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Target of Rapamycin kinase: central regulatory hub for plant growth and metabolism

The adaptation of plants to their environment requires tight regulation of metabolism and growth processes through central and highly connected signalling pathways. The signalling cascade involving the evolutionarily conserved Target of Rapamycin (TOR) represents just such a central regulatory hub, and research on this protein kinase in plants has progressed significantly during the past decade. TOR is now firmly established as a central player in plant responses to the availability of nutrients such as sugars, stresses including those from pathogens, and hormones. Moreover plant-specific targets and regulators have recently been identified. The reviews in this special issue explore the various facets of regulation exerted by this fascinating kinase as well as its potential for crop improvement.

Eukaryotic cells and organisms need to adjust basic processes such as cell division, growth and metabolism to the available resources and external conditions. These are sensed either directly, as in unicellular eukaryotes, or indirectly, for example through hormonal or nutrient signals, as occurs in multicellular organisms. Central to this regulation is the conserved kinase Target of Rapamycin (TOR), which has been shown to be a critical component of sensing mechanisms.

The discovery of TOR is a perfect example of the serendipitous nature of research. It all started with the identification of a molecule produced by *Streptomyces hygroscopicus*, a bacterium isolated in the 1970s in a soil sample from the remote and mysterious Easter Island, known as Rapa Nui in Polynesian. This compound was thus named rapamycin (Vezina *et al.*, 1975). Rapamycin was found to inhibit cell proliferation but the mechanism of action was unknown. It was only in the 1990s that Michael Hall's group in Basel identified mutations in yeast which conferred resistance to rapamycin. This led to the seminal discovery of TOR, inhibition of which by rapamycin leads to arrested growth (Heitman *et al.*, 1991; Montané and Menand, 2019). Michael Hall was later awarded the 2017 Lasker prize for medical research for this paramount discovery.

TOR was subsequently identified in humans, where it was given the name mTOR (mammalian or mechanistic TOR), in various animals including flies and worms (Saxton *et al.*, 2017; Mossmann *et al.*, 2018), flowering plants (Menand *et al.*, 2002) and algae (Perez-Perez *et al.*, 2017). In all eukaryotes, TOR is a

very large (around 250 kDa) serine/threonine kinase belonging to the phosphatidylinositol 3-kinase-related kinase (PIKK) family. Indeed, although TOR is a protein kinase, its catalytic domain is unconventional and resembles that of PI lipid kinases. Other members of this family include the conserved DNA damage checkpoint ataxia-telangiectasia mutated (ATM) and ATM-related (ATR) kinases, which are also present in plants.

In yeast and animals, where TOR has been studied extensively, various upstream regulators and downstream effectors have been discovered, forming a complex and highly connected signalling pathway (Blenis, 2017). In these organisms ScTOR and mTOR play a major role in the regulation of cell growth and metabolism through the control of gene transcription, cell trafficking, insulin responses as well as protein synthesis and degradation. Therefore, TOR is involved in many human diseases including cancer and diabetes. Thorough biochemical work showed that TOR belongs to two very large complexes, TORC1 and TORC2, containing common and specific companion proteins (Wullschlegel *et al.*, 2006; Saxton *et al.*, 2017; Mossmann *et al.*, 2018). Structural models for TOR complexes are now available (Aylett *et al.*, 2016; Karuppasamy *et al.*, 2017). In plants only the TORC1 complex has been described so far which, together with TOR, comprises the evolutionarily conserved LST8 and RAPTOR proteins (Box 1).

