TUMOUR SUPPRESSORS

Expanding the pathway

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URLs

Fat

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&md=Retrieve&dopt=full_report&list_uids=33627

Cyclin E

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&md=Retrieve&dopt=full_report&list_uids=34924

DIAP1

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&md=Retrieve&dopt=full_report&list_uids=39753

Expanded

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&md=Retrieve&dopt=full_report&list_uids=33218

Merlin

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&md=Retrieve&dopt=full_report&list_uids=32979

FAT4

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&md=Retrieve&dopt=full_report&list_uids=79633

Since its discovery there has been much interest in the Salvador–Warts–Hippo (Sav–Wts–Hpo) growth-regulating pathway, which was first described in *Drosophila melanogaster* and is conserved in humans. Three groups, led by Georg Halder, Kieran Harvey, and Helen McNeill and Nick Tapon, have identified the atypical cadherin **Fat** as an upstream regulator of this pathway.

The Sav–Wts–Hpo pathway limits organ size by restricting cell growth and proliferation, and by activating apoptosis. Using *D. melanogaster* eye and wing discs as models for tissue growth, the groups showed that loss of the tumour suppressor Fat induces tissue overgrowth, unperturbed cell cycling and an inability to enter senescence. This phenotype is the same as that generated by the loss of Sav–Wts–Hpo signalling in these tissues, in part owing to the deregulated expression of the Sav–Wts–Hpo target gene **cyclin E**. Intriguingly, although the anti-apoptotic protein **DIAP1** accumulates in *fat* mutant tissue, *fat* seems to be dispensable for developmental apoptosis. All three groups show that Fat is genetically

and biochemically upstream of, and a positive regulator of, members of the Sav–Wts–Hpo signalling pathway.

Fat is a large transmembrane receptor, and the groups show that Fat functions upstream of **Expanded** (Ex), one of the upstream components of the Sav–Wts–Hpo pathway. Fat is required for the stability and/or localization of Ex to the apical membrane of epithelial tissues. However, Fat was not required for the localization of **Merlin**, another upstream component, indicating that Merlin probably interacts with an alternative membrane-associated protein in a parallel pathway to Fat–Ex.

Together, these papers show that the Sav–Wts–Hpo pathway can respond to extracellular signalling through Fat and potentially other transmembrane receptors. However, the growth-regulatory signal remains unknown. In addition, the closely conserved human homologue of Fat, **FAT4**, is uncharacterized.

Deregulation of the Sav–Wts–Hpo pathway in human tumours has been reported. Therefore, identifying the signals that activate this pathway might have important

implications for our understanding of tumorigenesis and the treatment of cancer.

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ORIGINAL RESEARCH PAPERS Bennett, F. C. & Harvey, K. F. Fat cadherin modulates organ size in *Drosophila* via the Salvador/Warts/Hippo signalling pathway. *Curr. Biol.* 12 Oct 2006 (doi: 10.1016/j.cub.2006.09.045) | Silva, E., Tsatskis, Y., Gardano, L., Tapon, N., & McNeill, H. The tumour-suppressor gene *fat* controls tissue growth upstream of Expanded in the Hippo signalling pathway. *Curr. Biol.* 19 Sep 2006 (doi: 10.1016/j.cub.2006.09.004) | Willecke, M. *et al.* The Fat cadherin acts through the Hippo tumour-suppressor pathway to regulate tissue size. *Curr. Biol.* 19 Sep 2006 (doi: 10.1016/j.cub.2006.09.005)