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REVIEW PAPER

Integration of nutrient, energy, light, and hormone signalling via TOR in plants

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Abstract

The multidomain target of rapamycin (TOR) is an atypical serine/threonine protein kinase resembling phosphatidylinositol lipid kinases, but retains high sequence identity and serves a remarkably conserved role as a master signalling integrator in yeasts, plants, and humans. TOR dynamically orchestrates cell metabolism, biogenesis, organ growth, and development transitions in response to nutrient, energy, hormone, and environmental cues. Here we review recent findings on the versatile and complex roles of TOR in transcriptome reprogramming, seedling, root, and shoot growth, and root hair production activated by sugar and energy signalling. We explore how co-ordination of TOR-mediated light and hormone signalling is involved in root and shoot apical meristem activation, proliferation of leaf primordia, cotyledon/leaf greening, and hypocotyl elongation. We also discuss the emerging TOR functions in response to sulfur assimilation and metabolism and consider potential molecular links and positive feedback loops between TOR, sugar, energy, and other essential macronutrients.

Keywords: Energy, glucose, hormone, light, nitrogen, nutrient, phosphorus, signalling, sucrose, sulfur, target of rapamycin.

Introduction

Nutrient signalling is the most ancient and fundamental mechanism to regulate and sustain life, and is essential to modulate cellular activities and organismal development by integrating with other intrinsic regulators and environmental cues. In contrast to the previously prevailing notion that nutrients automatically feed into cellular metabolism and growth, nutrient signalling mechanisms are complex for the tailored regulatory networks in diverse cell types, tissues, and organs with specialized physiology, metabolism, and functions. Extensive studies have documented the pivotal role of target of rapamycin (TOR) protein kinase in the regulation of metabolism, translation, and transcription to fuel cellular proliferation and organismal development and growth (Xiong and Sheen, 2014, 2015; Dobrenel *et al.*, 2016*a*; Saxton and Sabatini, 2017; Schepetilnikov and Ryabova, 2018; Shi *et al.*, 2018). However, the molecular and cellular mechanisms underlying how plant TOR protein kinase transduces, co-ordinates, and integrates multiple nutrient, light, and hormone signals are only emerging.

The evolutionarily conserved TOR proteins in *Arabidopsis thaliana* and *Homo sapiens* share a remarkable 73% amino acid sequence identity in the kinase domains (Xiong and Sheen, 2012). At least two structurally and functionally distinct protein

complexes (TORCs) with several regulatory partners have been well characterized in eukaryotes. In mammals, mTORC1 (mammalian/mechanistic TOR complex 1) and mTORC2 share a common subunit LST8 (small lethal with SEC13 protein 8). RAPTOR (regulatory-associated protein of mTOR) is a distinct component in mTORC1, whereas RICTOR (rapamycin-insensitive companion of mTOR) is unique in mTORC2 (Saxton and Sabatini, 2017; Tatebe and Shiozaki, 2017). The multidomain RAPTOR protein regulates the stability, catalytic activity, and substrate binding of the dimeric mTORC1. LST8 is a WD40-domain protein positioned next to the ATP-binding active site cleft in mTORC1 for substrate selectivity and delivery (Aylett *et al.*, 2016). In plants, only TOR, LST8 (encoded by *LST8-1* and *LST8-2* in Arabidopsis), and RAPTOR (encoded by *RAPTOR1A* and *RAPTOR1B* in Arabidopsis) orthologues are present in all sequenced plant species, while no RICTOR orthologue could be identified in plant genomes (Anderson *et al.*, 2005; Mahfouz *et al.*, 2006; Moreau *et al.*, 2012; Xiong and Sheen, 2014; Kravchenko *et al.*, 2015; Dobrenel *et al.*, 2016*a*; Salem *et al.*, 2018).

Although TORC1 is rapamycin sensitive in mammals and yeasts, early research suggested that flowering plants were insensitive to rapamycin, and the FKBP-rapamycin-binding domain (FRB) of Arabidopsis TOR did not form a complex with rapamycin and FKBP12 (FK506-binding protein 12) in yeast two-hybrid and *in vitro* pull-down analyses. However, using a more sensitive split luciferase protein–protein interaction assay in Arabidopsis mesophyll protoplasts, it was demonstrated that Arabidopsis and human FKBP12 exhibited similar interactions with the FRB domain of Arabidopsis TOR stimulated specifically by rapamycin. In liquid culture of Arabidopsis seedlings, rapamycin rapidly and effectively inhibits Arabidopsis TOR activity based on the conserved and specific phosphorylation of T449 in S6K1, and strongly suppresses the growth of cotyledons, true leaves, petioles, and primary and secondary roots and root hairs, resembling the tor mutant phenotypes. Mesophyll protoplasts and seedlings were carefully cultured with a minimal volume of liquid medium to facilitate chemical uptake, and were monitored with sensitive hypoxia-inducible marker genes to avoid hypoxia stress (Baena-González *et al.*, 2007; Xiong and Sheen, 2012; Xiong *et al.*, 2013; Deng *et al.*, 2016; Li *et al.*, 2017). Importantly, ectopic expression of either human or yeast *FKBP12* or overexpression of Arabidopsis *FKBP12* can all further enhance rapamycin sensitivity in Arabidopsis. Moreover, two independent alleles of Arabidopsis *fkbp12* mutants exhibit reduced rapamycin sensitivity based on phosphorylation of T449 in S6K1 as well as seedling and root hair development (Xiong and Sheen, 2012; Deng *et al.*, 2016). Variable endogenous FKBP12 protein levels and low rapamycin uptake of plants in solid culture medium may account for the varied rapamycin resistance observed in flowering plants especially at low rapamycin concentrations (Xiong and Sheen, 2015). Recent studies have also demonstrated that the next generation of ATP-competitive and TOR-specific chemical inhibitors have significantly empowered the elucidation of diverse TOR functions in plants (Xiong and Sheen, 2015; Shi *et al.*, 2018).

The origins of organic carbon, nitrogen, phosphorus, and sulfur nutrients for animals and humans are mainly derived from plants' incredible ability to fix CO_2 and to take up and assimilate nitrate (Liu *et al.*, 2017; Y.Y. Wang *et al.*, 2018), phosphate (Chien *et al.*, 2018), and sulfate (Takahashi *et al.*, 2011) from the soil, which generate chemical energy, sugars, amino acids, proteins, nucleic acids, lipids, and vitamins essential to support all life forms (Xiong *et al.*, 2013; Li and Sheen, 2016). TOR protein kinase has been demonstrated to be activated by glucose, energy, oxygen, amino acids, hormones, and growth factors in yeast, animal, and plant systems (Xiong and Sheen, 2015; Dobrenel *et al.*, 2016*a*; Li and Sheen, 2016; Ben-Sahra and Manning, 2017; González and Hall, 2017; Saxton and Sabatini, 2017; Schepetilnikov and Ryabova, 2018; Shi *et al.*, 2018). In this review, we highlight our current understanding of how sugar, energy, light, and hormone signals modulate TOR activity, which governs transcription, translation, metabolism, cell cycle, and autophagy in diverse aspects of developmental processes in the reference plant *A. thaliana*. We also explore the emerging scenario that TOR may act as a central integrator to sense and relay carbon, sulfur, nitrogen, and phosphorus nutrient signals in positive feedback regulatory loops to orchestrate the complex nutrient uptake, assimilation, and signalling networks central to plant growth, adaptation, and reproduction.

