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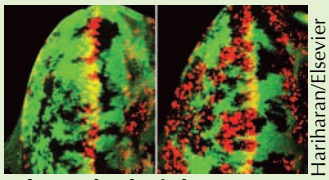
Stop and die


Hariharan/Elsevier

When *salvador* is lost (black patches, right image), replication (red) continues.

A single fly gene called *salvador* can both stop cell division and induce apoptosis, according to Nicolas Tapon, Iswar Hariharan, and colleagues (Massachusetts General Hospital, Charlestown, MA).

salvador is one of many genes that Hariharan isolated in a screen for cell growth mutants. Mitotic recombination in fly eyes rendered possible mutations homozygous. Then Hariharan's group (four postdocs working for two years) looked for mutant patches that grew larger than the corresponding wild-type patch. "One of the lessons is that there are many pathways that we know nothing about," says Hariharan. "That's why we did a phenotype-based screen, because that assumes nothing."

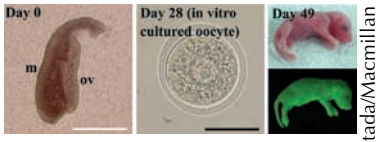
salvador appears to be part of a new pathway, but it can be tied to certain known cellular events. In late larval stages it induces cell cycle exit by down-regulating cyclin E, with cells lacking *salvador* undergoing one or more extra divisions. Then, in the pupal stage *salvador* is needed to down-regulate Diap1 (an apoptosis inhibitor) and thus induce apoptosis in the eye. This apoptosis eliminates extra cells that have not taken on a specific cell fate.

Both actions of *salvador* reduce cell numbers, but the logic for putting both functions in a single gene remains elusive. Clues may come from studies of the worm, mouse, and human homologues, or from inspection of human cancer cell lines, at least two of which have mutations in *salvador*. ■

Reference: Tapon, N., et al. 2002. *Cell.* 10.1016/S0092867402008243.

Brave new eggs

For anyone proposing to generate a clone army, or even to do therapeutic cloning for tissue repair, the culturing of oocytes is a major stumbling block. The poor success rate of cloning means that hundreds of oocytes are needed to receive transferred nuclei. Luckily, every woman has millions of oocytes. But almost all of those oocytes are trapped in an immature state that is not competent for either fertilization or productive receipt of a transferred nucleus.



Hatada/Macmillan

Culture and nuclear transfer make premeiotic female germ cells (left) fertilization competent.

Yayoi Obata, Izuho Hatada (Gunma University, Gunma, Japan), and colleagues have made some progress along these lines by successfully culturing female germ cells derived from mouse fetuses. Unfortunately, progression through meiosis and then efficient blastocyte development required successive nuclear transfers into the cytoplasm of mature oocytes. These nuclear transfer steps make this approach useless from the cloning point of view—you cannot get around the need for mature oocytes with a procedure that requires the use of mature oocytes. But Hatada points out that women about to undergo chemotherapy could store immature oocytes and then use a variation on his procedure to conceive later in life.

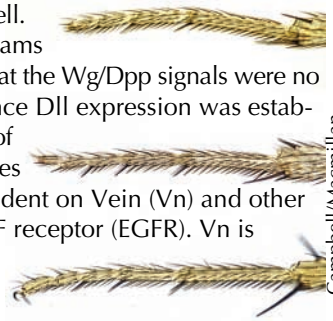
Hatada is not sure why the nuclear transfer steps are needed, although he points out that the in vitro cultured oocytes never reach the full size of a mature oocyte. For now, he is happy that his cultured oocytes establish imprinting, which will allow him to study this process in vitro. ■

Reference: Obata, Y., et al. 2002. *Nature.* 418:497–498.

Is that a fly in your leg?

A tantalizing finding from Gerard Campbell (University of Pittsburgh, Pittsburgh, PA) and Ibo Galindo, Juan Pablo Couso, and colleagues (University of Sussex, Brighton, UK) suggests that signaling pathways used in appendage development may be conserved between flies and mammals.

Until now, the fly and mammalian work had taken very different courses. Mammalian researchers concentrated on distal (i.e., near the fingers) FGF as a source of graded signals. But fly researchers felt that the key molecules were Wingless (Wg) and Decapentaplegic (Dpp), which are made in two stripes that intersect at the center of the area that will become a leg. (Fly larvae set up leg patterns in imaginal discs, flat layers of cells that later telescope out to form a limb.) Wg and Dpp act directly to turn on Distalless (Dll) and dachsund (dac), critical genes for leg formation. "Everyone assumed that if both of these were directly regulated, everything else must be as well," says Campbell.


Campbell/Macmillan

As EGFR function is decreased (bottom to top), fly legs get shorter.

Both research teams found, however, that the Wg/Dpp signals were no longer required once Dll expression was established. Expression of later patterning genes was instead dependent on Vein (Vn) and other ligands for the EGF receptor (EGFR). Vn is made where Wg and Dpp intersect at the center of imaginal disc, and thus could act as a source of graded signals akin to FGF. Campbell, in particular, showed that different levels of EGFR activity led to activation of different downstream genes, although Couso disputes a subset of these results.

FGF- and the EGF-related ligands both activate receptor tyrosine kinases and Ras, but the direct relationship between flies and mammals remains a stretch. "I cannot say they are homologous," says Couso. Campbell notes that the pathways may have skipped in and out of appendage development during evolution as they were co-opted for other functions. For now, he says, only one thing is sure: "You have to be very careful when you are dealing with all this evolutionary stuff." ■

References: Campbell, G. 2002. *Nature.* 10.1038/nature00971.
Galindo, M.I., et al. 2002. *Science.* 297:256–259.