



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 (Wullschleger *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

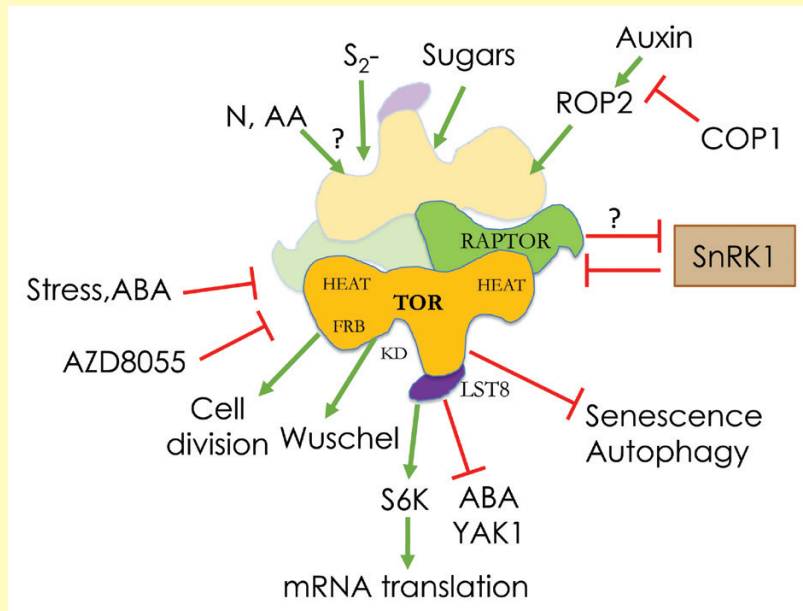
As in yeast and animals, TOR has been implicated in controlling plant growth and cell division (Caldana *et al.*, 2019) and prominent inducers of TOR activity have been shown to be sucrose and glucose (Xiong *et al.*, 2012; Dobrenel *et al.*, 2016a; Shi *et al.*, 2018). Indeed, a strong sugar–TOR growth-controlling 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 (Schaukelberger *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 oryzaea* (De Vleeschauwer *et al.*, 2018). TOR down-regulation or *raptor* 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 interatomic 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.

Acknowledgments

Reviews and research articles in this special issue were developed following the EMBO workshop 'TOR signaling in photosynthetic organisms' held in Alsace, France in 2018. *Journal of Experimental Botany* contributed to funding for this meeting. The authors were funded by the DecoraTOR ANR grant (ANR14-CE19-007). CM is also funded by a French State grant (LabEx Saclay Plant Sciences-SPS, ANR-10-LABX-0040-SPS).

Keywords: Abiotic stresses, abscisic acid, auxin, biotic stresses, mRNA translation, nutrient signaling, rapamycin, S6 kinase, SnRK1 kinase, sugars, TOR kinase.

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References

- Ahmad Z, Magyar Z, Bögre L, Papdi C. 2019. Cell cycle control by the target of Rapamycin signalling pathway. *Journal of Experimental Botany* **70**, 2275–2284.
- Ahn CS, Lee DH, Pai HS. 2019. Characterization of Maf1 in Arabidopsis: function under stress conditions and regulation by the TOR signaling pathway. *Planta* **249**, 527–542.
- Aylett CH, Sauer E, Imseng S, Boehringer D, Hall MN, Ban N, Maier T. 2016. Architecture of human mTOR complex 1. *Science* **351**, 48–52.
- Aznar NR, Consolo VF, Salerno GL, Martínez-Noël GMA. 2018. TOR signaling downregulation increases resistance to the cereal killer *Fusarium graminearum*. *Plant Signaling & Behavior* **13**, e1414120.
- Baena-González E, Hanson J. 2017. Shaping plant development through the SnRK1-TOR metabolic regulators. *Current Opinion in Plant Biology* **35**, 152–157.
- Bailey-Serres J, Juntawong P. 2012. Dynamic light regulation of translation status in *Arabidopsis thaliana*. *Frontiers in Plant Science* **3**, 66.

