# Recent Discoveries on the Role of TOR (Target of Rapamycin) Signaling in Translation in Plants[1][OPEN]

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Protein synthesis is an intricate, energy-demanding, and tightly controlled process that plays a fundamental role in cell growth, proliferation, and differentiation. The target of rapamycin (TOR) protein kinase integrates stress-, nutrient-, and energy-related signals to optimize protein synthesis outputs. In mammals, TOR is a main controller of capped mRNA translation; how TOR participates in translation initiation in plants is unclear, but active TOR is required for regulation of translation of mRNA with 5′-untranslated region (5′-UTR) upstream open reading frames (uORFs)—known translation regulatory elements in eukaryotes. Recent data implicates diverse signals such as stress, hormones, and metabolites in regulation of TOR signal transduction pathways and, thus, in response to environmental stress. Here, we review current knowledge of plant TOR complex composition and activation, and its function in translation, compiling data on downstream processes that are under stringent control of TOR in mammals but not yet investigated in plants.

Plants have evolved various adaptation mechanisms to ensure their optimal growth, with plant development and behavior being strongly responsive to various external and internal stimuli. By monitoring their environment, plants trigger signal transduction cascades in order to regulate downstream cellular processes, mainly via protein synthesis—a major energy-consuming process (Buttgereit and Brand, 1995). The TOR protein kinase integrates extracellular signals (hormones, biotic and abiotic stresses, growth factors) together with intracellular nutrient availability and energy status to control protein synthesis and other anabolic processes if conditions are favorable, and represses catabolic processes such as autophagy (Albert and Hall, 2015). The past 10 years has boosted research on plant TOR complex composition, highlighted TOR upstream signals and downstream targets, and revealed an interplay between TOR signaling and hormonal, stress, and other pathways in photosynthetic organisms. We are beginning to understand how TOR is activated, and how it controls many cellular processes, such as transcription, translation, and autophagy. Here, we give an overview of recent results on the role of TOR in plant translation control and draw the reader's attention to future questions to address. In plants, inactivation of TOR correlates with a decrease in total polysomal levels (Deprost et al., 2007; Schepetilnikov et al., 2011, 2013), strongly suggesting a role for TOR in plant translation. Although a role for TOR in global translation in plants has been documented, the players and mechanisms used to influence different steps of translation initiation —the step most controlled by TOR in mammals—are only starting to emerge. Here, we summarize the current state of knowledge of specific plant translation initiation mechanisms that are controlled by 5′-UTR elements of mRNAs and discuss regulation of these mechanisms by TOR/S6 kinase 1 (S6K1) signaling. Examples where TOR regulates specific mRNAs in other eukaryotic systems are presented. In addition, we

**ADVANCES**

- The emergence of TOR as a main regulator of growth-promoting pathways is orchestrated by light, sugars, and growth-related hormones.
- TOR acts as an essential factor for auxin signal transduction to the cytoplasm in Arabidopsis.
- Auxin mediates TOR activation via small GTPase ROP2, which binds and activates TOR, as an intermediate player in the auxin-TOR signaling axis.
- TOR stimulates translation of specific mRNAs harboring uORFs within their leader regions via a non-canonical translation initiation mechanism: reinitiation.
- There are a growing number of TOR/S6K1 downstream targets in plant translation: ribosomal protein S6 (eS6) is phosphorylated at Ser240 in a TOR-responsive manner.

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discuss current understanding of upstream signaling effectors that link TOR with protein synthesis and plant growth.

## PLANT TOR COMPLEX COMPOSITION

TOR belongs to the phosphoinositide 3-kinase-related protein kinase family that exhibits Ser/Thr but no lipid kinase activity (Abraham, 2004). The domain organization of Arabidopsis (*Arabidopsis thaliana*) TOR is complex and conserved among metazoans, mammals, and plants (Menand et al., 2002; Zoncu et al., 2011). The N-terminal part of TOR contains HEAT (Huntingtin, Elongation Factor 3, protein phosphatase 2A, TOR1) repeat motifs required for substrate recruitment and membrane association, followed by FAT (FRAP, ATM, TRRAP), FRB (FKBP12-Rapamycin Binding), Ser/Thr kinase catalytic, and FATC (FAT Carboxy terminus) domains; the FATC and FAT domains together contribute to kinase activation. TOR is encoded by a single gene in mammals and plants, while two TOR genes, *TOR1* and *TOR2*, are present in yeast (Shimobayashi and Hall, 2014). Mammalian TOR (mTOR) acts in two functionally and structurally distinct complexes—TORC1 and TORC2—that both contain mTOR, mLST8 (mammalian Lethal with Sec13 protein 8) and DEPTOR (DEP-domain-containing mTOR-interacting protein). In addition, mTORC1 harbors the scaffold protein mRaptor (mammalian Regulatory-Associated Protein of mTOR) and PRAS40 (Pro-Rich AKT Substrate 40 kD), while mTORC2 comprises Rictor (Rapamycin-insensitive companion of Introduction mTOR), mSIN1 (mammalian Stress activated protein kinase Interacting Protein 1), and Protor (Protein observed with Rictor; Zoncu et al., 2011). mTORC1 promotes biosynthesis of proteins, lipids, and nucleotides but inhibits autophagy in conditions of substrate sufficiency (Shimobayashi and Hall, 2014), while mTORC2 regulates cell metabolism and cytoskeleton reorganization (Oh and Jacinto, 2011). Furthermore, the TOR pathway is more complex than previously appreciated, and four distinct TOR kinases (TOR1–TOR4) have been identified in the parasite *Trypanosoma brucei* (Saldivia et al., 2013).

