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Journal club

FROM HIPPOS TO YORKIES IN ONE PATHWAY

In 2005, Duojia Pan's laboratory at Johns Hopkins University, Maryland, USA, reported a major discovery: they had identified Yorkie, the *Drosophila melanogaster* homologue of YAP and TAZ, as the key effector of the Hippo signalling pathway. Until this point, the Hippo pathway was known to consist of a series of tumour suppressor proteins, including the upstream Hippo kinase and downstream Warts kinase (LATS1 and LATS2 are homologues in mammals), but the mechanism by which they controlled growth was a mystery. The identification of Yorkie as the missing link between Warts and the control of transcription revolutionized the field of Hippo signalling and is proving to have a profound impact on cancer research.

The name Yorkie was chosen because the small size phenotype of the *D. melanogaster yorkie*-mutant tissues was reminiscent of Yorkshire Terriers, one of the smallest breeds of dog. However, Yorkie was not actually identified by its mutant phenotype but rather by a yeast two-hybrid screen for novel binding partners of the Warts kinase, which was also shown to directly phosphorylate Yorkie.

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Interestingly, the overexpression of Yorkie phenocopied the *warts*-mutant phenotype, causing tumour-like overgrowth; this suggested that Warts phosphorylation inhibited Yorkie, which is now a well-established fact. Loss of function of Yorkie reduced cell proliferation and increased apoptosis in a similar manner to the gain of function of Warts activity. Finally, epistasis experiments convincingly placed Yorkie downstream of Warts genetically.

The molecular mechanism of Yorkie function was revealed by fusing Yorkie to the yeast Gal4 DNA-binding domain, which demonstrated that it is a potent activator of transcription. Importantly, this transcriptional activity was suppressed by the activation of Hippo–Warts signalling, and this study thus identified transcriptional regulation as a crucial output of this signalling pathway.

Today, the Hippo–Warts–Yorkie pathway is presented in lectures and textbooks around the world, and it is hard to imagine that, just 10 years ago, the basic mechanism of this pathway was unclear. This finding by Pan and colleagues greatly aided research in this field, and the Hippo–YAP and Hippo–TAZ signalling pathways are now emerging as some of the most exciting new control mechanisms in both human stem cells and cancer.

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ORIGINAL RESEARCH PAPER Huang, J. *et al.* The Hippo signaling pathway coordinately regulates cell proliferation and apoptosis by inactivating Yorkie, the *Drosophila* homolog of YAP. *Cell* **122**, 421–434 (2005)