- Barrada A, Djendli M, Desnos T, Mercier R, Robaglia C, Montané MH, Menand B.** 2019. A TOR-YAK1 signaling axis controls cell cycle, meristem activity and plant growth in *Arabidopsis*. *Development* **146**, doi:10.1242/dev.171298
- Bechtold U, Field B.** 2018. Molecular mechanisms controlling plant growth during abiotic stress. *Journal of Experimental Botany* **69**, 2753–2758.
- Blanco NE, Liebsch D, Guinea Díaz M, Strand Å, Whelan J.** 2019. Dual and dynamic intracellular localization of *Arabidopsis thaliana* SnRK1.1. *Journal of Experimental Botany* **70**, 2325–2338.
- Blenis J.** 2017. TOR, the gateway to cellular metabolism, cell growth, and disease. *Cell* **171**, 10–13.
- Cai W, Li X, Liu Y, Wang Y, Zhou Y, Xu T, Xiong Y.** 2017. COP1 integrates light signals to ROP2 for cell cycle activation. *Plant Signaling & Behavior* **12**, e1363946.
- Caldana C, Martins MCM, Mubeen U, Urrea-Castellanos R.** 2019. The magic ‘hammer’ of TOR: the multiple faces of a single pathway in the metabolic regulation of plant growth and development. *Journal of Experimental Botany* **70**, 2217–2225.
- Chen GH, Liu MJ, Xiong Y, Sheen J, Wu SH.** 2018. TOR and RPS6 transmit light signals to enhance protein translation in deetioliating. *Proceedings of the National Academy of Sciences, USA* **115**, 12823–12828.
- Deprost D, Yao L, Sormani R, Moreau M, Leterreux G, Nicolai M, Bedu M, Robaglia C, Meyer C.** 2007. The *Arabidopsis* TOR kinase links plant growth, yield, stress resistance and mRNA translation. *EMBO Reports* **8**, 864–870.
- Deragon JM, Bousquet-Antonelli C.** 2015. The role of LARP1 in translation and beyond. *Wiley Interdisciplinary Reviews. RNA* **6**, 399–417.
- De Vleeschauwer D, Filipe O, Hoffman G, et al.** 2018. Target of rapamycin signaling orchestrates growth-defense trade-offs in plants. *New Phytologist* **217**, 305–319.
- Dobrenel T, Caldana C, Hanson J, Robaglia C, Vincentz M, Veit B, Meyer C.** 2016a. TOR signaling and nutrient sensing. *Annual Review of Plant Biology* **67**, 261–285.
- Dobrenel T, Mancera-Martínez E, Forzani C, et al.** 2016b. The *Arabidopsis* TOR kinase specifically regulates the expression of nuclear genes coding for plastidic ribosomal proteins and the phosphorylation of the cytosolic ribosomal protein S6. *Frontiers in Plant Science* **7**, 1611.
- Dong P, Xiong F, Que Y, Wang K, Yu L, Li Z, Ren M.** 2015. Expression profiling and functional analysis reveals that TOR is a key player in regulating photosynthesis and phytohormone signaling pathways in *Arabidopsis*. *Frontiers in Plant Science* **6**, 677.
- Dong Y, Silbermann M, Speiser A, et al.** 2017. Sulfur availability regulates plant growth via glucose-TOR signaling. *Nature Communications* **8**, 1174.
- Enganti R, Cho SK, Toperzer JD, Urquidi-Camacho RA, Cakir OS, Ray AP, Abraham PE, Hettich RL, von Arnim AG.** 2017. Phosphorylation of ribosomal protein RPS6 integrates light signals and circadian clock signals. *Frontiers in Plant Science* **8**, 2210.