Sugar and energy signalling

Plant life is centred around the production, transport, utilization, storage, and remobilization of sugars that serve as the primary supplies of energy and building blocks, as well as signalling cues to guide the growth, development, adaptation, defence, survival, and reproduction programmes (Eveland and Jackson, 2012; Ruan, 2014; Sheen, 2014; Eom *et al.*, 2015; Yu *et al.*, 2015; Hulsmans *et al.*, 2016; Li and Sheen, 2016; Wingler, 2018; Wurzinger *et al.*, 2018). Recent findings have illustrated how TOR acts as the central molecular switch to regulate metabolism, cell proliferation, and seedling and adult plant growth in response to sucrose and glucose derived directly or indirectly from photosynthesis. For example, after seed germination at the heterotrophic to photoautotrophic transition checkpoint, physiological levels of glucose and sucrose (15 mM) can replace photosynthesis as the most potent stimuli to promote rapid TOR-dependent root meristem proliferation, root elongation, cotyledon expansion, and root hair production. Other sugars, such as fructose, galactose, and xylose, are much less effective. Neither amino acids nor plant growth hormones can substitute for sugars in the inorganic nutrient medium with nitrate and ammonium. The indispensable role of glucose is explained by the requirement for glycolysis and mitochondrial bioenergetics to activate TOR protein kinase monitored by the phosphorylation of its direct and conserved substrates S6K1/2 at T449 and T455, respectively (Fig. 1A) (Xiong and Sheen, 2012; Xiong *et al.*, 2013).

The promotion of root and shoot growth in seedlings and adult plants by light and photosynthesis is significantly compromised in various conditional *tor*-deficient mutants or after treatment with rapamycin or specific ATP-competitive TOR

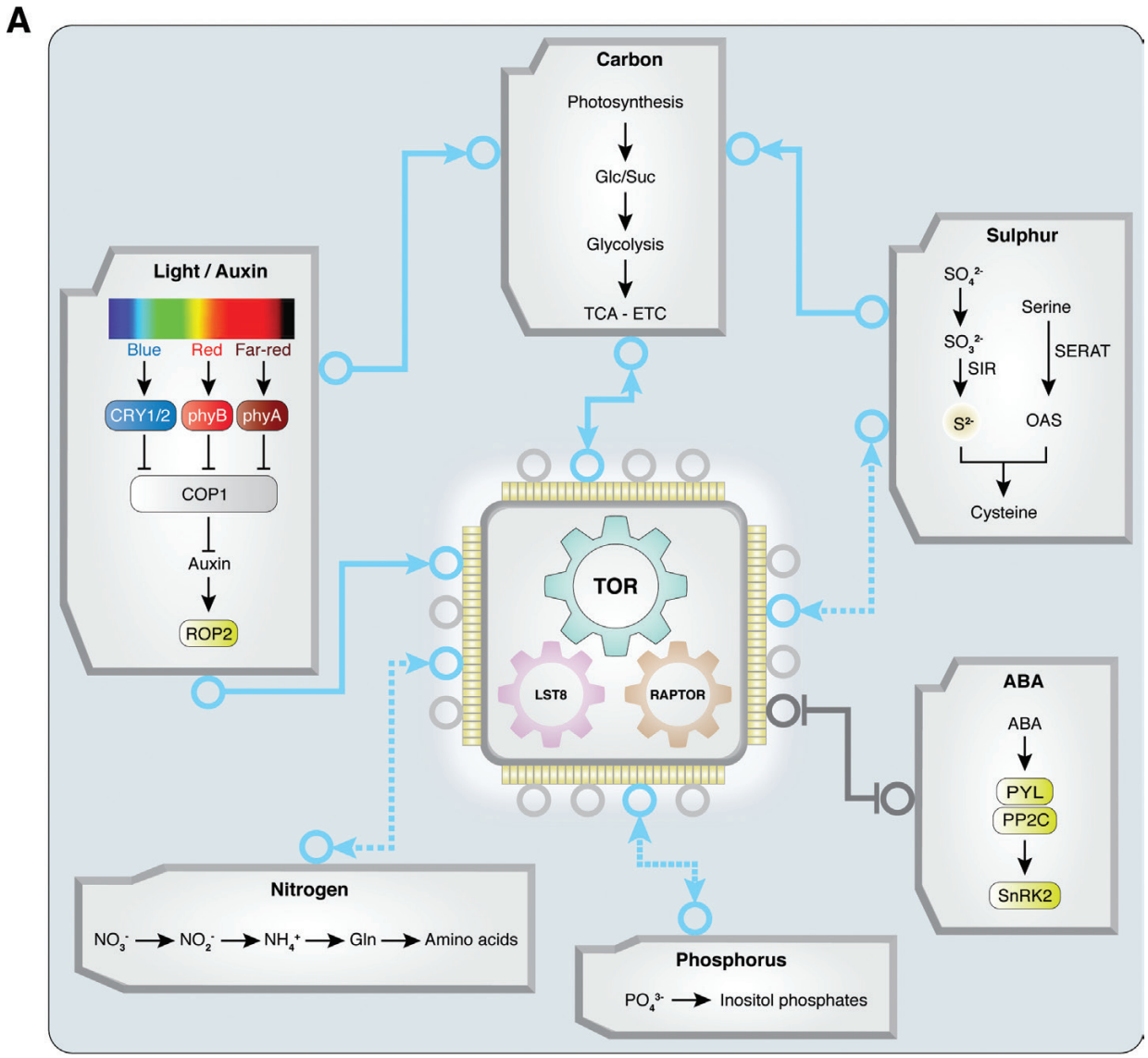

Fig. 1. TOR as a central integrator of nutrient, energy, light, and hormone signalling to regulate plant growth. (A) TOR integrates complex signalling pathways in a reciprocal manner. (B) Glucose–TOR target genes are involved in energy and nutrient regulation. The list of genes presented in (B) was extracted from supplementary table S1 of Xiong *et al.*, 2013. https://media.nature.com/original/nature-assets/nature/journal/v496/n7444/extref/nature12030-s2.xlsx. All microarray data published in Xiong *et al.*, 2013 are available at the Gene Expression Omnibus under accession number GSE40245. TOR, target of rapamycin; LST8, lethal with Sec13 protein 8; RAPTOR, regulatory-associated protein of mTOR; Glc, glucose; Suc, sucrose; Gln, glutamine; SIR, sulfite reductase; SERAT, serine acetyltransferase; OAS, *O*-acetylserine; ABA, abscisic acid; PYL, pyrabactin resistance 1-like; PP2C, protein phosphatase 2C; SnRK2, SNF1-related protein kinase 2; CRY, cryptochrome photoreceptors; phy, phytochrome; COP1, constitutive photomorphogenesis 1; UGP, UDP-glucose pyrophosphorylase; PGM, phosphoglucomutase; PFK, phosphofructokinase; FBA8, fructose-bisphosphate aldolase 8; GAPC, glyceraldehyde-3-phosphate dehydrogenase C; PGK, phosphoglycerate kinase; IPGAM, 2,3-biphosphoglycerate-independent phosphoglycerate mutase 1; ENO, enolase; PK, pyruvate kinase; ACO, ACC oxidase; IDH, isocitrate dehydrogenase; DLST, dihydrolipoamide succinyltransferase; SCS, succinyl coenzyme A synthetase; SDH, succinate dehydrogenase; FUM, fumarase; mMDH, lactate/malate dehydrogenase; CYTC-2, cytochrome c-2; HCC, homologue of the copper chaperone SCO1; QCR7, cytochrome b-c1 complex subunit 7.

