CANCER GENETICS

Networking on the fly

There are now many ways in which genes that are mutated in particular cancer types can be identified, including starting from less genetically complex organisms such as *Drosophila melanogaster*. Kevin White and colleagues have taken this approach and have identified SPOP as a protein that is overexpressed in renal cell carcinoma (RCC).

D. melanogaster has proved particularly useful for identifying gene networks that are conserved throughout evolution. White and colleagues started with two pair-rule genes — *eve* and *ftz* — homeobox genes that are part of a gene network often disrupted in human disease. Using a variety of information about Eve and Ftz, they built a predictive gene network model. Initially, gene expression patterns from wild-type embryos or embryos with mutated *eve* or *ftz* taken over a time course of 2–7 hours after egg laying (AEL) were compared. Chromatin immunoprecipitation analysed on DNA microarrays (ChIP–chip) was also used to map Eve and Ftz DNA binding sites 2 hours AEL. Genes that were both differentially expressed and identified by the ChIP–chip approach were considered as putative targets: 137 Ftz target genes and 98 Eve target genes. To extend the network further, the authors then added in information on the target genes obtained from automated literature-mining techniques and yeast two-hybrid protein–protein interaction data. The resulting network contained 4,084 genes and proteins and 6,648 interactions between them.

Having tested that specific links within the network behave as expected, the authors analysed the 150 genes that have validated human homologues. The top candidate (a major network hub) was *roadkill* (*rdx*), which is 79% identical to the human protein SPOP. The network model indicated that D-SPOP (Rdx) is a Ftz target 2–3 hours AEL and then becomes an Eve target 6–7 hours AEL, and that D-SPOP interacts with the Jun kinase phosphatase Puckered (Puc). Further analyses indicated that D-SPOP and Puc interact and this is important for the regulation of Eiger (tumour necrosis factor)-induced apoptosis in neurons. Indeed, the authors found that D-SPOP, like human SPOP, can induce protein ubiquitylation and degradation, and D-SPOP induced the degradation of Puc, which functions to inhibit Eiger-mediated JUN N-terminal kinase-induced apoptosis.

As homologues of Eve and Ftz targets are involved in tumorigenesis in humans, the authors investigated whether SPOP shows altered expression in tumours using a human tissue microarray. They found that SPOP is highly expressed in 85% of RCCs, whereas the protein is expressed at a low level in normal kidney tissue. Moreover, they found that SPOP expression can be used to identify different types of RCC. In clear cell RCC, which in some cases can be difficult to distinguish from other types of RCC, 99% of cases were positive for SPOP expression, as were 86% of chromophobe RCCs, whereas only 22% of papillary-type RCCs were positive.

The authors conclude that analysing gene networks on the basis of information in *D. melanogaster* is an effective method for understanding the biological function of these networks, for identifying conserved gene networks and identifying new genes within these networks that are deregulated in human disease.

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ORIGINAL RESEARCH PAPER Liu, J. *et al.* Analysis of *Drosophila* segmentation network identifes a JNK pathway factor overexpressed in kidney cancer. *Science* 22 Jan 2009 (doi 10.1126/science1157669)