- Floris M, Bassi R, Robaglia C, Alboresi A, Lanet E.** 2013. Post-transcriptional control of light-harvesting genes expression under light stress. *Plant Molecular Biology* **82**, 147–154.
- Forzani C, Duarte G, Clement G, Huguet S, Paysant-Le-Roux C, Mercier R, Leprince AS, Meyer C.** 2019. Mutations of the Atyak1 kinase suppress TOR deficiency in *Arabidopsis*. *Cell Press Sneak Peak*. doi:10.2139/ssrn.3305560 [Preprint].
- Gwinn DM, Shackelford DB, Egan DF, Mihaylova MM, Mery A, Vasquez DS, Turk BE, Shaw RJ.** 2008. AMPK phosphorylation of raptor mediates a metabolic checkpoint. *Molecular Cell* **30**, 214–226.
- Heitman J, Movva NR, Hall MN.** 1991. Targets for cell cycle arrest by the immunosuppressant rapamycin in yeast. *Science* **253**, 905–909.
- Inaba JI, Nagy PD.** 2018. Tombusvirus RNA replication depends on the TOR pathway in yeast and plants. *Virology* **519**, 207–222.
- Jamsheer K M, Jindal S, Laxmi A.** 2019. Evolution of TOR–SnRK dynamics in green plants and its integration with phytohormone signaling networks. *Journal of Experimental Botany* **70**, 2239–2259.
- Karuppasamy M, Kusmider B, Oliveira TM, Gaubitz C, Prouteau M, Loewith R, Schaffitzel C.** 2017. Cryo-EM structure of *Saccharomyces cerevisiae* target of rapamycin complex 2. *Nature Communications* **8**, 1729.
- Kim D, Ntui VO, Xiong L.** 2016. *Arabidopsis* YAK1 regulates abscisic acid response and drought resistance. *FEBS Letters* **590**, 2201–2209.
- Lee DH, Park SJ, Ahn CS, Pai HS.** 2017. MRF family genes are involved in translation control, especially under energy-deficient conditions, and their expression and functions are modulated by the TOR signaling pathway. *The Plant Cell* **29**, 2895–2920.
- Leiber RM, John F, Verherbruggen Y, Diet A, Knox JP, Ringli C.** 2010. The TOR pathway modulates the structure of cell walls in *Arabidopsis*. *The Plant Cell* **22**, 1898–1908.
- Li X, Cai W, Liu Y, Li H, Fu L, Liu Z, Xu L, Liu H, Xu T, Xiong Y.** 2017. Differential TOR activation and cell proliferation in. *Proceedings of the National Academy of Sciences, USA* **114**, 2765–2770.
- Li G, Xue HW.** 2007. *Arabidopsis* PLDzeta2 regulates vesicle trafficking and is required for auxin response. *The Plant Cell* **19**, 281–295.
- Loh PG, Yang HS, Walsh MA, Wang Q, Wang X, Cheng Z, Liu D, Song H.** 2009. Structural basis for translational inhibition by the tumour suppressor Pdc4. *The EMBO Journal* **28**, 274–285.
- Margalha L, Confraria A, Baena E.** 2019. SnRK1 and TOR: modulating growth–defense trade-offs in plant stress responses. *Journal of Experimental Botany* **70**, 2261–2274.
- Menand B, Desnos T, Nussaume L, Berger F, Bouchez D, Meyer C, Robaglia C.** 2002. Expression and disruption of the *Arabidopsis* TOR (target of rapamycin) gene. *Proceedings of the National Academy of Sciences, USA* **99**, 6422–6427.