inhibitors. Inhibiting TOR activity leads to transcriptomic and metabolomic reprogramming (Deprost *et al.*, 2007; Ren *et al.*, 2012; Caldana *et al.*, 2013; Montané and Menand, 2013; Xiong *et al.*, 2013; Dong *et al.*, 2015). Moreover, mutations in *raptor1b* and *lst8-1* display a spectrum of related plant growth defects in roots and shoots with delayed flowering and senescence (Anderson *et al.*, 2005; Mahfouz *et al.*, 2006; Moreau *et al.*, 2012; Ren *et al.*, 2012; Kravchenko *et al.*, 2015; Salem *et al.*, 2018). Genetic manipulation of a direct TORC1 phosphorylation substrate TAP46 (Type 2A phosphatase-associated protein of 46 kDa), a regulatory subunit of protein phosphatase 2A, shows that it positively regulates S6K phosphorylation. Transgenic plants overexpressing *TAP46* exhibits increased hypocotyl length, enlarged leaves, and enhanced seed size, as well as elevated expression levels of genes associated with ribosome biogenesis, lignin biosynthesis, and nitrogen assimilation. In *tap46* RNAi lines, translation and nitrogen assimilation gene expression are reduced, but autophagy is elevated (Ahn *et al.*, 2011, 2015). Defining the TAP46-PP2A substrates will help expand our understanding of TOR signalling in diverse growth processes.

As the conserved direct targets of TOR protein kinase, S6K1/2 relay signalling by phosphorylating RPS6 (the 40S ribosomal subunit S6) and MRF (MA3 domain-containing translation regulatory factor) in response to light, sugar, and energy status in plants (Ren *et al.*, 2012; Xiong *et al.*, 2013; Dobrenel *et al.*, 2016*b*; Enganti *et al.*, 2017; Lee *et al.*, 2017; Chen *et al.*, 2018). Comprehensive phenotypic analyses of *rps6a* and *rps6b* mutants and genetic complementation support downstream roles of RPS6 in light and nutrient-dependent TOR functions in root, leaf, and flowering regulation (Ren *et al.*, 2012), as well as in the control of rRNA synthesis (Kim *et al.*, 2014; Son *et al.*, 2015) (Fig. 2). A recent study shows that TOR plays a critical role in light-dependent RPS6 phosphorylation and protein translation control, but future research will be required to elucidate the precise molecular connection (Chen *et al.*, 2018). Furthermore, MRF1, as a substrate of S6K, was reported to be involved in translation control under dark/starvation conditions, which elevate *MRF1* transcripts. Transition from the energy-deficient condition to the light- and glucose-fed condition activates rapid phosphorylation of MRF1 and promotes its association with eIF4A-1 and light polysomal fractions, which may reboot translation (Lee *et al.*, 2017). Intriguingly, the glucose-activated root hair elongation is also suppressed in the oestradiol-inducible *tor-es* mutant or *raptor1b* seedlings, or by treatment with rapamycin or ATP-competitive chemical inhibitors in many plant species (Ren *et al.*, 2012; Xiong and Sheen, 2012; Montané and Menand,

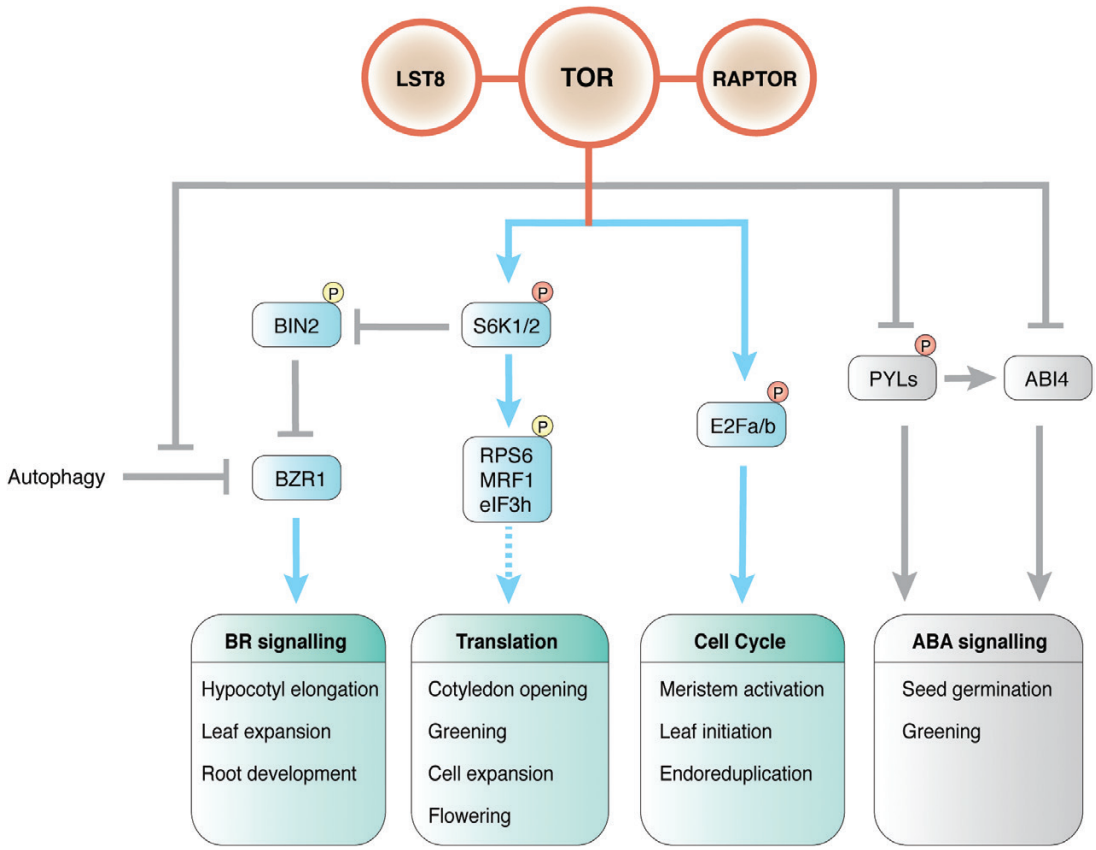

Fig. 2. The TOR signalling network. TOR promotes translation and BR signalling probably through the signalling relay mediated by S6K1/2 and BIN2 substrates. By directly phosphorylating key transcription factors, E2Fa/b, TOR positively regulates the cell cycle. Phosphorylation of ABA-receptor PYLs by TOR represses ABA signalling. TOR, target of rapamycin; LST8, lethal with Sec13 protein 8; RAPTOR, regulatory-associated protein of mTOR; S6K, S6 kinase; E2F, E2 promoter-binding factor; RPS6, ribosomal protein S6; MRF, MA3-containing translation regulatory factor; eIF3h, eukaryotic initiation factor 3h; BIN, brassinosteroid-insensitive; BZR, brassinosteroid signalling positive regulator; TAP46, type 2A-phosphatase-associated protein 46 kDa; PYL, pyrabactin resistance 1-like; PP2C, protein phosphatase 2C; ABI, ABA-insensitive.

