



# DIGITAL ACCESS TO SCHOLARSHIP AT HARVARD

## Moving beyond translation: Glucose-TOR signaling in the transcriptional control of cell cycle

The Harvard community has made this article openly available. [Please share](#) how this access benefits you. Your story matters.

<b>Citation</b>	Xiong, Yan, and Jen Sheen. 2013. "Moving beyond translation: Glucose-TOR signaling in the transcriptional control of cell cycle." <i>Cell Cycle</i> 12 (13): 1989-1990. doi:10.4161/cc.25308. <a href="http://dx.doi.org/10.4161/cc.25308">http://dx.doi.org/10.4161/cc.25308</a> .
<b>Published Version</b>	<a href="https://doi.org/10.4161/cc.25308">doi:10.4161/cc.25308</a>
<b>Accessed</b>	February 19, 2015 2:23:59 PM EST
<b>Citable Link</b>	<a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:11855814">http://nrs.harvard.edu/urn-3:HUL.InstRepos:11855814</a>
<b>Terms of Use</b>	This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at <a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA">http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA</a>

*(Article begins on next page)*

# Moving beyond translation

## Glucose-TOR signaling in the transcriptional control of cell cycle

Yan Xiong<sup>1,2,\*</sup> and Jen Sheen<sup>1</sup>

<sup>1</sup>Department of Molecular Biology and Centre for Computational and Integrative Biology; Massachusetts General Hospital and Department of Genetics; Harvard Medical School; Boston, MA USA; <sup>2</sup>Shanghai Center for Plant Stress Biology; Chinese Academy of Sciences; Shanghai, P.R. China

All living organisms must integrate nutrient and energy availability with environmental signals to coordinate their growth and development. This is at least partially achieved by the multifaceted roles of a highly conserved ancient protein kinase, target-of-rapamycin (TOR), which has been identified as a central growth regulator that modulates nutrient status and energy signaling to promote cell proliferation and growth.<sup>1,2</sup> In mammals, TOR signaling has mainly been linked to amino acid sensing and insulin/growth regulator signaling. However, the mechanisms underlying responses of TOR to glucose as a universal fuel remained enigmatic in plants and animals.<sup>1,3</sup>

Limited evidence supports mammalian TOR signaling in direct transcriptional control. Most research has focused on the roles of TOR in translational control through phosphorylation of S6K1, as a versatile activator of translation, or eukaryotic translation initiation factor 4E (eIF4E)-binding proteins (4E-BPs) to facilitate the translation of mRNAs encoding proteins promoting cell cycle progression.<sup>1,4</sup> Very recently, S6K1 was reported to stimulate the synthesis of nucleotides during S-phase progress of the cell cycle through posttranslational regulation of CAD (carbamoyl-phosphate synthetase2, aspartate transcarbamoylase, dihydroorotatase), the enzyme catalyzing the first three steps of de novo pyrimidine synthesis.<sup>5</sup>

Postembryonic growth and development in plants strictly relies on glucose availability.<sup>3</sup> By exploring the regulatory mechanisms at the transition checkpoint

of heterotrophic to photoautotrophic conversion in Arabidopsis seedlings, we discovered that TOR senses and transduces shoot photosynthesis-derived glucose signals through glycolysis and mitochondria energy relay to specifically control the proliferation of stem/progenitor cells in the root meristem.<sup>2</sup> Surprisingly, genome-wide expression profiling revealed that glucose-TOR signaling orchestrates global transcriptional reprogramming, which simultaneously regulates transcription, bioenergetics, metabolism, biosynthesis, signaling, folding, transport and cell cycle.<sup>2</sup> Remarkably, TOR, but not S6K1, directly phosphorylates the N terminus of E2Fa and promotes its activity in transcriptional activation of S-phase genes.<sup>2</sup> This finding uncovered a previously unrecognized TOR function in direct transcriptional regulation of cell cycle, which is beyond its well-known functions in stimulating the translation of proteins involved in cell cycle progression.<sup>1</sup>

The specific phosphorylation of E2Fa by TOR kinase provided a compelling example for how glucose-TOR signaling controls transcription of S-phase genes to promote root meristem activation. However, other related E2Fs might provide partially overlapping functions in the root meristem or in the meristem of other plant organs. There are six members in the Arabidopsis E2F gene family, but only E2Fa and E2Fb share overlapping functions in binding to and activating the promoters of S-phase genes. It is likely that E2Fb is also phosphorylated and regulated by glucose-TOR signaling. E2Fc exhibits different expression patterns and

does not appear to regulate the same cell cycle genes as E2Fa, and the atypical E2F members (E2Fd-f/DEL) were shown to exert distinct functions as repressors of gene transcription.<sup>6,7</sup> Future studies will be required to determine the precise target genes and functions of different plant E2Fs. Besides E2Fs, we also revealed that glucose-TOR signaling modulated other positive and negative regulators of the root meristem activity, e.g., the upregulation of root growth factor genes (*RGF6/9*) and genes in the glutathione synthesis pathway required for cell cycle progression, and the downregulation of *UPBI* encoding a bHLH transcription factor promoting root differentiation. The findings suggest that TOR controls a host of effectors and transcription factors for the concerted activation of cell proliferation in meristems (Fig. 1). Although the *RGF6/9* transcripts are relatively low in the quiescent root meristems, these genes are highly activated by glucose-TOR signaling.<sup>2</sup> It will be important to investigate how TOR kinase phosphorylates and regulates the potentially distinct functions of diverse substrates in glucose-TOR signaling.