- Meteignier LV, El Oirdi M, Cohen M, Barff T, Matteau D, Lucier JF, Rodrigue S, Jacques PE, Yoshioka K, Moffett P.** 2017. Translatome analysis of an NB-LRR immune response identifies important contributors to plant immunity in *Arabidopsis*. *Journal of Experimental Botany* **68**, 2333–2344.
- Montané M-H, Menand B.** 2019. TOR inhibitors: from mammalian outcomes to pharmacogenetics in plant and algae. *Journal of Experimental Botany* **70**, 2297–2312.
- Moreau M, Azzopardi M, Clément G, et al.** 2012. Mutations in the *Arabidopsis* homolog of LST8/GβL, a partner of the target of Rapamycin kinase, impair plant growth, flowering, and metabolic adaptation to long days. *The Plant Cell* **24**, 463–481.
- Mossmann D, Park S, Hall MN.** 2018. mTOR signalling and cellular metabolism are mutual determinants in cancer. *Nature reviews. Cancer* **18**, 744–757.
- Nukarinen E, Nägele T, Pedrotti L, et al.** 2016. Quantitative phosphoproteomics reveals the role of the AMPK plant ortholog SnRK1 as a metabolic master regulator under energy deprivation. *Scientific Reports* **6**, 31697.
- Ouibrahim L, Rubio AG, Moretti A, Montané MH, Menand B, Meyer C, Robaglia C, Caranta C.** 2015. Potyviruses differ in their requirement for TOR signalling. *The Journal of General Virology* **96**, 2898–2903.
- Park SH, Chung PJ, Juntawong P, Bailey-Serres J, Kim YS, Jung H, Bang SW, Kim YK, Do Choi Y, Kim JK.** 2012. Posttranscriptional control of photosynthetic mRNA decay under stress conditions requires 3’ and 5’ untranslated regions and correlates with differential polysome association in rice. *Plant Physiology* **159**, 1111–1124.
- Pérez-Pérez ME, Couso I, Crespo JL.** 2017. The TOR Signaling Network in the Model Unicellular Green Alga *Chlamydomonas reinhardtii*. *Biomolecules* **7**, doi:10.3390/biom7030054.
- Pfeiffer A, Janocha D, Dong Y, et al.** 2016. Integration of light and metabolic signals for stem cell activation at the shoot apical meristem. *Elife* **5**, e17023.
- Piques M, Schulze WX, Höhne M, Usadel B, Gibon Y, Rohwer J, Stitt M.** 2009. Ribosome and transcript copy numbers, polysome occupancy and enzyme dynamics in *Arabidopsis*. *Molecular Systems Biology* **5**, 314.
- Popa C, Li L, Gil S, Tatjer L, Hashii K, Tabuchi M, Coll NS, Ariño J, Valls M.** 2016. The effector AWR5 from the plant pathogen *Ralstonia solanacearum* is an inhibitor of the TOR signalling pathway. *Scientific Reports* **6**, 27058.
- Punzo P, Ruggiero A, Grillo S, Batelli G.** 2018. TIP41 network analysis and mutant phenotypes predict interactions between the TOR and ABA pathways. *Plant Signaling & Behavior* **20**, 1–4.
- Quilichini TD, Gao P, Pandey PK, Xiang D, Ren M, Datla R.** 2019. Live long and praise TOR: a role for TOR signaling in every stage of plant life. *Journal of Experimental Botany* **70**, 2285–2296.

