the protein levels and phosphorylation states of *Arabidopsis* ATG1 and ATG13 are sensitive to nutrient levels, potentially mediated by TOR regulation (Suttangkakul et al., 2011; Marshall and Vierstra, 2018). TOR is also involved in BR signaling, acting to stabilizing the transcription factor BZR1, and this role involves TOR-mediated regulation of autophagy (Zhang et al., 2016). However, the factors that link TOR to autophagy in this context remain unknown.

## TOR functions in plant development

Owing to inconsistent rapamycin sensitivity and the developmental arrest of *Arabidopsis tor* null mutants at the dermatogen embryo stage (Mahfouz et al., 2006; Menand et al., 2002; Ren et al., 2011), the precise functions of TOR in plant development have been challenging to elucidate. However, in recent years, improved experimental design and tools have enabled comprehensive analyses that have demonstrated pivotal roles of TOR in plant development, from embryogenesis, seedling growth, root and shoot meristem activation, through to root hair elongation, leaf primordia proliferation, leaf expansion, flowering and senescence (Fig. 5).

### Embryogenesis to seedling development

The early developmental arrest and lethality of loss-of-function *Arabidopsis tor* mutants suggest that TOR is indispensable for the embryogenesis transition from symmetric cell division to apical-basal polarized differentiation (Menand et al., 2002; Ren et al., 2011). Unlike the embryonic lethality of *Mtor*, *Rptor* and *Mlst8* knockout mice (Guertin et al., 2006; Murakami et al., 2004), *Arabidopsis raptor* mutants develop mature embryos with post-embryonic growth defects (Anderson et al., 2005). This suggests that plant TOR functions in embryogenesis are independent of RAPTOR, and may help uncover novel TOR complexes and pathways in plants.

Several studies have shown that, during seed germination under light, applying TOR inhibitors or suppressing *TOR* expression blocks TOR functions in promoting cotyledon greening, chloroplast development and seedling growth (Deprost et al., 2007; Dong et al., 2015; Li et al., 2015; Xiong et al., 2017). The subsequent identification of *trin1* (*tor-inhibitor insensitive1*) as an *abi4* (*aba*

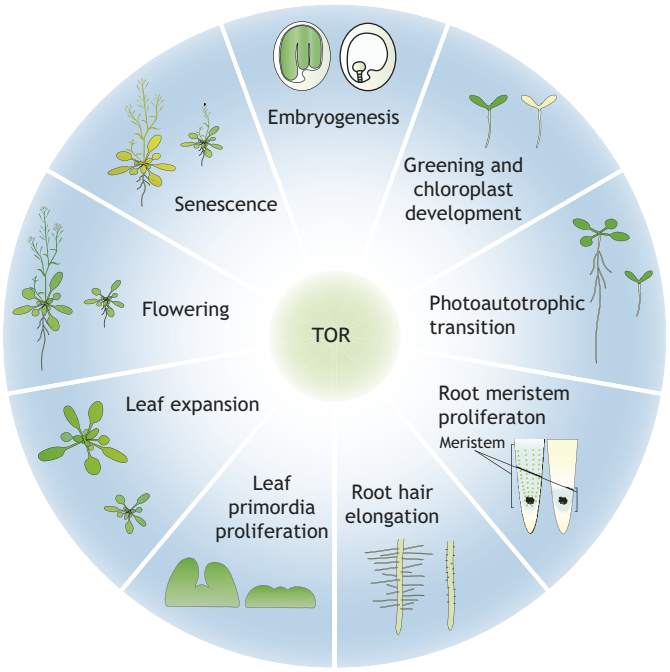


**Fig. 5. TOR plays central roles in plant development.** Summary of the developmental processes and events that are regulated by TOR signaling in plants. Schematics of the phenotypes of wild-type (left) and *tor* (right) plants are also shown for each process/event.

*insensitive 4*) mutant revealed antagonistic interactions between TOR and ABA signaling during seedling development (Li et al., 2015). TOR signaling reduces stability of the ABI4 transcription factor, which represses cotyledon greening and chlorophyll biosynthesis (Fig. 5). However, ABI4-independent TOR functions are still required to promote seedling growth (Li et al., 2015; Wang et al., 2018). A recent study has identified BIN2 (BR INSENSITIVE 2) as a new phosphorylation target of *Arabidopsis* S6K2. TOR-S6K2 signaling likely inactivates *BIN2*, which encodes a GSK3 kinase and a negative regulator of BR signaling, to promote chloroplast development and seedling growth (Xiong et al., 2017).