A TOR knockout mutant in Arabidopsis is embryo lethal, and TOR inactivation affects plant growth (Menand et al., 2002). *TOR* is expressed in all Arabidopsis tissues, particularly in primary and lateral roots, shoot apical meristems, and floral meristems (Menand et al., 2002). Up to now, two core subunits of TORC1 (Raptor and LST8) have been found in Arabidopsis; both are encoded by two genes (*RAPTOR1/RAPTOR2* and *LST8-1/LST8-2*, respectively; Deprost et al., 2007; Moreau et al., 2012). Unlike in yeast and mammals, mutations in *LST8* are not lethal but result in developmental defects, whereas *RAPTOR1* mutations are conditionally lethal in Arabidopsis (Anderson et al., 2005; Deprost et al., 2007; Moreau et al., 2012). Raptor is an important mTOR accessory protein that facilitates the recruitment and phosphorylation of TOR substrates via targeting both the N-terminal HEAT domain of TOR and a TOR signaling (TOS) motif present in the majority of TOR substrates (Schalm and Blenis, 2002), while mLST8 binds the mTOR kinase domain and likely modulates mTOR complex integrity and activity (Kim et al., 2002; Wullschleger et al., 2005). Accordingly, Raptor1 binding to the TOR HEAT domain and Lst8-1 to the TOR FRB domain was demonstrated in both Arabidopsis and the green alga *Chlamydomonas reinhardtii* (Anderson et al., 2005; Mahfouz et al., 2006; Deprost et al., 2007; Moreau et al., 2012), suggesting that both proteins are likely to fulfill functions similar to that of mammalian orthologs. Plants may be lacking a TORC2-related complex, since Rictor and SIN1 have not been found in photosynthetic organisms (Dobrenel et al., 2016a). However, we cannot exclude that plants constitute TOR-containing complexes with components that differ from those found in mammals; for example, in neural stem cells, G-protein-coupled receptor kinase-interacting protein 1 nucleates an mTOR complex lacking Raptor and Rictor (Smithson and Gutmann, 2016).

Arabidopsis TOR displays a weak sensitivity to the peptidyl-prolyl cis/trans isomerase (FK506-binding protein 12 [FKBP12])-rapamycin complex (Menand et al., 2002; Sormani et al., 2007), or becomes sensitive when human or yeast FKBP12 is overexpressed in Arabidopsis or high rapamycin concentrations are applied to inhibit growth (Mahfouz et al., 2006; Sormani et al., 2007; Ren et al., 2012; Xiong and Sheen, 2012). Currently, ATP-competitive inhibitors such as Torin-1 and the second-generation inhibitor AZD-8055 are used widely to block TOR in plants (Montané and Menand, 2013; Schepetilnikov et al., 2013, 2017). Nowadays,

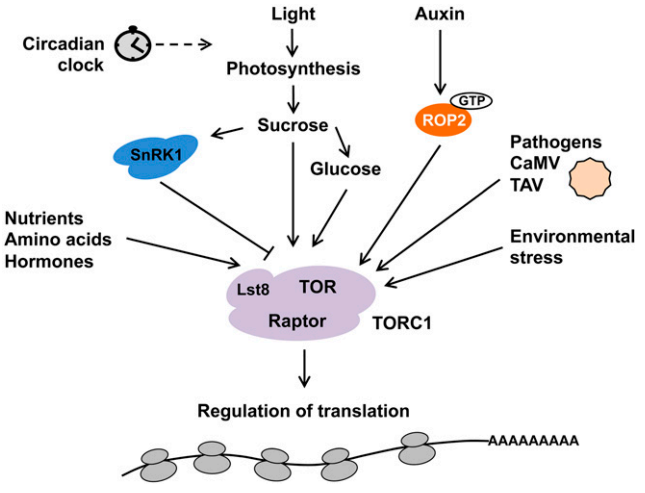


**Figure 1.** The TOR signaling pathway regulates global translation. The TOR complex integrates plethora of metabolic pathways and environmental signals to drive the global translational rates in photosynthetic organisms.

TOR-deficient, ethanol-inducible, and estradiol-inducible RNA interference lines are widely employed to elucidate TOR functions in planta and avoid the embryo lethality of null *tor* mutants (Deprost et al., 2007; Caldana et al., 2013; Xiong et al., 2013). mTOR activation status can be monitored by following phosphorylation at Ser-2448, which is likely phosphorylated by S6K1, if TOR is active (Chiang and Abraham, 2005). The corresponding epitope within the C terminus of Arabidopsis TOR is phosphorylated at Ser-2424 in response to TOR activation (Schepetilnikov et al., 2013, 2017).

