lineages in *Pdx1*$^{-/-}$ mice, indicating that *Ptf1a* might be expressed early in all pancreatic precursors. Immunohistochemical time-course studies confirmed that this expression is subsequently turned off in endocrine cells.

The authors' demonstration that *Ptf1a* expression is essential for cells to adopt and maintain pancreatic fate has important therapeutic potential. So far, attempts to form pancreatic precursors *in vitro*, which could be used to treat diabetes using transplantation therapy, have failed. It might be that with their discovery of the early role of *Ptf1a*, Kawaguchi and colleagues have uncovered one of the missing key players.

Magdalena Skipper

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just how many convergent signals it takes to make a vertebrate jaw remains to be seen.

Tanita Casci

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WEB SITE

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CANCER GENETICS

Dual control

Driving-instructors' cars are equipped with dual controls, but this might not always be a sensible safety feature. Cell-cycle exit and apoptosis are two crucial processes by which cells limit proliferation, so genes that control both of these would be a prime target for mutation in tumorigenesis. Now, Iswar Hariharan and colleagues have identified a *Drosophila* gene, *salvador* (*sav*), that regulates both of these processes; the human orthologue is also mutated in cancer cell lines.

The development of the *Drosophila* eye is tightly regulated — cell proliferation occurs throughout the larval stage, differentiation occurs during the late larval and pupal stages, and excess cells are eliminated by apoptosis. These characteristics make it an ideal system to screen for mutations that alter cell proliferation or apoptosis. The authors have identified mutations in at least 23 loci that, when homozygous mutant, cause an over-representation of mutant cells compared with wild-type cells, making them good candidates for tumour-suppressor genes. One of these, *sav*, was characterized further.

An increase in cell number could be caused by an increase in proliferation or a decrease in apoptosis, so both of these processes were examined in turn. In *sav* mutants, ectopic BrdU incorporation was observed posterior to the morphogenetic furrow — which moves from the posterior to anterior of the eye, causing cells to arrest, after which they synchronously enter S phase. This indicates that these cells continue to proliferate after wild-type cells have arrested. Flow-cytometry analysis confirmed that *sav* mutants are delayed in exiting the cell cycle.

However, this delay in cell-cycle exit is not sufficient to account for the increase in cell number, so might apoptosis also be inhibited in *sav* mutant cells? TUNEL analysis revealed that cell death seemed to be mostly confined to the wild-type regions of the eye. Hid and Rpr, which target the caspase inhibitor DIAP1, were unable to induce apoptosis in *sav*-mutant cells. DIAP1 protein levels remained high and the effector caspase Drice was not cleaved to generate the active form.

The *sav* gene was sequenced and contained two putative WW domains, which are involved in protein–protein interactions. The *warts* (*wts*) gene was also identified in the mutant screen and was shown to have a similar phenotype to *sav* in regulating cell-cycle exit and apoptosis. It contains five PPXY motifs, to which WW domains bind, and a precipitation experiment with GST-tagged Sav confirmed that Sav and Wts interact.

So, two genes have been identified that, when mutated, confer a selective advantage to cells. Might they be mutated in cancer cells? The human orthologue of *sav*, *WW45*, was sequenced in 52 tumour-derived cell lines, and *WW45* was altered in three of these. Two renal-cancer cell lines — ACHN and 786-O — had deletions in *WW45* that would inactivate the protein.

The authors have therefore identified a new potential tumour suppressor, and have proved, yet again, that *Drosophila* can be a useful model organism for cancer research.

Emma Greenwood, Associate Editor,
Nature Reviews Cancer

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Iswar Hariharan's lab:
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