Nutrient reserves in the *Arabidopsis* seed support germination and early seedling development before the transition to photoautotrophic growth, which instead relies on glucose and sucrose derived from photosynthesis in cotyledons and leaves (Xiong et al., 2013; Xiong and Sheen, 2012). By monitoring root meristem size, S-phase entry and transcriptomic changes, it has been shown that synchronized glucose-TOR signaling activates large gene sets involved in the cell cycle and in multiple anabolic pathways, but suppresses gene sets involved in multiple catabolic pathways (Xiong et al., 2013). This transcriptomic reprogramming nurtures the successful transition from heterotrophic to photoautotrophic development and promotes rapid root growth (Xiong et al., 2013). At the same seedling transition stage, glucose, light and auxin act synergistically to stimulate TOR-ROP2 signaling and cell division in the leaf primordia (Li et al., 2017) (Fig. 5).

In etiolated *Arabidopsis* seedlings grown in the dark, glucose-TOR signaling promotes hypocotyl elongation during skotomorphogenesis by preventing the degradation of BZR1. As mentioned above, this role of TOR is connected to autophagy repression because BZR1 degradation is blocked by an autophagy inhibitor (Zhang et al., 2016). Surprisingly, the elongation of root hairs is also regulated by TOR signaling (Deng et al., 2017; Ren et al., 2012; Xiong and Sheen, 2012; Montané and Menand, 2013). Notably, the development of root hairs is suppressed in glucose-deficient conditions (Xiong and Sheen, 2012) (Fig. 5). The transcriptional network that governs root hair cell fate and elongation is complex and is stimulated by auxin and ethylene (Bruex et al., 2012; Schiefelbein et al., 2014; Salazar-Henao et al., 2016). It will be interesting to define the molecular link between glucose-TOR signaling and the root hair transcription network, and to dissect further the role of auxin-ROP2-TOR signaling (Li et al., 2017; Schepetilnikov et al., 2017).

#### Leaf expansion, flowering and senescence

Analyses of *Arabidopsis tor*, *raptor*, *lst8*, *tap46* and *rps6* mutants and *TOR*, *TAP46* or *FKBP12* overexpression transgenic plants provide ample evidence that TOR signaling is involved in adult plant development, including during leaf expansion, flowering, shoot branching and senescence (Ahn et al., 2015; Anderson et al., 2005; Caldana et al., 2013; Deprost et al., 2007; Moreau et al., 2012; Ren et al., 2012). For example, *TOR* and *TAP46* overexpression plants produce larger leaves with longer petioles, and exhibit early flowering, whereas *TOR* and *TAP46* RNAi plants show the opposite phenotypes (Ahn et al., 2015, 2011; Deprost et al., 2007). The *raptor* and *lst8* null mutants display a similar reduction in leaf expansion and late flowering, and *raptor* mutants also produce sterile flowers. Moreover, as the primary apical shoot apex arrests, the promotion of axillary branches is observed in *raptor* and *lst8* mutants. When grown in soil, the retarded *lst8* mutant and *TOR* and *TAP46* RNAi plants display early leaf senescence (Ahn et al., 2015, 2011; Anderson et al., 2005; Deprost et al., 2007; Moreau et al., 2012). Although these findings clearly highlight a role for TOR in leaf development, the downstream effectors that mediate TOR function in this context remain unclear, and future investigation will hopefully identify new molecular links between TOR signaling and key regulators in endocycle, floral transition and senescence programs.