## UPSTREAM CONTROL OF TRANSLATION VIA TOR

### Hormone Signaling to Translation

Many experiments strongly suggest that TOR signaling is wired to hormonal control, light, and biotic and abiotic stresses, and recent research has identified some underlying pathways (Fig. 1). Several phytohormones, such as jasmonic acid, abscisic acid, salicylic acid, brassinosteroids, and cytokinin, were implicated in cross talk with the TOR signaling pathway (Dong et al., 2015; Kravchenko et al., 2015; Pfeiffer et al., 2016; Zhang et al., 2016; De Vleesschauwer et al., 2017; Song et al., 2017). However, the most prominent growth hormones, auxin and kinetin, are known to promote S6K phosphorylation in cell suspension cultures, which leads to phosphorylation of ribosomal protein S6 (Turck et al., 2004). A growing body of evidence now demonstrates that TOR acts as an essential factor for auxin signal transduction in Arabidopsis (Schepetilnikov et al., 2013; Deng et al., 2016; Pu et al., 2017). Moreover, auxin was identified as a TOR upstream effector molecule (Schepetilnikov et al., 2013) that acts on TOR via activation of a small GTPase, ROP2 (Schepetilnikov et al., 2017). Indeed, auxin-treated plants, plants with high endogenous auxin accumulation, are characterized by increased levels of active TOR. In addition, plants with high levels of active ROP2, including those expressing constitutively active ROP2 and ROP2-GTP-expressing Arabidopsis plants, display increased phosphorylation of TOR and S6K1 (Schepetilnikov et al., 2013, 2017; Li et al., 2017). Accordingly, TOR inactivation leads to severe gravitropic defects, described as auxin-mediated responses. Currently, the auxin/ROP2/TOR signaling axis represents the most well-studied example of upstream TOR regulation in plants. Auxin-mediated activation of TOR drives translation of specific messages (Schepetilnikov et al., 2013, 2017), inhibits stress-mediated autophagy (Pu et al., 2017), and, at a physiological level, promotes meristem activation (Li et al., 2017). Based on the observed effects of auxin on TOR signaling activation, it was suggested that the auxin-TOR signaling axis regulates translation of the specific class of uORF-mRNAs in the cytoplasm (Schepetilnikov et al., 2013).

Auxin-sensing ROP GTPases are conserved molecular switches that function in many signal transduction events (Fehér and Lajkó, 2015). Studies of the mechanism of TOR activation by ROP2 led to the discovery that ROP2 physically binds TOR and promotes its activation, if bound to GTP (Schepetilnikov et al., 2017). In response to ROP2, TOR associates with endosome-like structures, suggesting that plant endosomes serve as a hub for TOR activation upon perception of auxin signal. Currently, ROP2 GTPase represents the only example of plant TOR direct upstream effector that activates TOR in plants.

### Light, Energy, and Sugar Signaling in Translation

The most critical environmental input comes from light energy, and inactivation of TOR suppresses light-energy-dependent plant growth (Ren et al., 2012). Light, sugar, and brassinosteroid signaling through TOR maintain the balance between hormone-promoted growth and carbon availability in plants (Xiong et al., 2013; Dong et al., 2015; Zhang et al., 2016). TOR integrates light and metabolic signals for apical shoot meristem activation (Pfeiffer et al., 2016). During photosynthesis, light energy is captured to convert the carbon intake into production of sugars that can be used immediately as material for plant growth or stored as starch for long-term reserves (Zeeman and Ap Rees, 1999). Photosynthesis, the primary source of energy for plants, also appears to be under the control of the TOR pathway. Plants deficient in TOR signaling exhibit abnormalities in thylakoid grana architecture and normal photosynthetic ability (Sun et al., 2016). Interestingly, light promotes translation of mRNAs encoding proteins involved in photosynthesis (Petracek et al., 1997; Tang et al., 2003; Floris et al., 2013). Recent data suggested that sugars act not only as energy source, but also as signaling molecules through TOR, maintaining the balance between hormone-promoted growth and carbon availability (Xiong et al., 2013; Dong et al., 2015; Zhang et al., 2016).

The TOR complex is regulated by AMP protein kinase (AMPK), the main energy sensor in humans (Mihaylova and Shaw, 2011). A similar antagonistic relationship between the AMPK plant ortholog SnRK1 (Suc nonfermenting 1-related Kinase 1) and TOR-related signaling pathways in response to changing nutritional and energy conditions was suggested in Arabidopsis (Robaglia et al., 2012; Broeckx et al., 2016; Baena-González and Hanson, 2017). In mammals, being upstream of TOR, SnRK1 may inhibit TOR activity via direct interaction and phosphorylation of upstream components of TOR signaling and Raptor—the regulatory subunit of the TOR complex (Nukarinen et al., 2016)—possibly leading to complex disassembly (Hughes Hallett et al., 2015). Accordingly, in plants SnRK1 can interact and phosphorylate Raptor (Nietzsche et al., 2016; Nukarinen et al., 2016).

Different light regimes affect general translation; the massive increase in translation during photomorphogenesis (Liu et al., 2012, 2013), and changes in polysomal loading of specific pull of mRNAs after

reillumination (Juntawong and Bailey-Serres, 2012) and high light intensity stress (Floris et al., 2013), indirectly indicate the involvement of TOR signaling in response to light energy. Oxygen singlets, which are a consequence of excess light, repress translation and phosphorylation of 40S ribosomal protein S6 (Khandal et al., 2009), suggesting that TOR orchestration of translation and growth is light dependent and that, in turn, TOR controls photosynthesis at the level of gene expression.