TOR and the control of plant growth

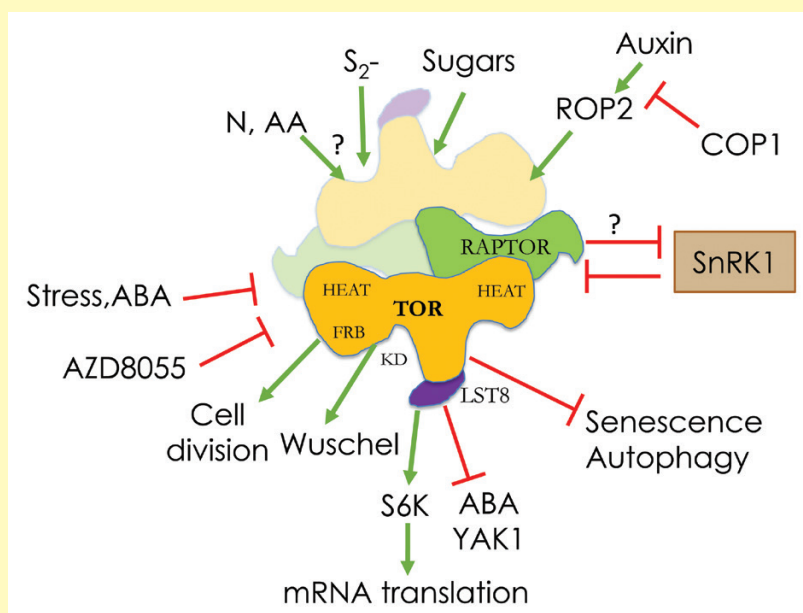
As in yeast and animals, TOR has been implicated in controlling plant growth and cell division (Caldana *et al.*, 2019) and prominent inducers of TOR activity have been shown to be sucrose and glucose (Xiong *et al.*, 2012; Dobrenel *et al.*, 2016a; Shi *et al.*, 2018). Indeed, a strong sugar–TOR growth-controlling axis has emerged from several studies in both roots and shoots (Xiong *et al.*, 2013; Pfeiffer *et al.*, 2016; Wu *et al.*, 2019). Basically, sugars like sucrose and glucose strongly up-regulate TOR activity by a largely unknown mechanism and TOR activates meristems by inducing E2F and Wuschel transcription factors in root and shoot apical meristems, respectively (Xiong *et al.*, 2013; Pfeiffer *et al.*, 2016). Nutrient starvation or defects in nutrient assimilation also affect TOR activity. For example, a decrease in sulfur assimilation due to mutations in the sulfite reductase gene diminishes TOR activity and growth through a reduction in sugar accumulation (Dong *et al.*, 2017). The review by Ahmad

Box 1. The basics of plant TOR

The conserved TOR (Target of Rapamycin) protein kinase acts in TORC1 (TOR complex 1) with LST8 and RAPTOR protein partners. This complex is found in all eukaryotes and is an important molecular element connecting nutrient, hormonal and stress signals to metabolism, growth and hormonal responses. TORC1 can be seen as a switch turning on anabolic and growth processes when conditions are favourable and inhibiting catabolism and nutrient recycling by autophagy. TORC1 controls mRNA translation globally but also the translation of specific mRNAs such as those encoding proteins needed for stress or hormone responses. Mounting evidence suggest that TOR and SnRK1/2 (Snf1-related kinases) act in an opposing way and it has been shown that SnRKs inhibit TOR activity by phosphorylating the RAPTOR protein.

In recent years, many targets of TOR have been identified in plants and algae including the ribosomal protein S6 kinase, the PP2A phosphatase partner TAP46, several components of the translation and cell division machinery, and also the PYL ABA receptors.

HEAT, HEAT [Huntingtin, elongation factor 3 (EF3), protein phosphatase 2A (PP2A), TOR1] repeat domain involved in protein–protein interactions; FRB, FKBP12-rapamycin binding domain; KD, kinase domain.



et al. (2019) presents further detail on regulation of the plant cell cycle by E2F and other conserved complexes in relation to TOR activity. TOR also influences the cell wall (Leiber *et al.*, 2010), and a new suppressor of *lrx1* (leucine-rich repeat extensin 1), a mutation which affects cell wall architecture and is compensated by TOR inhibition, has been identified and found to encode isopropylmalate synthase 1, a protein involved in leucine biosynthesis (Schaufelberger *et al.*, 2019).

