TOR tour to auxin

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Auxin is a principal growth hormone in plants. A study by Schepetilnikov *et al* (2013) now reports that TOR is activated by auxin and regulates expression of auxin-responsive genes by facilitating translation reinitiation of mRNAs with uORFs at their 5' UTRs. In this way, TOR acts at the crossroad of the plasma membrane and nuclear auxin signalling pathways to link auxin with general nutrient signalling.

Auxin signalling acts through concentration gradients to regulate developmental processes in plants and the flow of Auxin can be rapidly altered by environmental stimuli resulting in the redirection of plant growth. Auxin concentrations are read and translated into gradients of regulatory proteins, as seen for the PLETHORA (PLT) transcription factors, which determine cellular states, such as stem cell maintenance, cell proliferation, and cell elongation. The currently dominating view is that auxin is perceived by the nuclear TIR/AFB receptors, F-box proteins, which regulate turnover of the AUX/IAA transcriptional repressors to control gene transcription through a family of AUXIN RESPONSE FACTORS (ARFs; Figure 1; Hayashi, 2012). Schepetilnikov *et al* (2013) now show that auxin also controls the abundance of key regulators in a post-transcriptional manner involving selective protein translation. They report that auxin activates TARGET OF RAPAMYCIN (TOR), the evolutionary conserved central growth regulator in yeast, plants, and animals. TOR is known to control protein translation through translation initiation in yeast and animals, but its role is less well understood in plants. It was previously shown that TOR acts through the p70 RIBOSOMAL S6 KINASE (S6K) (Mahfouz *et al*, 2006) and Schepetilnikov *et al* (2013) now find that polysomes form a platform for TOR-dependent phosphorylation and activation of S6K. Inactive S6K is associated with polysomes; when TOR becomes activated by auxin, it is recruited to polysomes, leading to the phosphorylation and subsequent dissociation of active S6K. S6K in turn regulates the selective translation of mRNAs containing *cis*-acting regulatory sequences in the 5' untranslated region (5'UTR). These sequences are short untranslated open reading frames (uORFs) that disrupt translation when ribosomes cannot reinitiate. The presence of uORFs in around 30% of *Arabidopsis* mRNAs indicates that this type of translational control is abundantly used in plants, and includes mRNAs in functional categories

of hormone responses, sugar signalling, and cell-cycle control (Kim *et al*, 2007). Translation initiation factors (eIFs) can remain associated with the elongating ribosomes downstream of the uORFs to enable reinitiation (Roy *et al*, 2010). In animal cells, the eIF3 complex serves as a docking site for phosphorylation and activation of inactive S6K by TOR (Holz *et al*, 2005). Schepetilnikov *et al* (2013) show *Arabidopsis* S6K to phosphorylate eIF3h in a TOR-dependent manner leading to polysome loading of eIF3 and effective translation reinitiation of uORF-containing mRNAs in response to auxin. The regulation of translation reinitiation appears to be a principal component of the auxin response pathway, as plants depleted of TOR or expressing mutant *eif3h* display typical auxin-response phenotypes, such as altered root gravitropism (Figure 1B).

How auxin signalling activates TOR is unclear at present but candidates for linking the two pathways exist. Early auxin responses are signalled through the AUXIN BINDING PROTEIN 1 (ABP1) located at the extracellular face of the plasma membrane (PM) in the cell wall (CW) and numerous rapid auxin responses are attributed to ABP1, including the potassium uptake, cell expansion, cytoskeletal formation and cellular polarisation (Sauer and Kleine-Vehn, 2011). *Phospholipase D zeta2* (PLD₂₂) was shown to be required for auxin responses, but it is not clear whether this is signalled via ABP1 (Li and Xue, 2007). PLDs produce the signalling lipid second messenger, phosphatidic acid (PA) that in plants activates the PHOSPHOLIPID-DEPENDENT PROTEIN KINASE 1 (PDK1) (Anthony *et al*, 2004). PDK1 is a T-loop activator of a family of protein kinases, collectively known as AGC kinases, including S6K and PINOID (PID), the later regulating the polar localisation of the auxin efflux proteins, PINs. S6K is a convergence point between PDK1 and TOR signalling pathways, as S6K activation also depends on a conserved regulatory phosphorylation by TOR at its C-terminus. In animal cells, growth factors such as insulin connect to TOR through PDK1, AKT, and TSC1/TSC2, while the availability of sugars is signalled through AMP-activated kinase (AMPK). While plants lack TSC1/2 orthologues, it is becoming evident that TOR integrates cellular growth with availability of growth factors and nutrients in both plants and animals.

Growth and cell proliferation are connected by selective translation of key cell-cycle regulators like the G1-specific cyclins (CYCDs). The protein abundance of the plant

Figure 1 Regulation of cell growth and proliferation by the growth hormone, auxin, and nutrients. **(A)** Auxin (A) canonical signalling components are labelled red. Auxin has a two-receptor system for its signal transduction, and these as well as nutrient signalling might converge through TOR that regulates the selective translation of ARFs. For details, see text. **(B)** Plant growth is very plastic and adaptable to changing environmental conditions. A long known example is gravitropic growth of, for example, roots that is regulated by differential auxin distribution from the root cap in epidermal layers; auxin is being depleted in the upper face. This leads to a curvature that relies primarily on selective cell enlargement and in longer terms also on cell proliferation. Schepetilnikov *et al* (2013) show that TOR is involved in this process. **(C)** TOR integrates auxin and nutrient signalling primarily by regulated protein translation. Selective protein translation of key transcriptional regulators could sensitise the second auxin perception system within the nucleus to regulate auxin-responsive transcription. Protein translation underpins growth that drives cell proliferation. However, growth can also repress proliferation to allow cells to attain larger sizes in nutrient-rich condition, and proliferation can repress growth to maintain cells in a meristematic state.

orthologue to the ErbB3 binding protein 1 (EBP1), a growth regulator, was shown to depend on auxin and to regulate cell proliferation (Horvath *et al*, 2006), but the involvement of TOR, S6K, and eIF3h in controlling translation of mRNAs for cell-cycle and growth regulators remains to be investigated. In nutrient-rich conditions, cells divide at a larger size and both TOR and S6K are involved in a pathway to repress cell proliferation to determine cell size (Davie and Petersen, 2012). Overexpression of E2FB resulted in extremely small cell size and auxin-independent cell proliferation in cell cultures. S6K opposes CYCD3;1 and potentiates RBR to move into the nucleus and to repress E2FB and cell division (Henriques *et al*, 2010).

In summary, TOR integrates auxin and nutrient signalling to regulate translation reinitiation. Selective protein translation of key transcriptional regulators could sensitise the second auxin perception system within the nucleus to

regulate auxin-responsive transcription. The TOR and S6K signalling pathway controls the balance between cell enlargement and cell proliferation through multiple mechanisms (Figure 1C), being critical for directional growth regulated by auxin.

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Conflict of interest

The authors declare that they have no conflict of interest.

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