### Circadian Clock and TOR

An endogenous biological timekeeper that produces rhythmic outputs with roughly 24-h periodicity—the circadian clock—is based on an autoregulatory transcriptional feedback loop that schedules physiological processes to occur at specific and appropriate times of day (Nohales and Kay, 2016). Several studies in animals proposed that TORC1 activity is controlled by the circadian clock, providing some rhythmicity of TOR signaling (Cornu et al., 2014; Khapre et al., 2014; Lipton et al., 2015). In higher plants, translation of the core component of the circadian clock LHY occurs in a light-sensitive manner (Kim et al., 2003). More generally, overall translation efficiency in plants correlates with diurnal changes in energy status mediated by light perception and carbon metabolism (Piques et al., 2009; Pal et al., 2013). Accordingly, rhythmical oscillations of mRNA loading on polysomes support a connection between circadian clock and translational regulation (Missra et al., 2015). However, whether circadian oscillations regulate TOR signaling in plants remains to be elucidated.

### TOR Signaling under Biotic Stress

Viral and bacterial infection are significant stresses that affect many signaling pathways in plants, including TOR signaling—a significant target during viral infection in both mammals and plants (Walsh et al., 2013). TOR-deficient plants appear to be more resistant to both viral and bacterial infection (Schepetilnikov et al., 2011; Ouibrahim et al., 2015; Popa et al., 2016; Zvereva et al., 2016; Meteignier et al., 2017). There are several explanations for this phenomenon. First, TOR signaling is required for translation of specific polycistronic viral mRNAs; for example, the plant pararetrovirus *Cauliflower mosaic virus* (CaMV) protein transactivator/viroplasmin (TAV) directly binds and mediates TOR activation—a characteristic unique among plant and mammalian viruses (Schepetilnikov et al., 2011). Second, recent translatome analysis proposes a role for TOR-mediated translational control in immune response by regulation of defense gene expression (Meteignier et al., 2017). Finally, beside translational input, TOR-mediated stress induction of autophagy and innate immunity can eliminate pathogens, thus protecting plants from infection. The pathogenicity effectors can trigger TOR activity, thus modulating the timing, or extent, of autophagy induction (Popa et al., 2016; Zvereva et al., 2016).

## SIGNALING OF PLANT TORC1 COMPLEX TOWARD TRANSLATION

### S6K Activation by TORC1

The main downstream targets of TORC1 in mammals are found within the cell translation apparatus, including ribosomal protein S6Ks and eIF4E-binding proteins (4E-BPs; Albert and Hall, 2015; Rexin et al., 2015). In mammals, activation of the S6Ks p70S6K1 and p85S6K1 critically depends on direct phosphorylation by mTORC1 at the C-terminal hydrophobic motif residue, and the phosphoinositide dependent kinase 1 that contributes to full activation of S6K1 by phosphorylating a motif within the activation loop (Thr-389 and Thr-229 in S6K1, respectively; Fenton and Gout, 2011; Liko and Hall, 2015). According to the crystal structure of S6K1, phosphorylation of the hydrophobic motif residue occurs independently and likely precedes phosphorylation of the activation loop (Wang et al., 2013). Phosphorylation of S6K1 by TOR is aided by Raptor, which mediates interaction between TOR and the S6K1 TOS motif (FDIDL in S6K1; Kim et al., 2002; Schalm and Blenis, 2002).

Arabidopsis harbors two closely related homologs of mammalian S6Ks: AtS6K1 and AtS6K2 (Zhang et al., 1994; Mizoguchi et al., 1995). Mutational analysis suggests that Arabidopsis S6K single mutants show different expression patterns and stress sensitivity (Henriques et al., 2010). Accumulating data suggest that Arabidopsis AtS6K1 most likely substitutes for mammalian p70S6K1 (Mahfouz et al., 2006; Schepetilnikov et al., 2011; Xiong and Sheen, 2012), while AtS6K2, which is likely localized in the nucleus, may be functionally equivalent to p85S6K (Mahfouz et al., 2006). As in mammals, Arabidopsis TOR likely cooperates with Raptor in phosphorylation of direct targets, since interaction between Raptor and both TOR and S6K1 has also been found in Arabidopsis (Mahfouz et al., 2006). The TOS motif recently uncovered within the N terminus of Arabidopsis S6K1 displays a low level of conservation with canonical consensus motifs found in mTOR kinase substrates, indicating plant specificity in Raptor-substrate interactions (Son et al., 2016, 2017; Sun et al., 2016).