Reduction of TOR activity by starvation or other signals increases lifespan for several eukaryotes (Weichhart, 2018). Indeed, inhibition of TOR with rapamycin is currently the only known treatment that increases lifespan in all organisms that have been studied. In plants, however, there is a more complex relationship between TOR activity and aging (Quilichini *et al.*, 2019).

TORC1: master regulator of stress and adaptive responses

In plants, data suggests that activity of the nutrient- and energy-induced TOR kinase is balanced in an antagonistic and

probably reciprocal way with one of the starvation-induced kinases of the SnRK (Snf1-related kinase) 1 and 2 families (Box 1; Dobrenel *et al.*, 2016a; Baena-Gonzalez and Hanson, 2017; Jamsheer *et al.*, 2019; Margalha *et al.*, 2019). SnRK1 has been shown to phosphorylate the RAPTOR component of the TORC1 complex and to inactivate TOR (Nukarinen *et al.*, 2016); this function is evolutionarily conserved, since the animal orthologue of SnRK1, the AMP-activated kinase, performs the same post-translational modification to inactivate TOR in response to energy and carbon starvation (Gwinn *et al.*, 2008). Interestingly, changes in subcellular localization of SnRK1 could be involved in inactivating TOR in different compartments (Blanco *et al.*, 2019). SnRK2s have also recently been shown to phosphorylate RAPTOR and to inactivate TOR in response to ABA (Wang *et al.*, 2018). Consistently the same report showed that TOR is able to repress ABA signalling in normal, non-stressed conditions by phosphorylating and inactivating the ABA PYL receptor and that there is a close and antagonistic relationship between TOR and ABA signalling (Box 1; Deprost *et al.*, 2007; Punzo *et al.*, 2018; Forzani *et al.*, 2019, Preprint; Wu *et al.*, 2019). Furthermore, the YAK1

kinase, which is related to ABA signalling (Kim *et al.*, 2016), has been shown to suppress the effects of TOR inhibition (Box 1; Barrada *et al.*, 2019; Forzani *et al.*, 2019, Preprint).

TOR, as a central regulatory module, has connections with many plant hormones apart from ABA (Schepetilnikov and Ryabova, 2018; Jamsheer *et al.*, 2019). For example, brassinosteroids partly suppress the defects in hypocotyl elongation observed in TOR-deficient lines (Zhang *et al.*, 2016) and the ROP2 small Rho protein participates in the auxin-induced stimulation of TOR activity (Li *et al.*, 2017; Schepetilnikov *et al.*, 2017). Light is also an efficient inducer of TOR and recently the stimulation of auxin-ROP2-TOR signalling and mRNA translation observed in the light has been shown to be connected with COP1 (constitutive morphogenesis 1) (Cai *et al.*, 2017; Chen *et al.*, 2018; Ahmad *et al.*, 2019).

Involvement of TOR in the trade-off between growth and defence

Given the central role of the TOR pathway in regulating gene expression, protein synthesis and metabolic adjustments, it could be questioned whether it is also wired to defence responses or targeted during pathogen infection. Growth and defence responses are known to be antagonistic and TOR inhibition was found to prevent growth and activate the salicylic acid-dependent defence pathway in Arabidopsis (Moreau *et al.*, 2012; Dong *et al.*, 2015). Meteignier *et al.* (2017) found a significant subset of genes translationally regulated by both TOR silencing and activation of the immune response through conditional expression of the *Pseudomonas syringae* avrRPM1 elicitor. Consistently, TOR-silenced plants display enhanced resistance to *P. syringae*, leading to the hypothesis that active TOR negatively regulates immunity at the translational level.

In another study, the *avr5* effector of *Ralstonia solanacearum* when expressed in yeast produced similar effects to rapamycin (Popa *et al.*, 2016). TOR inhibition by AZD8055 was also found to block the growth of *Xanthomonas citri* in *Citrus* spp. (Soprano *et al.*, 2018). The *X. citri* effector PthA4 is an interactor of Maf1, a conserved target of TOR, and repressor of Pol III and growth. Maf1 phosphorylation levels decreased upon TOR knockdown and increased following knockdown of the catalytic subunits of PPP4 and PP2A (Ahn *et al.*, 2019).