A role for TOR in regulating senescence in plants has also been identified. In contrast to the early senescence observed in the ethanol-inducible *tor* RNAi and *lst8* mutants (Deprost et al., 2007; Moreau et al., 2012), some *TOR* overexpression plants can dramatically accelerate senescence via RPS6 in leaves and siliques (Ren et al., 2012). Rapamycin-treated transgenic plants overexpressing yeast *FKBP12* show higher rapamycin sensitivity and produce smaller leaves with a reduced leaf cell size (Ren et al., 2012). However, suppression of TOR activity by rapamycin-FKBP leads to delayed senescence on culture plates, which resembles the promotion of animal life span by rapamycin (Saxton and Sabatini, 2017). As rapamycin-FKBP only partially reduces TOR activity, a more careful examination and comparison of plant growth conditions and the modulation of TOR activities by rapamycin-FKBP, potent inhibitors or different genetic deficiencies will be required to resolve the complex functions of TOR in regulating senescence and understanding how these functions are integrated with different types of internal perturbations and environmental stimulations.

#### TOR-mediated regulation of stem/progenitor cells

Multipotent stem/progenitor cells give rise to various post-embryonic cell lineages through precisely controlled proliferation and differentiation, and hence are important for organismal development and tissue homeostasis in plants and animals. Both nutritional and developmental cues are known to regulate stem cell activities across both kingdoms (Gaillochet and Lohmann, 2015; Heidstra and Sabatini, 2014; Meng et al., 2018). Emerging findings, from both plant- and animal-based studies, have started to reveal important roles for TOR as a central hub where nutrient, hormone, growth factor and developmental cues are integrated to modulate stem cell fate, proliferation and differentiation (Fig. 6) (Li et al., 2017; Meng et al., 2018; Pfeiffer et al., 2016; Xiong et al., 2013).

Both plant and animal stem cells are under the control of the dynamic microenvironments in which they reside, which in plants are termed meristems. Two key meristems exist: the shoot apical meristem (SAM) and the root apical meristem (RAM), which are the self-renewable reservoirs that fuel leaf/stem/flower and root organogenesis, respectively. Recent studies have shown that nutrient and TOR signaling is implicated in the regulation of plant meristems. In the *Arabidopsis* RAM, for example, glucose supplied from shoot photosynthesis regulates the proliferation of stem cells and progenitor cells in the transit-amplifying zone (Fig. 6) (Xiong et al., 2013). Accordingly, when endogenous glucose is depleted, both stem and progenitor cells enter quiescence and root growth arrests. The characterization of this event revealed that either photosynthesis or exogenous glucose efficiently activates AtTORC1-E2Fa signaling and transcription. Following this, root stem cells and progenitor cells are dynamically and differentially stimulated to proliferate to expand the root meristem cell population. Endocycling (replication of the genome in the absence of cytokinesis) in the root elongation zone is also activated (Fig. 6) (Xiong et al., 2013). This response is reminiscent of that seen during the regulation of mammalian intestinal stem cells (ISCs) and progenitor cells in response to fasting or feeding (Igarashi and Guarente, 2016; Yilmaz et al., 2012). Interestingly, different cell types in the mouse ISC niche have distinct responses to nutrient signals. Calorie restriction suppresses mTORC1 activity in Paneth cells (the epithelial cells that are generally found adjacent to