### 4E-BPs in Plants

In eukaryotes, cap-dependent translation initiation requires mRNA binding to the eIF4F complex, which contains cap-binding eIF4E, an ATP-dependent helicase eIF4A and their interacting scaffold protein eIF4G (Browning and Bailey-Serres, 2015; Hinnebusch et al., 2016). mTOR, if active, maintains eIF4F integrity via phosphorylation of a family of translational initiation repressors, eIF4E-binding proteins (4E-BPs), in mammals and Drosophila (Jackson et al., 2010). In the generally

accepted scenario, 4E-BPs, when not phosphorylated by TOR, efficiently compete with eIF4G for eIF4E binding, inhibiting eIF4F complex formation and cap-dependent initiation of translation. TOR phosphorylates 4E-BPs in response to particular physiological conditions that trigger their release from cap-bound eIF4E and restoration of the eIF4F complex. Notably, 4E-BPs are the least abundant factors among eukaryotic translation initiation factors (eIFs), and misregulation of their expression leads to various diseases and cancers in animals (Furic et al., 2010). Additionally, 4E-BPs preferentially repress so-called eIF4E-sensitive mRNAs, translation initiation of which is strictly dependent on eIF4E binding to the cap structure (Koromilas et al., 1992). In plants, despite the growing number of eIF4E-binding proteins that harbor the so-called canonical eIF4E-binding motif, none is a known TOR target. However, we cannot exclude that the small size and low abundance of 4E-BP-like proteins might limit identification of their orthologs in plants. Thus, to date, there is no experimental evidence that TOR is involved in control of the main mechanism of translation initiation mediated by the mRNA 5′ cap structure, opening a door to future research.

### eIF3 and Polysomes Are Platforms for TOR Phosphorylation Events

In higher eukaryotes, including plants, eIF3 is a 700- to 800-kD multisubunit complex comprising 13 different subunits (eIF3a–eIF3m), with only five subunits—eIF3a, eIF3b, eIF3c, eIF3g, and eIF3i—that function in *Saccharomyces cerevisiae* (Hinnebusch, 2006). eIF3 was implicated at every step of translation initiation, including 43S and 48S preinitiation complex formation assembly, AUG start codon recognition, and reinitiation of translation, when ribosomes terminating translation of the leader uORF resume scanning and reinitiate at a further downstream ORF on the same mRNA (Park et al., 2001; Kim et al., 2004; Pöyry et al., 2007; Schepetilnikov et al., 2013).

A new connection between the TOR/S6K1 signaling axis and translation initiation was discovered (Holz et al., 2005), with eIF3 identified as a TOR-interacting partner serving as a platform for TOR phosphorylation events in humans. Later results have shown that polysomes serve as a docking site for plant TORC1 (Schepetilnikov et al., 2011, 2013) and yeast TORC2 (Oh et al., 2010). A simplified model states that, in the absence of extracellular stimuli such as auxin, for example, S6K1 associates with either eIF3-containing complexes or polysomes, while inactive TOR does not. Upon TOR stimulation, TOR is recruited to eIF3 and, to a lesser extent, polysomes, where it phosphorylates S6K1, triggering S6K1 concomitant release from both platforms. The patterns of association with TORC1 are opposite to those of S6K1. Indeed, in TOR-deficient mutants, characterized by nondetectable S6K1 activity, S6K1 is constitutively bound to polysomes (Schepetilnikov et al., 2011).

### Ribosomal Protein S6 Is a Major Target of S6Ks within the Cell Translation Machinery

S6Ks phosphorylate numerous targets to control various cellular functions (Ma and Blenis, 2009), with translation factors, ribosomal protein S6 (eS6; Fenton and Gout, 2011; Liko and Hall, 2015), and eukaryotic elongation factor-2 kinase (Wang et al., 2001) being the most famous S6K targets.

Initial observations that eS6 is a major TOR/S6K signaling downstream target prompted much subsequent research into the role in translation played by eS6 when phosphorylated in response to TOR activation. The crystal structures of the 80S ribosome and 40S ribosomal subunit have established that eS6 is located at the right foot of the 40S ribosomal subunit (Ben-Shem et al., 2011). The C-terminal $\alpha$-helix of eS6, which harbors multiple TOR/S6K1 phosphorylation sites, protrudes out of 40S, thus providing an alternative bridge to 60S or external protein binding (Ben-Shem et al., 2011). Despite these advances, the role of eS6 phosphorylation in initiation or elongation steps of mRNA translation remains a matter of debate (Meyuhas, 2015).

In plants, eS6 is encoded by two well-conserved genes encoding proteins having equivalent and interchangeable functions (Creff et al., 2010). Activation and phosphorylation of S6Ks strongly correlates with eS6 phosphorylation (Turck et al., 1998; Mahfouz et al., 2006). Comparative studies of eS6 posttranslational modifications occurring in response to hormones and various abiotic signals documented phosphorylation of several sites within the C-terminal $\alpha$-helix of eS6 (for review, see Browning and Bailey-Serres, 2015). Recently, phosphoproteomic analysis and western blot with an antibody specifically recognizing phosphorylated Ser-240 has suggested that phosphorylation of Ser-240 is TOR/S6K1 responsive, and, accordingly, TOR inactivation decreases eS6 phosphorylation at this site (Dobrenel et al., 2016b).

Recent work by Nukarinen et al. (2016) has indicated that activation of SnRK1 is implicated in repression of protein synthesis (as main energy consumer) and implicated SnRK1 in regulation of photosynthesis (as main energy source); Weckwerth and colleagues found that ribosomal protein S6 was highly phosphorylated in Arabidopsis SnRK-deficient plants at Ser-240, Ser-237, and Ser-231, indicating that these phosphorylation sites are responsive to TOR activation (Nukarinen et al., 2016).