2013; Deng *et al.*, 2016; Salem *et al.*, 2018). Although primary auxin-responsive transcription is not affected in the *tor-es* seedlings (Xiong *et al.*, 2013), a long-term TOR inhibitor treatment for 12 d suggests a link to auxin biosynthesis and signalling in root hair development (Deng *et al.*, 2016). It will require further investigation to determine the role of TOR protein kinase in the epidermal cell fate determination and the morphogenetic plasticity of cell differentiation modulated by complex integration of nutrient, hormone, and stress signals (Salazar-Henao *et al.*, 2016).

In plants growing under light, steady TORC1 mutants or long-term conditional suppression of TOR signalling for days/weeks influence the transcriptome encompassing diverse biological functions in a complex manner (Deprost *et al.*, 2007; Moreau *et al.*, 2012; Ren *et al.*, 2012; Caldana *et al.*, 2013; Dong *et al.*, 2015). The experimental design insuring synchronized glucose stimulation has uncovered transcriptome reprogramming in 3-day-old seedlings with minimal endogenous glucose levels, which maximize the detection sensitivity of primary TOR target genes by dynamic phosphorylation. Within 2 h of treatment at a physiological level of 15 mM glucose, 1318 up- and 1050 down-regulated genes have been identified, which are completely blocked in the *tor-es* mutant. The sugar- or CO_2-regulated transcriptome data sets derived from older seedlings or adult leaves significantly overlap with glucose–TOR target genes detected in young seedlings (Xiong *et al.*, 2013). However, comparative transcriptome analyses indicate that the regulation of some sucrose- or glucose-responsive genes is complex in Arabidopsis plants (Li and Sheen, 2016). It is possible that the precise extent of the regulation of TOR target genes is dictated by cell types, tissues, organs, developmental stages, nutrients, and environmental conditions. Consistently, the sensitivity of young seedlings with relatively abundant meristem tissues and developing cell types facilitates the discovery of previously unknown primary glucose–TOR target genes. Functional categories of cell cycle and DNA synthesis, transcription, and RNA processing are enriched among the novel glucose–TOR-activated genes, whereas those of transcription, protein degradation, and signalling are enriched in the glucose–TOR-repressed genes.

In general, the primary glucose–TOR target genes comprise a myriad of regulatory and metabolic functional categories (Xiong *et al.*, 2013; Xiong and Sheen, 2014). Significantly, rapid glucose–TOR signalling activates evolutionarily conserved bioenergetic and anabolic processes, including genes involved in glycolysis, the tricarboxcyclic acid (TCA) cycle, the mitochondrial electron transport chain (ETC) (Fig. 1B), the oxidative pentose phosphate (OPP) pathway, ribosome assembly, protein synthesis machineries, as well as amino acid, lipid, and nucleotide synthesis. These findings suggest a universal and conserved TOR function in controlling translation, and central carbon and energy metabolism in plants (Deprost *et al.*, 2007; Moreau *et al.*, 2012; Ren *et al.*, 2012 ; Caldana *et al.*, 2013; Xiong *et al.*, 2013; Dong *et al.*, 2015). Glucose–TOR signalling also represses genes mediating catabolism, for example autophagy and the degradation of proteins, amino acids, lipids, and xenobiotics that are critical for survival under starvation (Baena-González *et al.*, 2007; Deprost *et al.*, 2007; Moreau *et al.*, 2012; Ren *et al.*, 2012; Caldana *et al.*, 2013; Xiong *et al.*, 2013). Importantly, glucose–TOR signalling plays a pivotal role in regulating plant-specific processes. For example, the metabolic genes for enzymes involved in β-oxidation (triacylglyceride lipase and acyl-CoA oxidase) and the glyoxylate cycle (malate synthase and isocitrate lyase) required in the germination programme of Arabidopsis seeds are repressed (Graham, 2008). Plant-specific genes promoting the synthesis of cell wall polymers/proteins, glutathione, indolic/benzoic/aliphatic glucosinolates, lignins, flavonoids, nitrate transport, phosphate metabolism, as well as nitrogen and sulfur assimilation are activated for plant growth, defence, or communication to promote adaptation, fitness, and survival (Keurentjes *et al.*, 2006; Deprost *et al.*, 2007; Takahashi *et al.*, 2011; Moreau *et al.*, 2012; Ren *et al.*, 2012; Caldana *et al.*, 2013; Xiong *et al.*, 2013; Dong *et al.*, 2015; Malinovsky *et al.*, 2017).

Although the detailed molecular mechanisms mediating glucose activation of TOR protein kinase remain to be fully elucidated, emerging evidence indicates that functional glycolysis and the mitochondrial ETC are required for glucose–TOR signalling. Blocking hexokinase activities by 2-deoxyglucose at the first step of glycolysis and several chemical inhibitors, antimycin A, 2,4-dinitrophenol, and carbonylcyanide *m*-chlorophenylhydrazone, targeting different steps of the ETC, prevent TOR activation by glucose. Thus, sugar-mediated TOR activity reflects the cellular metabolic and bioenergetic status to mediate energy signalling in plants (Xiong *et al.*, 2013; Li and Sheen, 2016). Although phosphorylation of RAPTOR1B by the plant energy sensor SnRK1 (Snf1-related protein kinase) has been demonstrated under energy deprivation, the primary target genes of TOR and SnRK1 only partially and antagonistically overlap (Li and Sheen, 2016; Nukarinen *et al.*, 2016). Novel mechanisms for SnRK1-indepednent regulation of TOR probably exist for future research exploration. In recent research, the Rho-like small GTPase ROP2 is shown to bind to and activate TOR in the synergistic action of glucose and auxin signalling (Fig. 1A) (Li *et al.*, 2017; Schepetilnikov *et al.*, 2017). Furthermore, the TEL2–TTI1–TTI2 (TTT)–RUVBL1/2 (RuvB-like ATPase and ATP-dependent DNA helicase) complex in animals is important for TORC1 dimerization and activation in glucose signalling (Kim *et al.*, 2013; David-Morrison *et al.*, 2016). The putative TEL2, TTI1, TTI2, and RUVBL orthologues exist in the Arabidopsis genome. Whether the TTT–RUVBL1/2 complex can be formed and play a similar role in activating the TOR complex by sensing sucrose/glucose requires further investigation. It will also be interesting to determine the role of RAPTOR-bodies in plant TORC1 inactivation under glucose starvation (Hughes Hallett *et al.*, 2015).