- Roustan V, Weckwerth W.** 2018. Quantitative phosphoproteomic and system-level analysis of TOR inhibition unravel distinct organellar acclimation in *Chlamydomonas reinhardtii*. *Frontiers in Plant Science* **9**, 1590.
- Saxton RA, Sabatini DM.** 2017. mTOR signaling in growth, metabolism, and disease. *Cell* **169**, 361–371.
- Schaufelberger M, Galbier F, Herger A, de Brito Francisco R, Roffler S, Clement G, Diet A, Hörtensteiner S, Wicker T, Ringli C.** 2019. Mutations in the Arabidopsis ROL17/*isopropylmalate synthase* 1 locus alter amino acid content, modify the TOR network, and suppress the root hair cell development mutant *lrx1*. *Journal of Experimental Botany* **70**, 2313–2323.
- Schepetilnikov M, Dimitrova M, Mancera-Martínez E, Geldreich A, Keller M, Ryabova LA.** 2013. TOR and S6K1 promote translation reinitiation of uORF-containing mRNAs via phosphorylation of eIF3h. *The EMBO Journal* **32**, 1087–1102.
- Schepetilnikov M, Kobayashi K, Geldreich A, Caranta C, Robaglia C, Keller M, Ryabova LA.** 2011. Viral factor TAV recruits TOR/S6K1 signaling to activate reinitiation after long ORF translation. *The EMBO Journal* **30**, 1343–1356.
- Schepetilnikov M, Makarian J, Srouf O, Geldreich A, Yang Z, Chicher J, Hammann P, Ryabova LA.** 2017. GTPase ROP2 binds and promotes activation of target of rapamycin, TOR, in response to auxin. *The EMBO Journal* **36**, 886–903.
- Schepetilnikov M, Ryabova LA.** 2018. Recent discoveries on the role of TOR (Target of Rapamycin) signaling in translation in plants. *Plant Physiology* **176**, 1095–1105.
- Shertz CA, Cardenas ME.** 2011. Exploiting and subverting Tor signaling in the pathogenesis of fungi, parasites, and viruses. *PLoS Pathogens* **7**, e1002269.
- Shi L, Wu Y, Sheen J.** 2018. TOR signaling in plants: conservation and innovation. *Development* **145**, doi:10.1242/dev.160887.
- Soprano AS, Smetana JHC, Benedetti CE.** 2018. Regulation of tRNA biogenesis in plants and its link to plant growth and response to pathogens. *Biochimica et biophysica acta. Gene Regulatory Mechanisms* **1861**, 344–353.
- Tcherkezian J, Cargnello M, Romeo Y, Huttlin EL, Lavoie G, Gygi SP, Roux PP.** 2014. Proteomic analysis of cap-dependent translation identifies LARP1 as a key regulator of 5'TOP mRNA translation. *Genes & Development* **28**, 357–371.
- Tomé F, Nägele T, Adamo M, Garg A, Marco-Illorca C, Nukarinen E, Pedrotti L, Peviani A, Simeunovic A, Tatkievicz A, et al.** 2014. The low energy signaling network. *Frontiers in Plant Science* **5**, doi:10.3389/fpls.2014.00353
- Van Leene J et al.** 2019. Integration of phosphoproteomics and interactomics elucidates substrates of the target of rapamycin kinase in plants. *Nature Plants* **5**, 316–327.
- Vézina C, Kudelski A, Sehgal SN.** 1975. Rapamycin (AY-22,989), a new antifungal antibiotic. I. Taxonomy of the producing streptomycete and isolation of the active principle. *The Journal of Antibiotics* **28**, 721–726.
- Wang L, Li H, Zhao C, et al.** 2017. The inhibition of protein translation mediated by AtGCN1 is essential for cold tolerance in *Arabidopsis thaliana*. *Plant, Cell & Environment* **40**, 56–68.
- Wang P, Zhao Y, Li Z, et al.** 2018. Reciprocal regulation of the TOR Kinase and ABA receptor balances plant growth and stress response. *Molecular Cell* **69**, 100–112.e6.
- Weichhart T.** 2018. mTOR as regulator of lifespan, aging, and cellular senescence: a mini-review. *Gerontology* **64**, 127–134.
- Werth EG, McConnell EW, Couso Lianez I, Perrine Z, Crespo JL, Umen JG, Hicks LM.** 2019. Investigating the effect of target of rapamycin kinase inhibition on the *Chlamydomonas reinhardtii* phosphoproteome: from known homologs to new targets. *New Phytologist* **221**, 247–260.
- Wu Y, Shi L, Li L, Fu L, Liu Y, Xiong Y, Sheen J.** 2019. Integration of nutrient, energy, light, and hormone signalling via TOR in plants. *Journal of Experimental Botany* **70**, 2227–2238.
- Wullschlegel S, Loewith R, Hall MN.** 2006. TOR signaling in growth and metabolism. *Cell* **124**, 471–484.
- Xiong Y, McCormack M, Li L, Hall Q, Xiang C, Sheen J.** 2013. Glucose-TOR signalling reprograms the transcriptome and activates meristems. *Nature* **496**, 181–186.
- Xiong Y, Sheen J.** 2012. Rapamycin and glucose-target of rapamycin (TOR) protein signaling in plants. *The Journal of Biological Chemistry* **287**, 2836–2842.
- Zhang Z, Zhu JY, Roh J, Marchive C, Kim SK, Meyer C, Sun Y, Wang W, Wang ZY.** 2016. TOR signaling promotes accumulation of BZR1 to balance growth with carbon availability in arabidopsis. *Current Biology* **26**, 1854–1860.