## ROLE OF TOR IN REGULATION OF TRANSLATION OF SPECIFIC MRNAS

### mRNAs Harboring uORFs within Their Leader Regions

More than 30% of eukaryotic mRNAs are loaded with uORFs within their 5′-UTRs, and there is mounting evidence that uORFs are major repressors of translation and thus play a key role in growth and development (Tran et al., 2008; Calvo et al., 2009). uORF-

mRNAs, which are common in Arabidopsis (Hanada et al., 2007; Hayden and Jorgensen, 2007; Kim et al., 2007), encode many regulatory proteins, including transcriptional factors (e.g. auxin response factors [ARFs]), protein kinases, and other potent proteins, expression levels of which are limited by posttranscriptional mechanism such as ribosomal reinitiation. Where the 5′-UTR of mRNA contains a short uORF (typically $<$ 30–50 codons), a fraction of ribosomes (usually $<$ 50%) can resume scanning after translation of this uORF and reinitiate at a further downstream ORF (Kozak, 2001). According to the current model, the short translation elongation event leaves eIFs that have been recruited during the cap-dependent initiation event bound to the 80S ribosome, making the ribosome competent for reinitiation (Kozak, 1987; Mohammad et al., 2017). The temporary retention of these reinitiation-promoting factors (RPFs) can assist the terminating ribosome to resume scanning, rapidly reacquire the ternary complex, eIF2-GTP-Met-tRNA, and the 60S ribosomal subunit de novo. This model helps explain why reinitiation is precluded after a long elongation event, when all factors gradually dissociate from the translating ribosome before the termination step. eIF3 has been suggested as a ribosome-associated RPF in yeast (Cuchalová et al., 2010; Munzarová et al., 2011) and plants (Park et al., 2001; Schepetilnikov et al., 2013), while eIF4F, elongation factor 2, and DENR-MCT-1 promote reinitiation in mammals (Pöyry et al., 2004; Skabkin et al., 2013; Schleich et al., 2014).

Identification of noncanonical RPFs promoting efficient translation of uORF-mRNAs was pioneered in plants, implicating the 60S ribosomal protein L24B (Nishimura et al., 2005; Zhou et al., 2010), eIF3 subunit h (Kim et al., 2004; Zhou et al., 2010; Roy et al., 2010), and TOR (Schepetilnikov et al., 2013, 2017). Two critical Arabidopsis mutants, *eif3h-1*, which expresses C-terminal truncation alleles of eIF3h, and *rpl24b* (*short valve 1*), have contributed greatly to our understanding of reinitiation phenomena (Nishimura et al., 2005; Zhou et al., 2010). Both mutants result in strongly reduced translation of uORF-mRNAs that encode ARF transcription factors. Although the mechanisms of eIF3h and eL24 in reinitiation are not yet known, and likely differ (Tiruneh et al., 2013), both mutants display defects in translation reinitiation and auxin-mediated organogenesis (Nishimura et al., 2005; Zhou et al., 2010). Despite its critical role in translation reinitiation, there was no significant effect of eIF3h C-terminal truncation on cap-dependent initiation events (Zhou et al., 2010; Roy et al., 2010; Schepetilnikov et al., 2013). Moreover, eIF3h was identified as a new TOR/S6K1 target, and its phosphorylation site was mapped to Ser-178 (Schepetilnikov et al., 2013). Accordingly, auxin, which mediates activation of the TOR/S6K1 signaling axes, promotes phosphorylation of eIF3h in Arabidopsis extracts, in contrast to the TOR inhibitor Torin-1, which nearly abolishes its phosphorylation. Interestingly, the human ortholog of eIF3h is highly expressed in many cancer cells, and its high levels trigger dysregulation of protein synthesis. This oncogenic potential of eIF3h is strongly enhanced by phosphorylation at the conserved residue Ser-183 (Zhang et al., 2008). Recent research revealed that translation regulation via uORFs contributes to plant development, playing important roles in organogenesis. Indeed, translation of many meristematic mRNAs, including *CLV1* and *AS1*, appears to be under uORF control; their suppression leads to enlarged shoot apical meristem and defects in organ polarity (Zhou et al., 2014). Despite these findings, the mechanism by which eIF3h and its phosphorylation by TOR up-regulates the reinitiation capacity of ribosomes is unclear. The eIF3h C-terminal domain is critical to eIF3h integration within eIF3 (Roy et al., 2010), suggesting that the reinitiation function depends on the complete eIF3 complex. Interestingly, the eIF3 noncore subunit h was implicated in assembly of subunits e, d, k, and l into the functional eIF3 complex; however, there are no data on this complex formation in plants (des Georges et al., 2015; Smith et al., 2016).

In plants, TOR, when active, promotes translation of uORF-containing mRNAs, likely via the posttranscriptional regulation of the active phosphorylation state of some RPFs (Schepetilnikov et al., 2011, 2013). According to the current model (Fig. 2A), during the short elongation event, eIF3/other RPFs might still be bound to the translating ribosome, and TOR is required to maintain the active phosphorylation status of eIF3h and possibly other RPFs in polysomes. When active, TOR is recruited to polysomes, leading to phosphorylation of bound and inactive S6K1 at Thr-449 and its dissociation. Notably, association of TOR and eIF3h with polysomes is a hallmark of efficient polysomal loading of uORF-containing mRNAs and their translation (Schepetilnikov et al., 2013). Indeed, active TOR promotes polysomal loading of many uORF-containing mRNAs, including auxin-related ARFs and auxin-unrelated *bZIP11*.