Light and hormone signalling

During post-embryonic development after seed germination, the root apical meristem (RAM) and shoot apical meristem (SAM) are the primary reservoir for self-renewable stem cells, which supply new cells to support root, leaf, stem, flower, and fruit organogenesis. TOR expression is enriched in meristems

(Menand *et al.*, 2002), and glucose–TOR-mediated energy signalling, which requires glycolysis and mitochondrial relays, plays an essential role in activating the quiescent root meristem under light (Xiong *et al.*, 2013). Based on EdU (thymidine analogue 5-ethynyl-2'-deoxyuridine) staining, systemic glucose derived from photosynthesis or exogenously applied glucose rapidly activates DNA synthesis in the mitotic progenitor cells of the primary root meristem and in the endocycling cells of the root elongation zone. TOR directly phosphorylates the E2Fa transcription factor to activate transcription of S-phase genes involved in DNA synthesis. The stem cells surrounding the quiescent centre (QC) are also activated by glucose–TOR signalling to divide, but at a much lower rate than the progenitor cells (Fig. 2) (Xiong *et al.*, 2013). In the SAM, sucrose and red light additively promote the expression of *WUSCHEL* (*WUS*) encoding a homeodomain master transcription factor for stem cell regulation in the organizing centre (OC). Genetic analyses reveal the involvement of the red light photoreceptor phytochrome B (phyB) and blue light photoreceptors cryptochrome 1/2 (CRY1/2) in *WUS* activation by suppressing the master negative regulator COP1 (constitutive photomorphogenesis 1). Importantly, *WUS* activation by glucose or sucrose mediating energy signalling in the wild type is prevented by 5 μM AZD-8055 inhibiting TOR protein kinase. *WUS* expression promoted by red light in the wild type or in *cop1* in the dark is reduced by AZD-8055. These results support a role for TOR in integrating energy and light signalling to promote stem cell activation in the SAM (Fig. 1A) (Pfeiffer *et al.*, 2016). However, in the QC of the RAM, the expression of *WOX5*, encoding a homeodomain transcription factor and functionally related to WUS, is not diminished in the *tor-es* mutant (Xiong *et al.*, 2013). TOR activation stimulated by sugar, energy, and light signalling may exert differential regulations and functions in the RAM and SAM. It will be interesting to identify the molecular regulators mediating TOR activation of *WUS* in the SAM.

Recent studies have started to unravel the mechanisms underlying glucose–TOR-mediated energy signalling in promoting cell proliferation in leaf primordia. Although glucose alone is sufficient to active RAM proliferation via TOR signalling, glucose and light are synergistically required for the activation of robust cell proliferation based on the expression of *pCYCB1;1::GUS* as a mitotic marker in leaf primordia (Xiong *et al.*, 2013; Li *et al.*, 2017). The activation of S6K phosphorylation at T449, *pCYCB1;1::GUS* expression in leaf primordia, as well as expansion and greening of cotyledons and true leaves stimulated by glucose and light are abolished in *tor-es* plants or by TOR inhibitors, rapamycin and torin2. Genetic analyses support the roles of white, red, and blue light mediated by phyA/B and CRY1/2 photoreceptors to activate the cell cycle in leaf primordia through the suppression of COP1 (Fig. 1A) (Cai *et al.*, 2017; Li *et al.*, 2017). Both E2Fa and E2Fb are phosphorylated and activated by TOR, and support S-phase gene expression and leaf primordia expansion (Fig. 2).

As light particularly activates auxin biosynthesis genes, *YUC2*, *YUC4*, and *YUC7*, in the shoot apex, the effect of light on TOR activation is probably mediated via stimulating auxin biosynthesis (Li *et al.*, 2017). Consistently, light-enhanced auxin accumulation can be monitored and quantified by the DII-VENUS auxin biosensor, and exogenous auxin can replace light to activate TOR signalling in leaf primordia in darkness. Yucasin as an auxin biosynthesis inhibitor prevents light-stimulated auxin accumulation and TOR signalling in leaf primordia. Significantly, ROP2 interacts with TOR, and constitutively activated ROP2 stimulates S6K phosphorylation, *pCYCB1;1::GUS* expression, and true leaf expansion in the presence of exogenous glucose without light (Fig. 1A) (Li *et al.*, 2017). These thorough analyses and comprehensive evidence corroborate a new report on TOR-dependent promotion of gene expression, proliferation, and expansion of young leaves by sucrose in older seedlings with access to auxin synthesis and transport, or in *cop1* (Mohammed *et al.*, 2018). Another finding suggests that sucrose and light are necessary for organogenesis, and sucrose is essential to promote leaf expansion even in *cop1* exhibiting features of constitutive photomorphogenesis with open cotyledons and a short hypocotyl (Pfeiffer *et al.*, 2016). Moreover, independent studies have demonstrated a critical role for ROP2 in mediating the well-characterized auxin activation of TOR–S6K–eIF3h signalling on endosomes contributing to translation regulation of mRNAs via upstream ORFs in the 5'-untranslated regions (Figs 1A, 2) (Schepetilnikov *et al.*, 2013, 2017; Schepetilnikov and Ryabova, 2017, 2018). Although plants lack a homologue of the small GTPase RHEB (Ras homologue enriched in brain), which is the key activator of TORC1 in animal and human cells (Saxton and Sabatini, 2017), ROP2 and related proteins may serve similar functions in activating plant TORC1 (Roustan *et al.*, 2016; Li *et al.*, 2017; Schepetilnikov *et al.*, 2017).

Light-stimulated photomorphogenesis regulates an array of rapid and long-term responses and biological processes by triggering massive reprogramming of the transcriptome and translatome (Wu, 2014). A new study reports that light-enhanced translation is orchestrated by white, blue, and far-red light perception via phyA and CRY1/2 photoreceptors and a signalling pathway composed of COP1, auxin, TOR, and RPS6 (Fig. 1A) (Chen *et al.*, 2018). In de-etiolated young seedlings, light alone inactivates the negative regulator COP1 within 4 h, which leads to activation of auxin signalling for TOR–S6K-dependent phosphorylation of RPS6 without exogenous sugars. Mutants defective in *TOR*, *RPS6A*, or *RPS6B* exhibit delayed cotyledon opening, a characteristic of the de-etiolating process to ensure timely vegetative development of a young seedling. This finding provides a mechanistic view of light-specific translational enhancement in de-etiolation via TOR activation (Chen *et al.*, 2018). As very young etiolated seedlings grown in the dark were used, it would be important to probe the sugar requirement for TOR–S6K–RPS6 activation in older etiolated seedlings when endogenous sugars are completely depleted. For example, in 12-day-old etiolated seedlings grown without sucrose, RPS6 phosphorylation at S237 and S240 is elevated by light exposure for 2 h, but not for 0.5 h. However, RPS6 phosphorylation is promoted by light exposure of as short as 0.5 h in etiolated seedlings grown with 1% sucrose (Enganti *et al.*, 2017). It is possible that the requirement for sugar, light, and/or hormones to activate TOR signalling can vary in biological contexts and developmental stages.

