CELL SIGNALLING

Cilia downsize mTORC1

> “the bending of cilia by fluid flow activates the LKB1 … pathway … to downregulate mTOR signalling and inhibit cell size.”

The mammalian target of rapamycin (mTOR) signalling pathway, which is driven by the multi-protein complexes mTOR complex 1 (mTORC1) and mTORC2, regulates cell size in response to growth factors and amino acids. Primary cilia, the assembly of which depends on kinesin molecular motors, serve as sensory organelles and signalling platforms. Boehlke *et al.* now show that the bending of cilia by fluid flow activates the LKB1 (also known as STK11) pathway tumour suppressor to downregulate mTOR signalling and inhibit cell size.

mTOR signalling is deregulated in polycystic kidney disease, in which mutations in ciliary proteins result in a failure to sense urine flow. As cells that line kidney cysts are enlarged, the authors postulated that cilia might regulate mTOR signalling and cell size. They first investigated whether loss of primary cilia affects cell size *in vivo*. Mouse kidneys with a mutation in the Kinesin-2 family member KIF3A lose cilia and have larger collecting duct cells than control animals, suggesting that primary cilia regulate cell size. The authors next generated a Madin–Darby canine kidney (MDCK) cell line in which KIF3A could be conditionally knocked down (termed KIF3A-i). These cells lack cilia and are larger than control cells when grown under fluid flow. Thus, loss of cilia increases cell size *in vivo*, and *in vitro* in the presence of flow.

Do cilia regulate cell size through mTOR? Under flow, the phosphorylation of mTOR and its downstream target S6 kinase (S6K) — a marker of mTORC1 activity — decreases in control cells but not in KIF3A-i cells, suggesting that cell size is mediated through cilia-dependent downregulation of the mTOR pathway. To test this further, the authors inhibited mTORC1 in KIF3A-i cells under flow, which resulted in decreased cell size despite the loss of cilia. Conversely, mTORC1 activation in ciliated MDCK cells counteracted the flow-mediated reduction in cell size. Thus, the mTOR pathway and cell size are downregulated by the mechanical stimulation of cilia.

Finally, the authors sought to identify how mTORC1 is regulated by cilia. LKB1 phosphorylates AMP-activated protein kinase (AMPK), enabling it to inhibit mTORC1. The authors observed that knockdown of LKB1 in MDCK cells decreased AMPK phosphorylation and increased cell size in the presence of flow. Phosphorylation of S6K also increased, demonstrating that the size increase of LKB1-deficient cells is accompanied by mTOR activation. As LKB1 localizes to cilia and the basal body, and phosphorylated AMPK accumulates here under flow, the authors propose that “bending of the cilium by flow activates the LKB1 pathway in the cilia-basal body compartment to inhibit mTORC1 activity and cell size”.

This study provides another important example of how cilia can regulate key signalling cascades and adds yet another level of control — mechanosensing — to the already complex mTOR signalling pathway.

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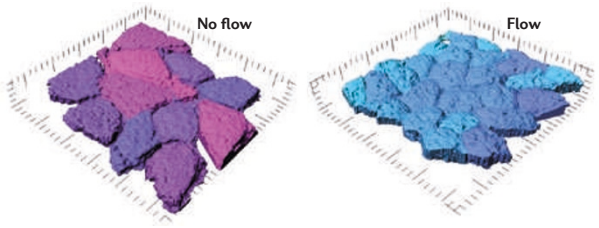

Reduced cell size under flow, as shown by three-dimensional reconstruction of cell volumes in cells with stained membranes. Image courtesy of W. Kuehn, Albert-Ludwig-University of Freiburg, Germany.

ORIGINAL RESEARCH PAPER Boehlke, C. *et al.* Primary cilia regulate mTORC1 activity and cell size through Lkb1. *Nature Cell Biol.* **12**, 1115–1122 (2010)