DEVELOPMENTAL BIOLOGY

# Genes Seen Turning Imaginal Fly Eyes Into Reality

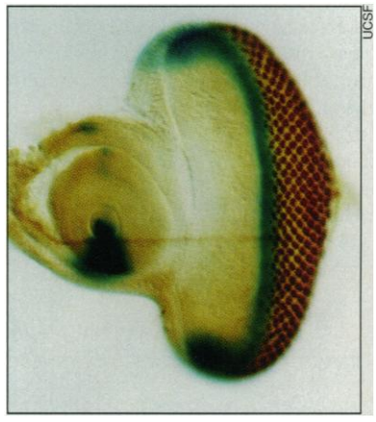
NASHVILLE, TENNESSEE—Deep within the larvae of most flies, beetles, moths, and butterflies lie quiescent but power-packed clusters of undifferentiated cells known as imaginal discs. In a process that developmental researchers would dearly love to understand, the discs suddenly explode into life during metamorphosis: While the rest of the larva withers, they generate all the specialized cells that make up the adult insect's body. Now, after gazing deeply into developing fly eyes, researchers have gotten a better look at genes that make one imaginal structure real.

The genes help control a feature called the "morphogenetic furrow." It's a wavelike indentation that sweeps across the eye imaginal discs of the fruit fly *Drosophila melanogaster*, transforming featureless cells into photoreceptors that make up the 800-some subunits of the fly's compound eye. The molecules driving the furrow on this crucial trip have eluded researchers. But at the national meeting of the Society for Developmental Biology 2 weeks ago in Nashville, developmental geneticist Ulrike Heberlein of the University of California, San Francisco, reported on four genes involved in the process. One, she says, helps kick off furrow movement, while a second controls furrow shape, and two more may play key roles in the signaling "loop" that inches the furrow forward.

These findings "make so much sense," says Kevin Moses, a developmental geneticist at the University of Southern California (USC) in Los Angeles, because they add to the picture of *Drosophila* eye development being assembled by a few laboratories around the world (*Science*, 24 March 1995, pp. 1766 and 1788). "We have this elephant, and we are the blind men patting it on all sides." And the way the work is coming together, he says, could mean that "with any luck, it's the same elephant under there." If the fly genetic program is anything like that in real elephants, then what the researchers are glimpsing may be replayed in vertebrates as well.

Scientists have been chasing the moving furrow for several years now, and they have identified several molecular signals that transform the cells it touches. In 1993, Heberlein was among two groups of researchers who showed that cells just behind it express the gene *hedgehog* (*hh*). That gene encodes a signaling protein that diffuses forward and triggers expression of the gene *decapentaplegic* (*dpp*) inside the furrow. There, *dpp* activates genes in some cells that eventually change them into "R8" photoreceptors, pivotal cells in each eye subunit or ommatidium.

But the researchers suspected that *dpp* might also be involved in furrow movement itself. They had found that *dpp* (but not *hh*) was expressed all around the rim of the imaginal disc before the furrow makes its appearance. Because the furrow starts from one spot on this rim—the disc's posterior tip, known as the optic stalk—that led to speculation that *dpp* could help push the furrow off, if the gene was somehow held in check everywhere else.




**Transformer.** A "furrow" that sweeps across a developing fly eye, turning cells into photoreceptors, may be launched by the gene *dpp (dark areas)*.

Indeed, last year two independent teams of developmental geneticists found a gene that could be acting as the brake on *dpp*. Moses and colleague Chaoyong Ma at USC and Jessica Treisman and Gerald Rubin at the University of California, Berkeley, showed that removing the gene *wingless* (*wg*) sent the furrow rushing inward from all the disc edges at once. The result was an eye with muddled clumps of ommatidia instead of the orderly rows produced by a normal furrow.

Researchers still were not sure that it was *dpp* that put the furrow in gear. So Heberlein and postdoctoral researcher Françoise Chanut decided to supercharge it, engineering the gene to be overexpressed while leaving on the *wg* brake. Souped-up *dpp* apparently overwhelmed *wg*, and the abnormal inrushing furrow appeared—direct proof that *dpp* can initiate the furrow.

The gene gets some help, though, in controlling the furrow's shape. Working with Treisman, now at New York University's Skirball Institute, Heberlein found a mutation in another, novel gene, *eyelid* (*eld*), that prevents the furrow from widening to wash over the entire eye disc, as it normally does while spreading away from the optic stalk. Based on this abnormality and related disruptions they observed in wing and leg imaginal discs, Heberlein and Treisman believe that *eld* normally attenuates *wg* expression, releasing the brake and allowing *dpp* to spread the furrow out.

A third set of experiments may help explain how the furrow, once under way, keeps rolling forward. This is a self-renewing process that can only occur if the *dpp*-expressing cells inside the furrow start expressing *hh*, to signal the cells in front of them to express *dpp* and draw the furrow ahead. Something has to activate *hh* expression—but what? Heberlein had been working with mutant flies in which part of the regulatory region of the *hh* gene is deleted, stopping the furrow from moving forward. And she observed that another gene called *Rough-eye* (*Roi*) compensates for this mutation, getting the furrow moving again. In mutants with increased *Roi* function, moreover, Heberlein found that *hh* expression was enhanced. Both observations suggested that *Roi* holds one of the keys to *hh*'s ignition.

That leads Heberlein to propose an intricate mechanism that could keep the furrow moving. Heberlein had previously shown that the same *hh* signal from behind the furrow that activates *dpp* also leaps ahead of the furrow to trigger expression of another gene, *atonal* (*ato*). *ato*, like *dpp*, helps turn certain cells into R8 photoreceptors. Perhaps *ato* also turns on expression of *Roi*, which in turn sends a signal that diffuses back into the furrow to activate *hh*, Heberlein suggests. That signaling loop would keep the furrow moving forward, one row of cells at a time.

The scenario "is completely plausible," says Moses, although he notes that other details of the furrow's movement remain to be worked out, including the identity of the gene or genes that work with *dpp* to launch the furrow in the first place. But similar molecular conversations may underlie metamorphosis throughout the fruit fly body. "One learns things from morphogenetic-furrow studies that suggest what to look for in other discs," says Larry Marsh, a developmental geneticist at the University of California, Irvine.

The fly-eye furrow could also provide clues to the workings of retinal development in vertebrates; indeed, one developmental biologist, William Harris of the University of California, San Diego, is already referring to an area on the perimeter of fish and frog retinas as the "fish/frog furrow." The eye imaginal disc, in other words, promises to keep researchers' imaginations working overtime.

–Wade Roush