Chloroplast biogenesis and maturation is a key process dependent on light to establish photosynthesis during cotyledon and leaf development. Several studies suggest that TORC1 plays a crucial role in the biogenesis and maturation of chloroplasts to promote cotyledon and leaf greening (Dong *et al.*, 2015; Li *et al.*, 2015; Deng *et al.*, 2016; Sun *et al.*, 2016; Li *et al.*, 2017; Xiong *et al.*, 2017; Mohammed *et al.*, 2018; Shi *et al.*, 2018; Zhang *et al.*, 2018). Treatment with the TOR chemical inhibitor AZD-8055 for 10 d eliminates greening and cotyledon expansion, which is consistent with a broad repression of photosynthesis genes involved in chlorophyll biosynthesis, light reactions, and CO_2 fixation (Dong *et al.*, 2015; Li *et al.*, 2015). The characterization of *trin1* (*tor-inhibitor insensitive 1*) reveals a role for ABI4 [abscisic acid (ABA)-insensitive 4], a chloroplast retrograde regulator, in mediating TOR signalling in the seed to seedling transition. Based on the analysis of TRIN1–GUS (β-glucuronidase) activity, it has been suggested that TOR promotes ABI4 degradation and greening (Li *et al.*, 2015). The direct or indirect molecular connection between TOR and ABI4 regulation remains to be elucidated (Fig. 2).

A large-scale phosphoproteomics experiment has identified a conserved serine in the PYL4 ABA receptor exhibiting ABA-dependent dephosphorylation. Functional analyses of the phosphomimetic version of the ABA receptor PYL1 (S119D) indicates that the specific phosphorylation of the ABA receptor abolishes ABA binding, ABI1 (phosphatase PP2C) interaction, as well as the ability to activate SnRK2.6 for ABF2 transcription factor phosphorylation and *RD29-LUC* reporter gene activation in protoplast assays. An *in vitro* protein kinase screen identified TOR for specific phosphorylation of related PYL1 at the conserved S119. Furthermore, *raptor1* mutants are hypersensitive to ABA but display decreased ABA synthesis. ABA diminishes S6K1 phosphorylation through ABA-activated SnRK2.6 phosphorylation of RAPTOR in TORC1. These findings reveal reciprocal negative regulations between TOR and ABA signalling to balance plant growth and stress responses, consistent with TOR activation and ABA repression of seedling development and greening of cotyledons and leaves (Figs 1A, 2) (Kravchenko *et al.*, 2015; Li *et al.*, 2015; P. Wang *et al.*, 2018). Genetic and biochemical studies with *s6k1*, *Osraptor2*, and *tor* mutants in rice have provided evidence that TOR–RAPTOR2–S6K signalling regulates thylakoid galactolipid biosynthesis and grana modelling for photosynthesis performance (Sun *et al.*, 2016).

Unexpectedly, in seedlings after extended etiolation, TOR inhibition by AZD-8055 or *raptor1b* mutants increase greening in the dark to light transition. This paradoxically improved greening response after exposure to light reflects a decrease of the chlorophyll precursor Pchlide (protochlorophyllide), ROS (reactive oxygen species) reduction, enhanced POR (NADPH:protochlorophyllide oxidoreductase) activity, and available metabolites, as the greening difference can be overridden by sucrose supply. Furthermore, *raptor1b* mutants are impaired in GA (gibberellin) signalling, ABA hypersensitive, and epistatic to PIF1/3 (phytochrome-interacting factor 1/3) as negative regulators for greening and ROS (Kravchenko *et al.*, 2015; P. Wang *et al.*, 2018; Zhang *et al.*, 2018). In larger seedlings with more nutrient and hormone access, sucrose-activated plastid biogenesis is promoted by TOR signalling based on AZD-8055 treatment (Mohammed *et al.*, 2018). Thus, it is important to determine the roles of TOR signalling in different physiological, metabolic, and developmental states with comprehensive analyses to provide logical explanations for the observed phenotypes.

In the dark, the elongation of etiolated hypocotyls is strongly enhanced by sucrose and glucose. The sugar promotion of hypocotyl elongation is blocked in the *tor-es* seedlings or by rapamycin treatment, but enhanced by overexpression of *TAP46* (Ren *et al.*, 2012; Ahn *et al.*, 2015; Zhang *et al.*, 2016). A key plant hormone promoting the elongation of etiolated hypocotyl is brassinosteroid (BR), and the expression of several target genes of the BR signalling transcription factor BZR1 involved in cell expansion is suppressed in the *tor-es* mutant. As increasing the concentration of BR and the gain-of-function *bzr1-D* mutation partially restore hypocotyl elongation in *tor-es*, TOR probably activates the BR pathway to promote plant growth. Further experimental evidence suggests that glucose–TOR signalling stabilizes BZR1 in the dark, which is degraded via autophagy suppressed by TOR activation (Fig. 2) (Zhang *et al.*, 2016). Recent findings also uncover a new link between TOR and BR signalling by identifying BIN2 (BR-insensitive 2) as a downstream effector of TOR–S6K2 signalling based on a yeast two-hybrid screen using S6K2 as a bait protein. *BIN2* encodes a GSK3β protein kinase, which is a negative regulator of BZR1 via direct phosphorylation and nuclear exclusion in BR signalling (Chaiwanon *et al.*, 2016). S6K2 directly phosphorylates BIN2 at S187 and S203, and presumably inhibits the BIN2 function. *BIN2-RNAi* plants strongly promote shoot development and are relatively insensitive to multiple TOR-specific chemical inhibitors in seedling growth under light, whereas *BIN2*-overexpressing plants are hypersensitive (Xiong *et al.*, 2017). These results provide novel molecular mechanisms for dual regulation of BR responses by glucose–TOR signalling through autophagy suppression and BZR1 stabilization, as well as TOR–S6K2-mediated BIN2 inactivation to enhance BZR1 nuclear translocation (Fig. 2) (Chaiwanon *et al.*, 2016; Zhang *et al.*, 2016; Xiong *et al.*, 2017). However, novel molecular mechanisms will be required to explain the proposed function of BIN2 in suppressing photoautotrophic growth, which is also suppressed by BR synthesis and signalling (Fig. 2) (Chory *et al.*, 1991).

Sulfur signalling

Sulfur is an essential nutrient for plant growth, and plant sulfur assimilation is carried out by ATP sulfurylase (APS) and APS reductase (APR) to reduce sulfate to sulfite, and sulfite reductase (SIR) further reduces sulfite to sulfide (Fig. 1A) (Takahashi *et al.*, 2011). The relationship between sulfur signalling and the TOR function has been advanced by investigating the SIR-deficient mutant for sulfide production. TOR signalling monitored by S6K phosphorylation and EdU staining in the root meristem are significantly reduced in *sir1-1* (Dong *et al.*, 2017; Speiser *et al.*, 2018). Moreover, limitation of sulfide in *sir1-1* leads to severe growth retardation, depletion of TCA cycle

intermediates, decreased rRNA, reduced global translation, and induced autophagy, all downstream targets of TOR signalling (Xiong *et al.*, 2013; Dong *et al.*, 2017; Speiser *et al.*, 2018). Significantly, grafting the wild-type shoot to the *sir1-1* root or supply of glucose restores S6K phosphorylation and the root growth defect associated with the reduced glucose and sucrose, but enhanced fructose levels in *sir1-1*. As sulfide fumigation can cause fast and significant up-regulation of glucose levels and TOR activity, TOR may play an integrative role in modulating sulfur nutrient sensing in plants (Dong *et al.*, 2017; Speiser *et al.*, 2018). It will be interesting to determine whether sulfide produced in chloroplasts promotes photosynthesis, sugar production, and nitrogen assimilation, all of which are decreased by sulfur deficiency and in *sir1-1* (Khan *et al.*, 2010).