Several studies have highlighted the role of auxin in TOR signaling activation (Schepetilnikov et al., 2013, 2017). Translation reinitiation control by TOR appears to be an important component of the auxin response pathway, as TOR-deficient plants and *eif3h-1* mutants are characterized by altered root gravitropism (Zhou et al., 2010; Schepetilnikov et al., 2013). Accordingly, TOR inactive plants expressing yeast FKBP12 display auxin-defective phenotypes if treated by rapamycin (Deng et al., 2016).

### Virus-Activated Reinitiation after Long ORF Translation

An extreme case of reinitiation—reinitiation after long ORF translation—operates on the polycistronic 35S RNA from CaMV and artificial bicistronic RNAs under the control of a CaMV reinitiation factor, TAV (Bonneville et al., 1989; Ryabova et al., 2006). TAV can interact with the cell translation machinery via the 60S ribosomal subunit, where it targets at least two ribosomal proteins, eL18 and eL24 (Park et al., 2001).

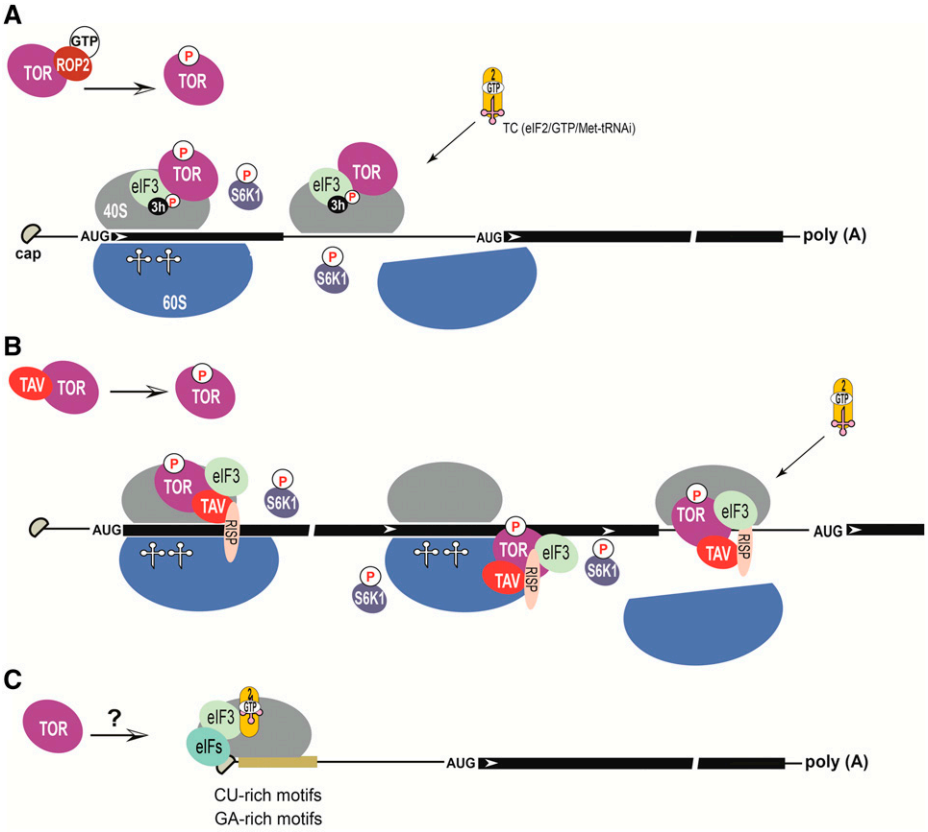


**Figure 2.** TOR activates translation reinitiation mechanisms. A, The pattern of reinitiation after short uORF translation. TOR is activated in response to various stimuli. For example, TOR can be activated by auxin, which acts on TOR through GTP-bound ROP2. TOR-P binds polysomes to maintain the high phosphorylation status of S6K1 and thus the eIF3 subunit h (3h), which promotes the reinitiation event. eIF3, together with other eIFs, remains associated with the translating ribosome during the short elongation event to form reinitiation-competent ribosomal complexes capable of resuming scanning, as well as recruiting ternary complex (TC) and the 60S ribosomal subunit. B, The pattern of virus-activated reinitiation after long ORF translation. TAV binds and activates TOR (TOR-P). TAV retains eIF3/RISP on the translating ribosome during the long elongation event, likely by transferring to the rear side of the 60S subunit through association with eL18 or eL24 in the 60S subunit (Park et al., 2001; Thiébeauld et al., 2009). TOR-P associates with polysomes, where it maintains high RISP phosphorylation status. During translation termination and release of 60S, eIF3/TAV/RISP-P might be transported back to 40S and assist in 60S/TC recruitment. C, Sequence features of mRNA 5′-UTRs that might influence translation initiation.