The role of TOR in the trade-off between growth and immunity was further substantiated in rice; genetic experiments involving overexpression or silencing of OsTOR or OsRAPTOR, combined with rapamycin treatments, showed that TOR negatively regulates several defence-related WRKY and MYB transcription factors, JA and SA signalling and resistance to various pathogens such as *Xanthomonas oryzae* (De Vleeschauwer *et al.*, 2018). TOR down-regulation or *rap-tor* mutation were also reported to reduce susceptibility to *Fusarium graminearum* in an Arabidopsis infection model (Aznar *et al.*, 2018). In this work the TOR inhibitor PP242 was also found to reduce leaf infection by *Fusarium*, although a direct role of the TOR inhibitor on the eukaryotic pathogen itself is probable and cannot be ruled out. Indeed, beside its emerging

role in the trade-off between growth and immunity in plant hosts, an active TOR pathway is also involved in the virulence of several eukaryotic pathogens (Shertz and Cardenas, 2011).

Several links between TOR and pathogen infection emerged from virus studies (Margalha *et al.*, 2019). One of the first discoveries was the direct interaction between TOR and the Cauliflower mosaic virus transactivator protein (TAV) which promotes reinitiation of translation along the CaMV multicistronic mRNA (Schepetilnikov *et al.*, 2011). The role of TOR was also investigated in the case of potyviruses, the largest group of plant RNA viruses. It was found that TOR-silenced or AZD8055-treated plants were resistant to Watermelon Mosaic Virus (WMV). Remarkably, AZD8055 treatment was able to eliminate the virus from infected plants (Ouibrahim *et al.*, 2015). More recently, repression of TOR activity by Tombusvirus infection was observed in plants and yeast, and TOR pathway inhibition or genetic repression was shown to reduce virus replication (Inaba and Nagy, 2018). It was further hypothesized that Tombusviruses may recruit the glycolytic pathway, which is regulated by TOR, to furnish energy for virus replication and that TOR repression is part of the plant defence response.

TOR controls mRNA translation

Stress negatively affects plant growth and development, triggering transcriptional, translational and metabolic reprogramming (Bechtold and Field, 2018; Margalha *et al.*, 2019). Indeed, cells can increase or decrease the production of proteins to accommodate changes in response to stress (Bailey-Serres and Juntawong, 2012; Schepetilnikov and Ryabova, 2018).

TOR-related pathways and molecular mechanisms that mediate the impact of stress signals on translation are largely unknown. Low energy stress can drastically decrease global protein synthesis rates, manifested by low levels of active ribosomes (polysomes), but this is reversible in conditions of energy supply (Tomé *et al.*, 2014).

Cold treatment can reduce global polysome levels in rice (Park *et al.*, 2012), while in Arabidopsis they are not significantly affected. Whether TOR is involved in cold stress tolerance in Arabidopsis, as was suggested for AtGCN1 (Wang *et al.*, 2017), would require further research. However, the authors suggest that decreased translation levels in conditions of TOR inhibition might increase the ability of Arabidopsis seedlings to survive under cold stress (Wang *et al.*, 2017).

The most critical TOR upstream input comes from light and photosynthesis; suppression of TOR activity negatively affects light-dependent plant growth (Chen *et al.*, 2018). Although there is a tight link between light, TOR activity, RPS6 (ribosomal protein S6) phosphorylation and global protein synthesis efficiency (Piques *et al.*, 2009; Floris *et al.*, 2013; Enganti *et al.*, 2017), mechanisms used by TOR to impact global protein synthesis have not yet been properly elucidated.