A recent study dissecting the resource allocation between stress response pathways and growth-promoting pathways based on blocking sulfur flux from cysteine to glutathione has also generated new insight into sulfur signalling and TOR regulation (Speiser *et al.*, 2018). It is shown that reducing the glutamate–cysteine ligase activity for glutathione synthesis in the *cad2 sir1-1* double mutant partially restores plant growth, rescues meristematic activity, and increases TOR activity in *sir1-1*. It is suggested that TOR may trigger reallocation of cysteine from glutathione to protein synthesis. Moreover, 3-hydroxypropylglucosinolate, a downstream cysteine metabolite mediating plant defence, reversibly inhibits root elongation and meristem activation similar to TOR inhibitors (Malinovsky *et al.*, 2017). Thus, sulfur and its derived metabolites appear to serve a role in balancing plant development and defence via TOR regulation in response to environmental cues. Interestingly, genome-wide transcript profiling data have provided evidence that glucose–TOR signalling activates genes in the sulfur assimilation pathways and glucosinolate biosynthesis (Xiong *et al.*, 2013). There is a reciprocal positive feedback loop between glucose–TOR and sulfur–TOR signalling (Fig. 1A).

Nitrogen and phosphorus signalling

Although sugars derived from photosynthesis drive plant growth and development, and are the most potent nutrient cues to activate TOR signalling immediately, inorganic nitrogen and phosphorus nutrients may serve as the gatekeeper in integrating carbon–nitrogen and carbon–phosphorus nutrient signalling networks to co-ordinate bidirectional shoot–root nutrient communications, developmental plasticity, and adaptation, and to shape organ biomass and architecture (Gojon *et al.*, 2009; Gruber *et al.*, 2013; Liu *et al.*, 2017; Xuan *et al.*, 2017; Chien *et al.*, 2018; Gutiérrez-Alanís *et al.*, 2018; Y.Y. Wang *et al.*, 2018). Depending on the relationship with glucose or glucose-derived energy and metabolite status, the connection between glucose–TOR signalling and sulfur, nitrogen, or phosphorus availability could be different (Fig. 1A). For instance, sulfur deficiency is tightly linked with low endogenous glucose and sucrose levels, and inhibits photosynthesis (Takahashi *et al.*, 2011; Dong *et al.*, 2017). Enhancing photosynthesis or exogenous glucose supply effectively stimulates TOR–S6K signalling and root meristem activity under a low sulfur status. As sulfur deficiency also decreases nitrogen assimilation, adding nitrogen instead of glucose may not relieve this specific nutrient demand (Takahashi *et al.*, 2011; Dong *et al.*, 2017; Forzani *et al.*, 2018; Speiser *et al.*, 2018). In striking contrast, nitrogen or phosphorus deficiency is often associated with higher levels of sugars, and supplying higher glucose enhances expression of nitrate or phosphate starvation response genes (Moore *et al.*, 2003; Price *et al.*, 2004; Karthikeyan *et al.*, 2007; Chien *et al.*, 2018; Leong *et al.*, 2018; Wagner *et al.*, 2018). As nitrogen- or phosphorus-derived metabolites, such as NADH, NADPH, $FADH_2$, ADP, or phosphate, are essential to support the glucose-stimulated bioenergetic processes (Wagner *et al.*, 2018), we surmise that TOR signalling is probably compromised when the nitrogen or phosphorus nutrient status is low in plants. Despite abundant sugars, we speculate that the metabolic and energy generation processes are suppressed until nitrogen or phosphorus nutrients are replenished. Recent characterization of a mitochondrial ATP synthase mutant overcoming phosphite (Phi) (non-metabolizable but triggers phosphorus signalling) responses lends some support to the connection between ATP synthesis and sugar regulation in phosphorus signalling. This *phi1* (*phosphite-insensitive 1*) mutant displays root growth defects and constitutive mitochondrial impairment, resembling treatment with oligomycin (a specific mitochondrial ATPase inhibitor) (Leong *et al.*, 2018). It will be important to determine whether *phi1* exhibits lower TOR activity in this phosphorus signalling relay.

Despite the presence of abundant glucose or sucrose, it is conceivable that the TOR signalling pathway cannot be fully activated when either nitrogen or phosphorus is missing. We propose that nitrogen and phosphorus and/or their metabolic derivatives may serve as important nutrient cues to activate TOR signalling in plants (Fig. 1A). Although multiple amino acid sensors for leucine, arginine, and glutamine have been discovered in mammalian systems in the past decade, none of these sensor genes could be identified in plant genomes (Stracka *et al.*, 2014; González and Hall, 2017; Saxton and Sabatini, 2017). Notably, the molecular mechanism of the glutamine–TOR signalling, which requires a functional mitochondrial TCA and ETC, may exist in plants. However, leucine or arginine signalling is different, activating mTORC1 through different sensors and converging on RAG GTPases on the lysosomal surface in animals or the vacuole membrane in budding yeast (Stracka *et al.*, 2014; Saxton and Sabatini, 2017). As no RAG GTPase homologues have been identified in plants, plant TOR probably relies on novel sensors to perceive amino acids (Roustan *et al.*, 2016).

It has been reported that overexpressing TOR results in hypersensitivity to the root growth inhibited by high nitrate (Deprost *et al.*, 2007), whereas the inhibited root growth in nitrogen-free medium is more obvious than in normal nitrogen-containing medium in *TOR RNAi* lines (Liu and Bassham, 2010). Very recent studies have shown that nitrate, ammonium, or amino acid rapidly activates TOR–S6K phosphorylation in seedlings starved for nitrogen nutrients. These new findings provide the first clue suggesting possible innovative pathways for diverse nitrogen nutrient sensing and signalling mechanisms in nitrogen-deficient plants (Liu *et al.*,

