

# A Tale of Two Torcs and How They Differentially Regulate Cell Growth

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All organisms are equipped to adapt their metabolism, cell size and cell numbers in response to nutrient availability. In eukaryotes, the regulation of growth is controlled by the TOR signaling pathway, which senses nutrient dependent signals and controls diverse aspects of cellular metabolism.

In *Drosophila*, this pathway is managed by two complexes that both involve the evolutionarily conserved TOR protein kinase: TOR complex (TORC) 1 and TORC2. TORC1, whose core components include the proteins TOR, Raptor and LST8, controls protein synthesis in response to growth factors (e.g., insulin) and nutrients (e.g., amino acids). TORC2, whose core components include the proteins TOR, Sin1, Rictor and LST8, regulates cell survival, cell cycle progression, and metabolism by phosphorylating and activating other effector kinases. There is mounting evidence that TORC2 may also be involved in regulating cell growth (e.g., by establishing and maintaining protein synthesis). However, unlike TORC1, it is less clear what activates TORC2, including whether or not it is regulated through TORC1.

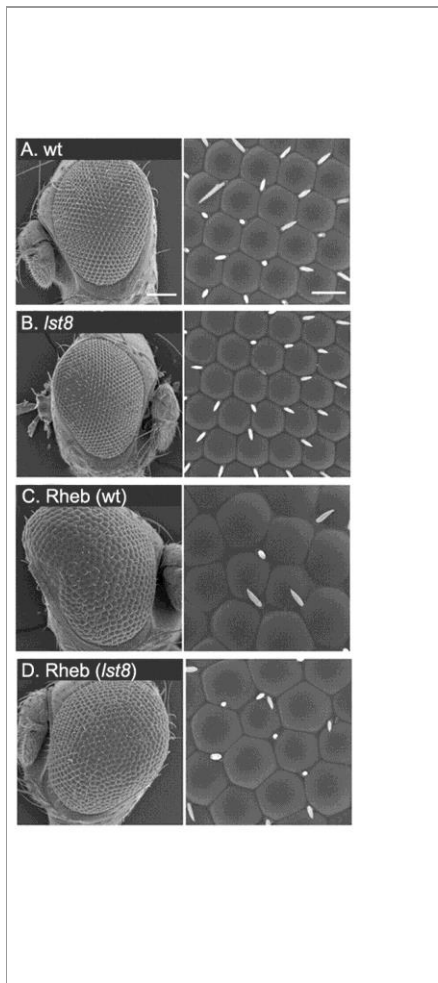
To understand whether TORC2 affects cell growth independently of TORC1, Dr. Tao Wang and colleagues in Dr. Bruce Edgar's lab (formerly of the Basic Sciences Division) knocked out the first exon of *lst8* using homologous recombination. Although LST8 binds TOR and associates with both TORC1 and TORC2 core complexes, the authors find that it is only required for TORC2 function and not TORC1 activity. However, flies homozygous for the *lst8* mutation, which are otherwise normal in appearance, do exhibit a ~25% reduction in body size compared to their wild-type counterparts, with all tissues affected to a similar extent. Moreover, upon examination of eye, wing and fat body cells in *lst8* mutant flies, the authors found that this reduction in growth is due to a reduction in cell size, not a reduction in cell number. This suggests that TORC2 does indeed regulate cell growth independently of TORC1 and reflects the findings of other studies that observed reduced body sizes in mice, *Drosophila* and *Caenorhabditis elegans* with disrupted TORC2 complexes following genetic silencing of *rictor*.

To then ascertain whether the loss of *lst8* affects growth cell autonomously or systemically (e.g., through extracellular signaling molecules as previously found for *C. elegans rictor* mutants), the

authors generated genetic mosaic flies where homozygous *Ist8* mutant cells were introduced into heterozygous *Ist8* flies. In this context, homozygous *Ist8* mutant cells were smaller than neighboring heterozygous cells, indicating that *Ist8*, and thus TORC2, regulates growth cell autonomously.

Although the authors did not uncover the mechanism by which TORC2 regulates cell growth, they did rule out TORC2 signaling through AKT, a potent oncogene that has been implicated in many cancers. Not only does this finding further support the identification of TORC2 as a new therapeutic target in cancers of deregulated cell growth, but the group's discovery that TORC2 growth regulation is cell autonomous suggests that locally applied inhibitors of LST8 or TORC2 could provide less toxic chemotherapies.

[Wang T, Blumhagen R, Lao U, Kuo Y, Edgar BA](#). 2012. LST8 Regulates Cell Growth via Target-of-Rapamycin Complex 2 (TORC2). *Molecular and Cellular Biology* 32:2203-13.



*Image modified from manuscript.*

LST8 is a protein that associates with two cellular complexes that regulate cell growth, TORC1 and TORC2. *Drosophila* homozygous for a deletion in *Ist8* exhibit reduced cell size in all tissues. However, this affect appears to be attributable to TORC2 alone, as the activity of TORC1 is not affected by the loss of *Ist8*. Shown here is a compound eye and a magnification of its cells (left and right images of each panel, respectively) corresponding to a) a wild-type fly, b) a fly homozygous for the *Ist8* deletion where the size of all tissues are reduced by ~25%, c) a fly where local overexpression of the Rheb protein selectively upregulates TORC1 activity, resulting in increased cell growth, and d) a fly homozygous for the *Ist8* deletion where Rheb activation of TORC1 is unaffected by the loss of *Ist8*. Scale bars represent 100 micrometers.