Recent work has identified an MRF (Ma3 Domain-Containing Translation Regulatory Factor) family of proteins that function in translation, especially under energy-deficient conditions (Lee *et al.*, 2017). Strikingly, the human homologue

of the MRFs, hPDCD4, inhibits translation initiation by binding eIF4A and preventing its interaction with eIF4G and, thus, formation of the functional eIF4F complex (Loh *et al.*, 2009). In addition, similarly to hPDCD4, which is phosphorylated by S6K1/TOR, MRF1 phosphorylation was regulated positively by S6K1/TOR (Lee *et al.*, 2017).

One efficient way of rapidly altering protein production in response to internal and external stimuli is to regulate mRNA translation selectively. In eukaryotes, TOR is implicated in translational regulation of a specific set of TOP (5'-terminal oligopyrimidine tract)-containing mRNAs via phosphorylation of an La RNA binding protein (LARP1) (Tcherkezian *et al.*, 2014). In plants, heat stress can dramatically induce an mRNA degradation process that is dependent on Arabidopsis LARPs (La-related Proteins) (Deragon and Bousquet-Antonelli, 2015). Although LARP1 was identified as a TOR/S6K1 downstream target in *Chlamydomonas reinhardtii* and Arabidopsis (Werth *et al.*, 2019; Van Leene *et al.*, 2019), its role in translation of TOP-containing mRNAs (Dobrenel *et al.*, 2016b) remains to be identified.

Active TOR impacts translation of a specific set of mRNAs that harbour upstream open reading frames (uORFs) within their leader regions (Schepetilnikov *et al.*, 2013). Moreover, subunit h of eukaryotic translation initiation factor 3 (eIF3h) was identified as a new TOR/S6K1 target, and its phosphorylation site mapped to Ser178 (Schepetilnikov *et al.*, 2013). The authors proposed that TOR, when activated, promotes phosphorylation of eIF3h and maintains its active phosphorylation status in Arabidopsis to ensure efficient reinitiation events (Schepetilnikov and Ryabova, 2018). However, other players in auxin signalling, such as phospholipase D zeta2 (PLD; required for auxin responses) (Li *et al.*, 2007), which is controlled by auxin, might also participate in TOR activation either directly or via production of phosphatidic acid (PA).

The growing wealth of phosphoproteomic data reveals hundreds of proteins with quantitative changes in their phosphorylation status in response to TOR inhibition in *C. reinhardtii* (Roustan and Weckwerth, 2018; Werth *et al.*, 2019) and Arabidopsis (Van Leene *et al.*, 2019). Among these TOR signalling-related targets are homologues of an elongation factor 2 kinase (EEF2K), components of the eIF2B complex, eIF4E-binding protein, LARP1 and CTC-interacting domain 4 (CID4). RPS6 Ser240 was clearly identified as a robust and conserved TOR/S6K1-dependent phosphosite in Arabidopsis and *Chlamydomonas* 40S ribosomal subunit (Dobrenel *et al.*, 2016b; Enganti *et al.*, 2017; Werth *et al.*, 2019). Consistently, an increase in RPS6 phosphorylation was also observed after loss of SnRK1 activity (Nukarinen *et al.*, 2016). However, the role of this evolutionarily conserved TOR-dependent phosphorylation event in the control of mRNA translation is not very well defined and will need further research.

Conclusion and future directions

It is now clear that, as in other eukaryotes, the plant TOR signalling pathway integrates information about external conditions, either directly or through hormonal signals, to mount

the necessary physiological, molecular and developmental responses. In recent years the plant TOR field has been blooming. Compared to animals and yeasts, the TOR pathway may be even more critical and integrate specific functions in algae and multicellular plants, which cannot escape from adverse environmental conditions or nutrient scarcity.

A better understanding of the role and regulation of the TOR kinase is still needed but recent phosphoproteomic and interactomic resources will be a great help for deciphering this fascinating regulatory hub (Van Leene *et al.*, 2019). This should open novel routes for increasing crop yield through stimulation of growth, improved pathogen defence and manipulation of metabolite partitioning.

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