Previously, it was shown that TAV is involved in the complex formation with eIF3 and a reinitiation supporting protein, RISP, that lead to both protein accumulation in polysomes of TAV transgenic plants, indicating that TAV can prevent a loss of eIF3/RISP by the translating ribosome during the long elongation event, such that a terminating ribosome is competent to reinitiate translation of the downstream ORF (Thiébeauld et al., 2009). Relatively recent research has uncovered TOR as a critical TAV partner in reinitiation of translation, demonstrating that TAV directly binds to, and activates, TOR and thus promotes its association with polysomes (Schepetilnikov et al., 2011). Moreover, the same study identified RISP as a downstream target of the TOR/S6K1 signaling axis and showed that phosphorylated RISP promotes TAV-activated reinitiation of translation (Schepetilnikov et al., 2011). According to the current model, TOR, if active, associates with polysomes, where it can maintain the high phosphorylation status of RISP and possibly other RPFs bound to polysomes in the presence of TAV during the long elongation event. Finally, after termination of translation, 40S ribosomal subunits equipped with necessary RPFs, including eIF3 and phosphorylated RISP (RISP-P), are capable to resume scanning, rebind the ternary complex, and reinitiate (Fig. 2B). Although many details of RISP function in reinitiation are now known, the mechanism remains to be established.

### 5′-UTR Motifs That Are Controlled by TOR in Animals

5′-leader motifs and secondary structures can significantly modulate ribosome loading on mRNA, movement toward the start codon, and thus translation of the downstream ORF. In animals, mRNAs with a 5′-

### OUTSTANDING QUESTIONS

- Although Raptor and Lst8 have been identified as TOR partners, a systematic search for TOR complex regulatory subunits is required to understand TORC1 complex function. An intriguing question concerns the TORC2 complex in plants, and whether it employs another TOR partner that can substitute for Rictor in plants.
- Whether TOR functions in cap-dependent translation initiation remains an open question. For example, are eIF4E-binding proteins regulated by TOR?
- Recent work suggests several players in reinitiation of translation. Their function in promoting ribosome reinitiation competence is still unclear. Exploring other TOR/S6K1 signaling axis downstream targets in translation may reveal intrinsic mechanisms of TOR function in promoting translation of uORF-containing mRNAs.
- While hormones, light, biotic-, and abiotic stresses are all implicated in signaling through TOR, the underlying pathways and intermediate components of these pathways are largely unknown, and this fascinating field is ripe for further investigation.

terminal oligopyrimidine (TOP) motif (CCUUUCU) at the 5′-end, encoding mainly ribosomal proteins and translation factors, are subject to TOR control, regulating protein synthesis and thus cell growth (Jefferies et al., 1994; Meyuhas and Kahan, 2015). It was first thought that the S6K/eS6 signaling axis was required for TOP mRNA translation regulation (Jefferies et al., 1994); however, this hypothesis was discarded following experiments showing that TOP mRNA translation was not disturbed in S6K-deficient mice or in phosphorylation site knockout eS6 (Tang et al., 2001; Barth-Baus et al., 2002; Ruvinsky and Meyuhas, 2006). Relatively recently, global high-resolution transcriptome-scale ribosome profiling revealed that another TOR downstream target, 4E-BPs, might mediate mTOR effects in translation of TOP-mRNAs (Thoreen et al., 2012). Several other potential regulatory factors, including the RNA-binding protein LARP1 (La-related protein), have been demonstrated to function under TOR control in TOP mRNA regulation (Tcherkezian et al., 2014). In plants, TOP-like motifs are abundant within mRNA 5′-UTRs of ribosomal proteins (Dobrenel et al., 2016b), but whether these cis-elements are involved in translation regulation in plants requires further research. Interestingly, several recent publications revealed the existence of so-called R-motifs containing GA, $G(A)^3$, $G(A)^6$, etc., repeats (Dobrenel et al., 2016; Xu et al., 2017), and provided evidence that the R-motif regulates translation of its mRNA via interaction with poly(A)-binding proteins during immune regulation in plants (Xu et al., 2017). Whether R-motifs are targets of TOR signaling in plants remains a very interesting subject of study (Fig. 2C).

## CONCLUSIONS AND PERSPECTIVES

Gene expression is intensively controlled, particularly at the level of transcription and translation, but control of mRNA translation has to date been much less studied than mechanisms of transcription. In plants, many strategies of protein synthesis and the role of TOR in regulation of mRNA translation remain to be discovered. The past 10 years of TOR research provided clear evidence that TOR is a critical regulator of cell growth and proliferation in photosynthetic organisms that acts, at least in part, via promoting protein synthesis in favorable environmental conditions. Several reports have uncovered the role of TOR and translation initiation factors in both short- and long-term reprogramming of the translational landscape. Today, the mechanisms by which TOR regulates translation of specific plant mRNAs, for example, to control reinitiation events used to modulate production of critical effector proteins, are under intensive investigation. Further work will be required to understand the mechanisms and function of TOR and its downstream targets in plant translation. An important question is to understand whether, and if so how, TOR regulates cap-dependent translation initiation in plants. Several growth hormones have been implicated in cross talk with the TOR signaling pathway, and our focus now is to study the components of these pathways and how hormones are wired into TOR translation control.

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