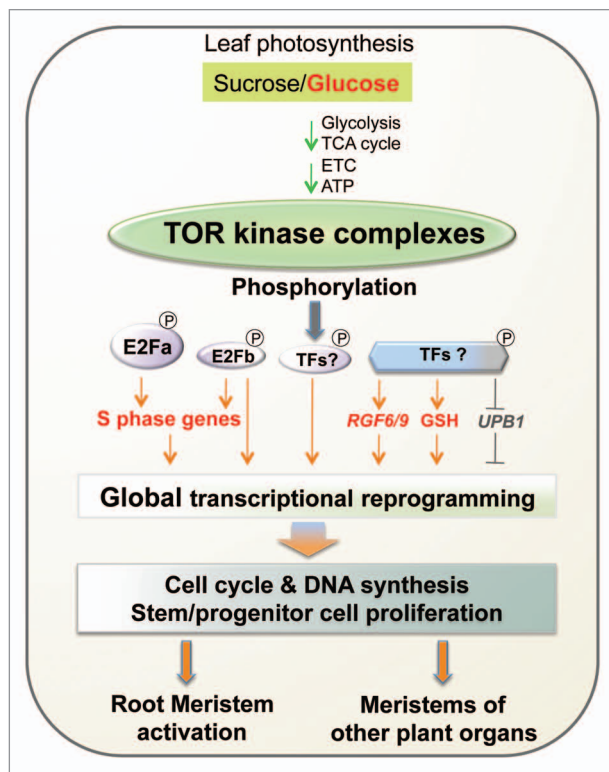
The rapid and global transcriptional reprogramming triggered by glucose-TOR signaling was not observed in animals or plants before our studies. Over the past decade, mostly long-term (18–24 h) or limited gene expression changes have been observed in mammalian cultured cells after treatments with TOR inhibitors<sup>1</sup> or after partial reduction of TOR expression in growing plants supported by active photosynthesis.<sup>8</sup> The manifestation of gene expression changes might

\*Correspondence to: Yan Xiong; Email: xiong@molbio.mgh.harvard.edu

Submitted: 05/16/13; Accepted: 05/24/13

<http://dx.doi.org/10.4161/cc.25308>

Comment on: Xiong Y, et al. Nature 2013; 496:181-6; PMID:23542588; <http://dx.doi.org/10.1038/nature12030>



**Figure 1.** Model of glucose-TOR signaling in transcriptional regulation of cell cycle. Leaf photosynthesis-derived glucose is indispensable for activating TOR kinase via glycolysis and mitochondrial bioenergetic relay to control a host of effectors and transcription factors for the concerted activation of the proliferation of progenitor and stem cells in meristems. ETC, electron transport chain; *RGF*, root growth factors; *UPB1*, UPBEAT1 transcription factor; *GSH*, the glutathione synthesis pathway; TFs, transcription factors.

take longer, as the mammalian experiments were conducted at the condition with constitutively high TOR activity stimulated by insulin, serum, amino acids or *tsc* (tuberous-sclerosis-complex) mutants when TOR inhibitors were applied. The unique experimental design using the 3-d-after-germination seedlings

at the heterotrophic to photoautotrophic transition checkpoint, exhibiting normal growth and development in the absence of photosynthesis or exogenous sugars, offered a low TOR signaling background to observe rapid, dynamic and clear glucose induction in global transcriptional changes.<sup>2</sup> Therefore, it appears crucial to

probe the rapid changes in TOR-mediated transcriptome in a bioenergetically quiescent state with minimal TOR signaling background before adding specific TOR-stimulating signals and TOR inhibitors. Cell cycle regulation occurs mostly in meristems of intact plants, enriching the meristem tissues and cells for expression profiling is also critical to reveal the clear involvement of glucose-TOR signaling in the control of S-phase genes. As glucose is a universal fuel and metabolic/biomass precursor for most cells, the unexpected findings in plants may illuminate future research on novel and fundamental regulatory mechanisms in glucose-TOR signaling in plants, animals and humans, which share complexity in cell cycle controls by nutrient and energy signaling through communication and coordination among different organs.

#### References

1. Laplante M, et al. Cell 2012; 149:274-93; PMID:22500797; <http://dx.doi.org/10.1016/j.cell.2012.03.017>
2. Xiong Y, et al. Nature 2013; 496:181-6; PMID:23542588; <http://dx.doi.org/10.1038/nature12030>
3. Xiong Y, et al. J Biol Chem 2012; 287:2836-42; PMID:22134914; <http://dx.doi.org/10.1074/jbc.M111.300749>
4. Dowling RJ, et al. Science 2010; 328:1172-6; PMID:20508131; <http://dx.doi.org/10.1126/science.1187532>
5. Ben-Sahra I, et al. Science 2013; 339:1323-8; PMID:23429703; <http://dx.doi.org/10.1126/science.1228792>
6. de Jager SM, et al. Plant Mol Biol 2009; 71:345-65; PMID:19662336; <http://dx.doi.org/10.1007/s11103-009-9527-5>
7. Lammens T, et al. Trends Cell Biol 2009; 19:111-8; PMID:19201609; <http://dx.doi.org/10.1016/j.tcb.2009.01.002>
8. Dobrenel T, et al. Frontiers in Plant Biology 2013; <http://dx.doi.org/10.3389/fpls.2013.00093>