2018). The puzzling observation of amino acid accumulation upon TOR inhibition is associated with a rapid increase in ammonium uptake and assimilation in *Chlamydomonas*, which suggests possible regulation by TOR of differential nitrogen usage. ^{13}C- and ^{15}N-isotope labelling experiments show that the imported ammonium is used to support *de novo* synthesis of amino acids only when carbon and nitrogen sources are available (Mubeen *et al.*, 2018). This finding presents a new carbon–nitrogen connection in the context of TOR signalling. Similar studies have not been conducted to test the activation of phosphate or phosphate-derived metabolites to stimulate TOR signalling in phosphate-deficient plants. However, recent progress in the elucidation of the phosphate sensing and signalling mechanisms will facilitate new discoveries to connect phosphorus signalling to TOR regulation, possibly wired into the elaborate sugar–phosphate metabolic and signalling networks (Péret *et al.*, 2011; Valluru and Van den Ende, 2011; Kuo *et al.*, 2014; Couso *et al.*, 2016; Wild *et al.*, 2016; Chien *et al.*, 2018; Gutiérrez-Alanís *et al.*, 2018; Leong *et al.*, 2018). For example, studies in *Chlamydomonas* and Arabidopsis have indicated the potential roles of inositol polyphosphates (InsPs) or pyrophosphates (PP-insPs) in phosphorus nutrient sensing and TOR signalling (Fig. 1A) (Kuo *et al.*, 2014; Couso *et al.*, 2016). As the null *inositol pentakisphosphate 2-kinase1* (*ipk1*) plant mutant is lethal, analyses of the weaker *ipk1* mutants suggest a link to growth defects in shoots and roots, increased phosphate accumulation in shoots, up-regulation of phosphorus starvation response (PSR) genes with phosphate repletion, and a genetic dependence on PHR1 (PHOSPHATE STARVATION RESPONSE 1) and PHL1 (PHR1-LIKE 1), key transcription factors for PSR gene expression (Kuo *et al.*, 2014). The *Chlamydomonas vip1-1* mutant lacking inositol hexakisphosphate kinase exhibits hypersensitivity to TORC1 inhibitors, rapamycin, torin1, and AZD-8055, with reduced $InsP_7$ and $InsP_8$ in the presence of acetate, which is reminiscent of high sugar stimulation of the PSR in plants. The accumulation of triacylglycerol in *vip1-1* hints at a potential nutrient signalling link among carbon, nitrogen, and phosphorus sensing converged on TOR regulation (Fig. 1A) (Couso *et al.*, 2016).

How fast TOR signalling could be stimulated by nitrogen, phosphorus, or their metabolites will depend on the timing required to generate the signalling molecules, perhaps through the integration of mitochondrial bioenergetics to activate TOR signalling. Curiously, phosphorus starvation leads to primary root meristem exhaustion, but extensive root hair and lateral root growth. The latter traits are the opposite of the root system responses observed in nitrate-deficient conditions (Ren *et al.*, 2012; Xiong and Sheen, 2012; Liu *et al.*, 2017). It is suggested that the adaption of the unique root system architecture to phosphorus starvation is geared to access phosphate more likely in the surface soil. Nitrogen signalling is adjusted to different levels of availability (starvation, low, and high), and promotes primary and lateral root development to forage for nitrogen nutrients deeper in the soil. Nutrient-stimulated specific adjustment in the plasticity and adaptation of plant root architecture probably serves to maximize the best strategies for a broad range of available nutrient concentrations (Gruber *et al.*, 2013).

Perspectives

By integrating recent research progress and key findings on the molecular mechanisms of sugar, sulfur, nitrogen, and phosphorus sensing and signalling processes, our analyses have suggested the possibility that TOR as the energy signalling master regulator plays a central role as a universal and multifaceted nutrient signalling integrator. Emerging molecular connections to photoreceptors perceiving a distinct spectrum of light as well as hormone biosynthesis and signalling pathways have been discovered as the upstream regulators in modulating TOR activation or repression (Fig. 1A). The sensing and signalling components are molecularly wired to target and relay specific nutrient, hormonal, or environmental cues in different organs, tissues, cells, and subcellular compartments. The sites for sensing and signalling could be local or systemic. One major convergent output from the integrated sensing and signalling of macronutrients, light, and hormones is to activate TOR protein kinase to promote bioenergetics, biogenesis, metabolism, cell proliferation, and cell growth in diverse plant developmental programmes (Fig. 2) (Gojon *et al.*, 2009; Takahashi *et al.*, 2011; Gruber *et al.*, 2013; Xiong *et al.*, 2013; Liu *et al.*, 2017; Chien *et al.*, 2018; Gutiérrez-Alanís *et al.*, 2018; Y.Y. Wang *et al.*, 2018). Future research will identify the precise molecular regulators and elucidate their dynamic actions in these fundamental cellular processes. It will also be fruitful to dissect the relatively unexplored regulatory domains to unravel how TOR signalling represses an equally vast spectrum of primary target genes and pathways in stress and immune responses (Ahn *et al.*, 2011; Moreau *et al.*, 2012; Caldana *et al.*, 2013; Xiong *et al.*, 2013; Dong *et al.*, 2015). Innovative experimental design and new technologies in genomics, proteomics, phosphoproteomics, and metabolomics, as well as in single-cell imaging and biochemical analyses will complement genetic and natural variation screens to uncover new molecular mechanisms underlying fundamental growth activities in the nutrient–TOR signalling network (Caldana *et al.*, 2013; Gruber *et al.*, 2013; Xiong *et al.*, 2013; Li *et al.*, 2015; Couso *et al.*, 2016; Dobrenel *et al.*, 2016*a*; Liu *et al.*, 2017; Saxton and Sabatini, 2017; Chien *et al.*, 2018; Schepetilnikov and Ryabova, 2018; Shi *et al.*, 2018; P. Wang *et al.*, 2018).

New TOR chemical inhibitors have been deployed for biological assays and genetic screens to probe the functions and regulations of TOR in diverse signalling pathways. It is critical to interpret the findings in immediate or long-term molecular connections by examining the link to direct TOR protein kinase substrates. Unlike rapamycin, which is suggested specifically to inhibit TORC1, the ATP-competitive inhibitors appear to suppress a broader spectrum of TOR functions. It will be informative to combine and compare the effective range and specificity of these distinct inhibitors in future molecular studies of the plant TOR signalling networks. A better understanding of how nutrient availability is transduced to TOR signalling may allow novel strategies in improving efficient sensing and uptake of diverse essential nutrients and their integration into the central growth, anabolic, and biogenesis networks mediated by TOR. As TOR controls global transcription reprogramming and diverse metabolic, cellular,

and developmental processes, it remains possible that additional TOR protein complexes may be discovered to modulate novel substrates and functions in the TOR signalling network in plants (Ahn *et al.*, 2011; Ren *et al.*, 2012; Caldana *et al.*, 2013; Xiong *et al.*, 2013; Dong *et al.*, 2015; Dobrenel *et al.*, 2016*a*; Schepetilnikov and Ryabova, 2018; Shi *et al.*, 2018).

The plant TOR signalling network has evolved to monitor diverse inorganic and organic nutrient availability, including carbon, nitrogen, phosphorus, and sulfur, to support anabolic activities that require integrated inputs of multiple nutrients to promote ribosome biogenesis, protein translation, cell cycle, cell expansion, and photosynthesis. Transcriptome reprogramming stimulated by glucose–TOR signalling in turn up-regulates gene sets encoding functions for sugar, nitrate, phosphate, and sulfate transport, assimilation, and metabolism (Fig. 1). Future efforts will elucidate the molecular mechanisms underlying nitrogen or phosphorus sensing and signalling connections to the TOR regulatory network. The complex interactions and positive feedback loops that tie multiple essential nutrients and their metabolic derivatives as upstream regulatory signals and downstream targets of the plant TOR signalling network will be further unfolded (Fig. 1A). Developing an integrative view of how cells in different organs co-ordinate the acquisition of diverse nutrients required for growth, adaption, and survival will improve our understanding of the local and systemic nutrient sensing and signalling networks.

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