in particular? The authors suggest that as Hh is a known stem-cell factor and a mitogen in the developing cerebellum, this pathway might allow cancerous stem cells to continuously undergo self-renewal. The high expression levels of the neuronal stem-cell marker nestin in mouse and human tumours supports this theory. If they can be used in humans, Hh antagonists might be developed as a useful therapy for this cancer.

*Kristine Novak*


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**Nature's Alliance for Cell Signalling (AfCS) update (Hedgehog signalling models: taking the rough with the Smoothened):**
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**Philip Beachy's lab:**
http://www.bs.jhmi.edu/mbg/dept/beachy.html


CELL PROLIFERATION

# 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 proliferation or apoptosis. The authors have identified mutations in at least 23 loci that, when homozygous, 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*


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**Iswar Hariharan's lab:**
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