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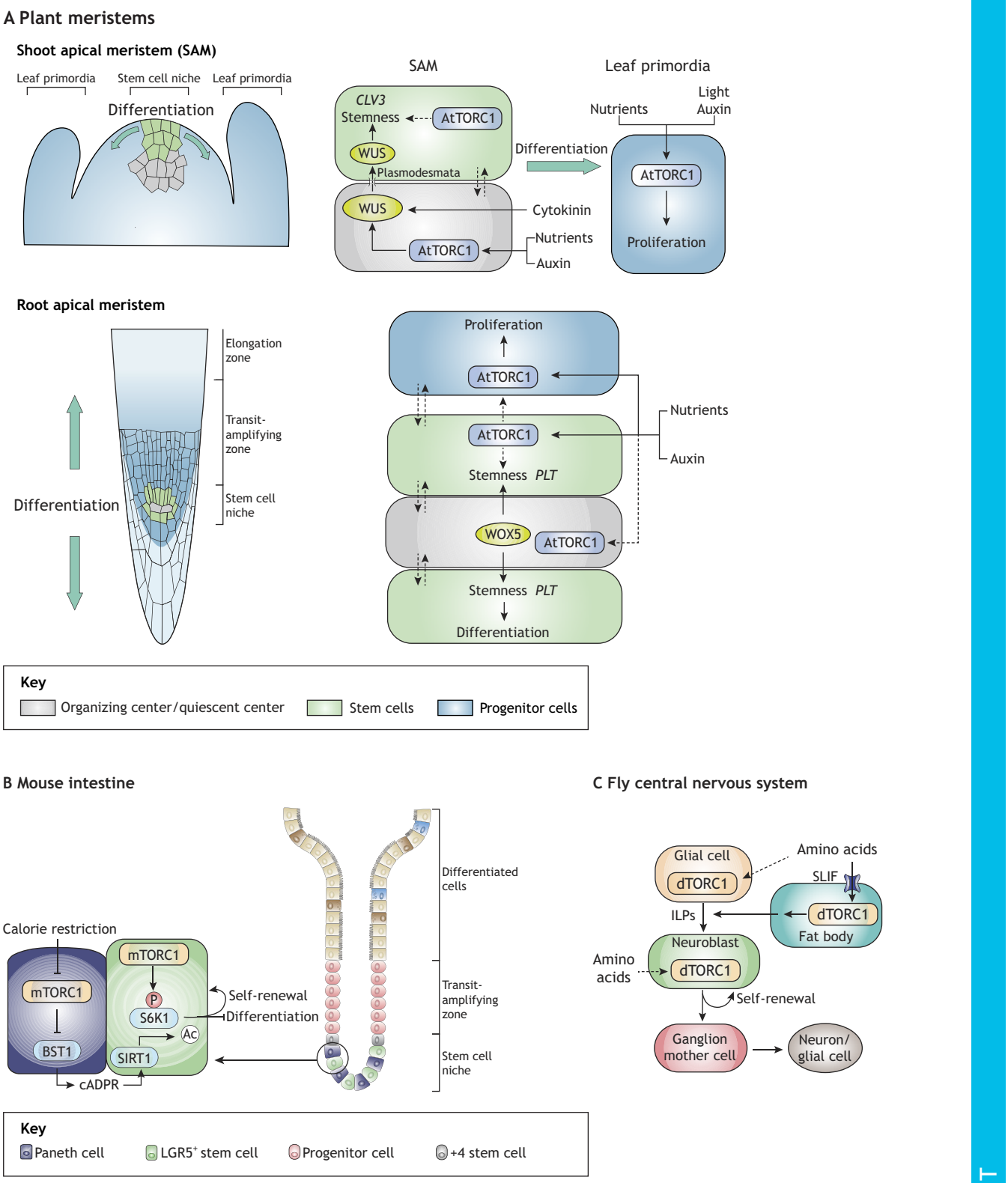


**Fig. 6. TOR regulates stem and progenitor cells in plants and animals.** (A-C) Summary of TOR-mediated regulation of stem cells in plant meristems (A), as well as in the mouse intestine (B) and the fly central nervous system (C). TORC promotes the proliferation of stem and progenitor cells in a nutrient/hormone-dependent manner, which is conserved across kingdoms. In mouse intestinal crypts and the fly central nervous system, stem cell functions are regulated non-cell-autonomously. Such regulation depends on TORC1 activities. Ac, acetylation; dTORC1, *Drosophila melanogaster* TOR complex 1; cADPR, cyclic ADP ribose.

putative ISCs) and reduces S6K1 and RPS6 phosphorylation. Among the genes upregulated by calorie restriction is *Bst1* (bone stromal antigen 1), which encodes an ectoenzyme that produces and releases cyclic ADP ribose (cADPR). The neighboring ISCs take up cADPR and activate a signaling cascade that results in the deacetylation of S6K1 by SIRT1 (sirtuin1) and mTORC1 phosphorylation and

activation. This, in turn, promotes ISC self-renewal at the expense of differentiation (Igarashi and Guarente, 2016; Yilmaz et al., 2012) (Fig. 6). Such non-cell-autonomous regulation of stem cells by nutrients and hormones has also been found in the stem cell niche of the fly central nervous system (Sousa-Nunes et al., 2011). In this context, amino acid signals activate dTORC1 in cells of the fat body (which is considered to be the equivalent of vertebrate adipose tissue/liver) and send out a signal to glial cells in the brain to stimulate the secretion of insulin-like peptides, which can then trigger the reactivation of neuroblasts from quiescence (Fig. 5) (Sousa-Nunes et al., 2011). The common theme is that TORC1 signaling plays a central role in stem-progenitor cell regulation in response to nutrient and energy availability in plants, mice and flies.

