Of life, death, and the wings of a fly

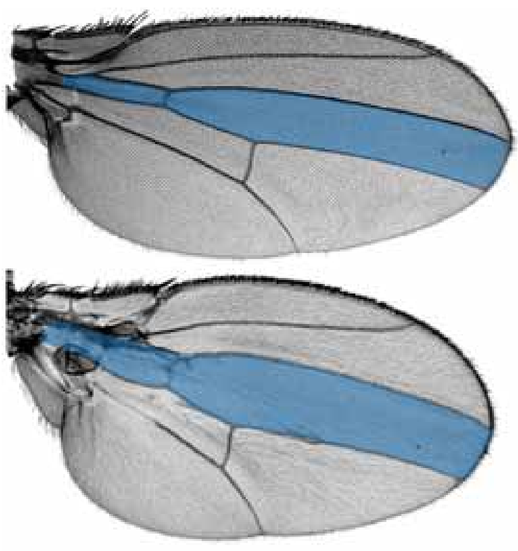
Unraveling the connections between growth and cell death

Looking to a fly's wings for the secrets of life and death sounds poetic, like looking for fear in a handful of dust, but it has become a practical pursuit in the lab of Steve Cohen. His group is working on how cells form patterns in the bodies of developing organisms, and along the way they are discovering the functions of genes that have control over cells' fates.

Cells receive instructions in the form of molecules – often secreted by neighboring cells – that tell them when to divide, how to differentiate and behave, and when to die. Curiously, the same molecule can trigger different processes. That might not be surprising in cells which are strikingly different from each other – say, a neuron and a skin cell – because they produce very diverse sets of molecules, creating completely new contexts for the interpretation of signals.

But some messages can have dramatically varied effects even in a single cell type. In recent years, for example, scientists have discovered that many signals that tell cells to divide can also trigger apoptosis, a genetic self-destruct program. That's useful for the same reason fire extinguishers are stored close to the site of a likely fire. If cell division gets out of control, it needs to be stopped quickly to avoid serious problems such as tumors. The best case would be to have a sort of "dead-man's switch" where cell division automatically shuts off, unless there are very clear instructions for it to continue. Steve and his colleagues think they've found an example of this.

David Hipfner, a postdoc in the lab, has been studying genes that play a role in both processes. Division, differentiation and death are tightly coordinated as an embryo develops. Understanding the control systems that determine how a signal is interpreted, he says, will help us understand what happens in diseases such as cancer, where cell division has gone haywire.



Left: David Hipfner and Steve Cohen, in front of a small selection of the 11,000 strains of flies that Steve's group has investigated in search of genes that control growth and other processes.

Above: Cells that produce too much of the protein Slik lead to larger tissues. In the lower wing, cells between the third and fourth veins express abnormally high amounts of the molecule. That makes this part of the wing larger than in a fly with normal amounts of Slik.

Drosophila has at least 13,500 genes, and Steve's group has been combing them one-by-one in search of molecules that influence cell division. In 2000 they completed an examination of nearly 11,000 strains of flies that had been modified to overproduce proteins from single genes. Each strain had to be carefully examined under the microscope in search of defects in tissue growth – about ten months of intense work.

The team discovered several strains of flies with abnormal growth in imaginal discs – structures that will give rise to adult body structures such as legs and wings – and they began investigating the genes involved. One of these, which they gave the name *Slik*, caused regions of the wing in which it was overexpressed to become slightly larger. They created a strain of *Drosophila* in which Slik doesn't function, to see what would happen.

If flies with too much Slik grow unexpectedly large, it's predictable that flies without it will be small, and that's what they found. "It's very dramatic," David says. "At a time when normal larvae have reached full size and stopped growing, the largest of the mutants is only a third of the normal size. When we looked into it, we realized that there was something else going on: the whole process of development was slowed down. The larvae that survived took three times as long to reach the final stage in larval life, and by the time they finally did, many of them had reached normal size."

If the cells of a fly embryo don't produce Slik, the embryo will develop much more slowly, and larvae will be much smaller (**below**) than their normal counterparts (**above**) at any given time. These larvae are five days old.

More work revealed that cells without Slik are able to differentiate normally, but they have what David calls an "intrinsic survival deficit" – something makes it hard for them to survive.

David and Steve decided to have another look at *Drosophila* that produce too much Slik protein. They discovered that this increases cell division in wing tissues – but simultaneously a higher level of cell death. The two effects balance each other out fairly well, explaining why tissues with too much Slik don't become enormous.

But what would happen if they blocked cells' ability to undergo apoptosis? Another round of experiments showed that this led Slik-producing cells to reproduce without constraint, creating much larger imaginal disks and tumor-like growths under the surface of the wing. Neighboring cells also start dividing at a high rate, probably because they receive signals that tell them it's the right thing to do.

How does Slik work, and how important is it? Is the molecule simply one "command line" in a long genetic program that stimulates cell growth (and death), or does it have a more powerful role? The scientists began looking for a link to familiar cell-division programs. They discovered that Slik works through a partner called *Raf*, which must be present for cells to feel its effects. The two molecules probably work together directly, by binding to each other. But more experiments showed that Raf isn't acting in its typical way – it's usually one step in a program that controls a pathway called *ERK*, which regulates cell division and survival, among other things. In this case it doesn't seem to be working along that pathway. This might hint, David says, at the existence of a new genetic program for tissue growth.

An offshoot of the project will now be to look at the closest human relative of Slik to see if it has the same dual functions in our tissues. Scientists are highly interested in such molecules because many of them are oncogenes – genes which lead to cancer when they are defective.

Is human Slik an oncogene? That's the next question, David says. What's important is that the latest experiments have strongly confirmed a hypothesis that cell division and death are inherently connected. A signal that triggers cell division may by its very nature prepare the cell to die.

In fact, there may not need to be another signal actively making this happen. Dividing cells may be pre-programmed to die – unless they get sufficient cues from their surroundings to go on living. It would be a safer type of programming for an organism. It would mean that cancer can't start simply through an increase in cell division; there would be a built-in brake that could only be released by a second defect. That would add an additional layer of security. Slik may be archetypal of such behavior.