CELL SIGNALLING

Regulation and crosstalk

CORBIS

The expansion of the Salvador (SAV)–Warts (WTS)–Hippo (HPO) pathway continues with three recent papers that extend the list of upstream regulators and identify links to Wnt signalling.

Richardson and colleagues had previously noted that loss of function of the tumour suppressor Lethal (2) giant larvae (L(2)GL) in the developing eye of *Drosophila melanogaster* results in aberrant proliferation and cell survival. A similar effect is also seen when atypical protein kinase C (aPKC) or Crumbs (CRB) are overexpressed. L(2)GL, aPKC and CRB regulate apicobasal polarity, so their effect on proliferation and survival was intriguing. Further examination of the loss of L(2)GL expression or overexpression of aPKC or CRB in eye epithelial cells showed increased expression of genes that are targets of the transcription co-activator Yorkie (YKI), the activity of which is suppressed by the SAV–WTS–HPO kinase pathway. So, why is the HPO pathway inactive in cells that have lost L(2)GL expression? HPO and Ras-associated domain family protein (RASSF) are mislocalized, with both present in the basal region of the cell. RASSF competes with SAV for HPO binding and so functions as an inhibitor of HPO. L(2)GL and aPKC work in opposition to one another, explaining why the loss of one and overexpression of the other induces the same phenotype. However, overexpression of CRB resulted in the mislocalization of the FERM domain protein Expanded (EX), a known regulator of the HPO pathway.

Robinson *et al.* were also interested in the overgrowth phenotype that results from the increased activity of CRB. Their experiments in *D. melanogaster* wing discs showed that the expression of an oncogenic form of CRB (the transmembrane region and the 37 amino acid intracellular domain) resulted in the loss of EX from the apical membrane and reduced protein expression levels of EX through an uncharacterized post-translational mechanism. This resulted in the increased activity of YKI. Conversely, loss of CRB function increased the expression of EX, with the excess protein being mislocalized. So how does CRB regulate EX? The intracellular portion of CRB has two domains: a juxtamembrane FERM-binding motif (JM) that facilitates interaction with FERM-domain proteins, and a carboxy-terminal PDZ-binding motif (PBM) essential for the interaction with proteins that constitute the CRB polarity complex. Further experiments showed that the effects of increased or reduced expression levels of CRB on EX that result in increased YKI activity map to the JM domain of CRB. However, despite the fact that both EX and CRB contain a FERM domain, numerous approaches failed to detect a direct interaction between these proteins, indicating that other proteins are probably involved.

Varelas *et al.* were investigating regulators of the Wnt pathway in mammalian cells using cDNA expression, small interfering RNA and protein–protein interaction assays. They found that changes in the expression of the transcriptional regulator TAZ, an orthologue of YKI, affected WNT3A signalling and that TAZ bound the Wnt intracellular signalling mediator dishevelled 2 (DVL2). Knock down of endogenous TAZ induced transcription of WNT3A target genes and increased the nuclear accumulation of β-catenin. The authors found that TAZ inhibits the phosphorylation of DVL2 by casein kinase 1ε (CK1ε) and CK1δ in response to WNT3A by preventing the interaction between DVL2 and CK1ε. TAZ is regulated by LATS and MST, mammalian orthologues of HPO pathway components. Further experiments showed that the phosphorylation of TAZ by LATS1 resulted in its localization to the cytoplasm where it can bind DVL2 and inhibit WNT3A signalling. Loss of LATS1 resulted in the nuclear accumulation of TAZ and activation of the Wnt pathway.

Together, these papers uncover more molecular links between cell polarity, cell division and cell fate.

Nicola McCarthy, Chief Editor,
Nature Reviews Cancer

ORIGINAL RESEARCH PAPERS Greschik, N. A. *et al.* Lgl, aPKC and Crumbs regulate the Salvador/Warts/Hippo pathway through two distinct mechanisms. *Curr. Biol.* **20**, 573–581 (2010) | Robinson, B. S. *et al.* Crumbs regulates Salvador/Warts/Hippo signaling in *Drosophila* via the FERM-domain protein Expanded. *Curr. Biol.* **20**, 582–590 (2010) | Varelas, X. *et al.* The Hippo pathway regulates Wnt/β-catenin signaling. *Dev. Cell* **18**, 579–591 (2010)
FURTHER READING McNeill, H. & Woodgett, J. R. When pathways collide: collaboration and connivance among signalling proteins in development. *Nature Rev. Mol. Cell Biol.* **11**, 404–413 (2010)

these papers uncover more molecular links between cell polarity, cell division and cell fate.