Non-cell-autonomous regulation is also seen in plant meristems (Gaillochet and Lohmann, 2015; Heidstra and Sabatini, 2014). Here, the transcription factors WUS (WUSCHEL) and WOX5 (WUSCHEL RELATED HOMEOBOX 5) regulate stem cell activities by moving from the organizing center in the SAM and the quiescent center (QC) in the RAM to neighboring stem cells, respectively (Fig. 6) (Daum et al., 2014; Pi et al., 2015; Yadav et al., 2011). Whether AtTOR is involved in the communication between stem cells and niche cells, and whether AtTOR signaling generates metabolic signals transmitted within the stem cell niche, remains unclear and requires further investigation. A recent finding has reported that *WUS* expression induced by glucose or light requires AtTOR signaling, whereas *WOX5* and *PLT1* expression in the RAM stem cell niche is seemingly unaltered in the absence of AtTOR signaling (Fig. 6) (Pfeiffer et al., 2016; Xiong et al., 2013). AtTOR signaling may also regulate other novel signaling or metabolic components involved in stem cell functions. Based on treatment with a potent TOR kinase inhibitor AZD8055 and the *WUS* marker gene, it was shown that glucose-TOR and light-TOR signaling is required for activation of the dark-grown quiescent SAM by light and cytokinin (Pfeiffer et al., 2016). Whether AtTOR activities also increase as stem cells differentiate in the SAM needs further investigation. Despite *AtTOR* expression in the QC of the RAM, its function in QC cells remains elusive (Barrada et al., 2015). Future discoveries of novel AtTOR signaling regulators may thus shed light on the mechanisms by which AtTOR regulates stem cell activities.

## Conclusions and outlook

Extensive research has demonstrated that TOR acts as a master regulator to sense and transduce nutrient, energy, hormone, growth factor and stress inputs into metabolic and biological processes that fuel cellular, tissue and organismal growth. Glucose, amino acids and energy deprivation are conserved upstream regulators, whereas the cell cycle, translation, metabolism and autophagy are downstream cellular processes that are conserved in both plant and animals. Significantly, even for the regulation of conserved cell cycle or translation processes, distinct direct or indirect TOR phosphorylation substrates and regulatory mechanisms have been discovered in plants and animals. Recent studies have also uncovered plant-specific TOR functions that are modulated by light, plant hormones and inorganic nutrient signals. Emerging evidence supports TOR signaling innovations for plant-specific regulation of N- and S-assimilation, cell walls and secondary metabolism, as well as plant embryogenesis, stem cell regulation, root and shoot development and senescence. As nutrient conditions dictate plant growth and development, it is likely that TOR signaling plays a central role in stem and progenitor cell function and regulation to modulate proliferation, maintenance, lineage commitment and differentiation in the SAM and RAM. TOR signaling likely also influences other post-embryonic stem cell populations and specialized plant cells, tissues and organs, including gametes, flowers, fruits, trichome, stomata, xylem and phloem serving diverse plant-specific functions. TOR signaling may also dictate cell-cell interactions and sink-source organ communication. Further investigations are therefore required to unravel the fascinating molecular mechanisms underlying the versatile TOR signaling networks.

Studies of mutant plants indicate that, besides the conserved TORC1 complex, novel TOR complexes are likely to exist at multiple subcellular sites within plants and probably include different partners. There could also be molecular rewiring of TOR substrates in different cell types and biological contexts. Future research will thus be needed to discover new upstream and downstream regulators in TOR signaling. It will be especially exciting to integrate genetics, genomics, proteomics, metabolomics and computational analyses to identify a broad spectrum of plant TOR kinase substrates and TOR protein complexes to help elucidate the molecular components and mechanisms underlying multiple cellular processes and many aspects of plant development. Precise quantitative measurement of TOR activities and specific signaling output markers will also facilitate a more accurate interpretation of the different or even opposite phenotypes manifested in plants when TOR pathway components are perturbed.

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#### Competing interests

The authors declare no competing or financial interests.

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