A "Mitey" Theory for Gene Jumping

A tiny mite may have transferred the DNA sequences known as P elements into the common fruit fly from another Drosophila *species about four decades ago*

ACCORDING TO THE CLASSICAL TENETS OF biology, genes aren't supposed to jump from one species to another—you need sex to exchange genes. But molecular geneticists noticed that sometime around 1950, *Drosophila melanogaster*, the common lab fruit fly, had apparently acquired movable bits of DNA, known as P elements, from some other species. Since then, these "jumping genes" have spread like wildfire so that today, essentially all fruit fly populations, except those maintained in isolation in the lab, carry P elements. But while the spread is no doubt attributable to sexual mating, how did P elements jump into that first fruit fly?

Now, new results from Marilyn Houck, Margaret Kidwell, and their colleagues at the University of Arizona, Tucson, may provide an explanation—and one with controversial evolutionary implications. On page 1125, they report that P elements may have been transferred into *D. melanogaster* from another *Drosophila* species, *D. willistoni*, by a tiny parasitic mite that lives in association with both species. "It's an exciting finding, and not just in terms of the P element," says evolutionary biologist John McDonald of the University of Georgia in Athens. While there have been other reports of possible gene transfer between species, principally by viruses, this is, he notes, the first indication that "a mite or anything like that" can do it. And in a related article on page 1110, William Engels' group at the University of Wisconsin, Madison, describes new findings that may not only help explain how P elements were able to spread through natural fruit fly populations in such a short time, but should also provide a major improvement in the techniques for introducing new genes into *Drosophila* (see box).

Transfer of genetic material, especially P elements, between species might have a major impact on evolution. The elements are "transposons," DNA sequences that can move around in the genome, causing mutations if they happen to land in genes or their regulatory sequences. "Invasion of a new transposon could be a major source of diversity," says P element expert Allan Spradling of the Carnegie Institution of Washington in Baltimore. Although Spradling points out that the idea is controversial, the elements could, he notes, help create new species—or eliminate existing ones. And all this could happen, "on a time scale evolutionists don't think about."

If lateral transfers of genetic material between species occur frequently, however, they could complicate the lives of researchers who are trying to work out the evolutionary relationships among species by comparing their gene sequences. Those studies assume that genes are inherited, while slowly accumulating changes. But, says molecular evolutionist David Hillis of the University of Texas in Austin, "with lateral gene transfer, that's not the case. It could mislead about gene history." Nevertheless, Hillis points out that nobody knows how frequent such lateral transfers are, and the Kidwell group's work might help in that regard by providing a system that would allow the question to be tackled experimentally for the first time.

New host. *The fruit fly* D. melanogaster.

Kidwell, who is a pioneer of P element research, zeroed in on the mite her group has implicated as the vector that introduced the elements into *D. melanogaster* largely, she says, by the process of elimination. Evidence from several groups, including her own, had already pointed to *D. willistoni* as the probable donor species. P elements from the two species have nearly identical sequences, for example, even though *D. willistoni* and *D. melanogaster* diverged about 50 million years ago—ample time for the sequences to have undergone numerous mutations. What's more, the geographical ranges of the two *Drosophila* species overlap, a necessity for gene exchange.

But since the two organisms can't breed, the material had to have been transferred by some agent. "It just couldn't float through the air," as Kidwell puts it. Her first efforts to identify the agent focused on insect viruses, but those efforts didn't turn up any candidates, apparently because the viruses are too host-specific to infect both fruit fly species and so couldn't transfer genes between them.

Several different mites infest lab *Drosophila* cultures, however, and Kenneth Peterson, then a postdoc in Kidwell's lab, turned to Houck, a mite expert who is now at Texas Tech University in Lubbock, for help in identifying the best candidate from among them. The researchers chose *Proctolaelaps regalis* DeLeon partly because it feeds on fruit fly eggs, often moving from one to another—behavior that might enable it to pick up and inject new genetic material into the eggs, much as human researchers do in their gene transfer experiments. *P. regalis* had something else going for it as well. The original P element transfer is thought to have occurred in North America, spreading from there to the rest of the world. And the mite habitat overlaps with those of the two *Drosophila* species in North America.

Kidwell and her colleagues have now woven the web of circumstantial evidence implicating the mite even tighter. They have shown that the mite is able to pick up P element DNA when grown in culture with a *D. melanogaster* strain known to carry the elements. "We're not claiming that we have shown that the mite is the mechanism of transfer," says Kidwell, "but we've shown that the conditions are right. We do definitely say it's possible." And since the mite also picked up sequences of a *Drosophila* gene encoding a ribosomal RNA, it may transfer other genes besides P elements.

Kidwell and her colleagues are already setting up experiments in which they hope to catch gene transfer in the act. They will grow mixed populations of *D. melanogaster* and *D. willistoni*, with and without *P. regalis*, to see whether the mite is indeed capable of carrying P elements from one to the other. Kidwell expects that such transfers will be relatively rare, and that the mixed cultures may have to be maintained for several fruit fly generations to establish their existence. But if all goes well, she may be able to duplicate in the lab an evolutionary event that happened in nature 40 years ago. ■ JEAN MARX

Getting a Jump on Gene Transfer in *Drosophila*

When the DNA sequences known as P elements moved into the fruit fly genome, they did so with a vengeance. Just a few decades after they first crossed the species barrier around 1950—possibly the result of a gene transfer achieved by a parasitic mite (see accompanying story)—they had invaded fruit fly populations worldwide. How P elements could spread so quickly has been something of a mystery, but new work reported on page 1110 by Gregory Gloor, William Engels, and their colleagues at the University of Wisconsin, Madison, appears to have solved it.

The research, moreover, has provided an added bonus: The discovery of a way to use P elements to replace or modify fruit fly genes in their normal chromosomal locations—the first time such targeted gene replacement has been possible for that species. Such a technique should be a boon to researchers who want to make systematic changes in fruit fly genes to see how they affect such biological activities as embryonic development or nervous system function. "I think it [the new method] is very exciting in terms of improving the understanding of *Drosophila* genetics," says Allan Spradling of the Carnegie Institution of Washington in Baltimore, who is himself well familiar with gene transfer in *Drosophila*.

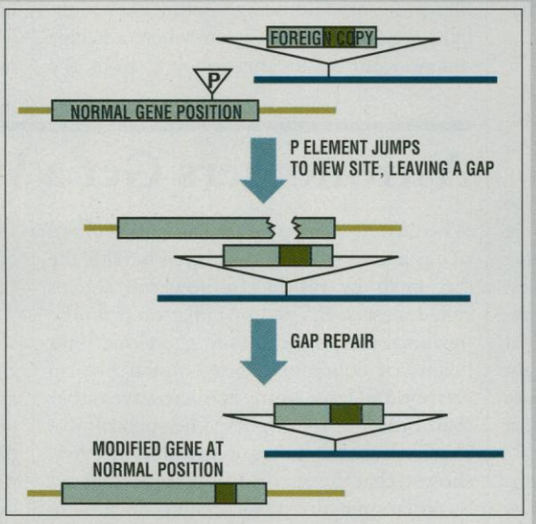
The Engels group hit on the new gene replacement method while studying another mysterious property of P elements—their ability to jump from place to place in the genome. Last year, the researchers proposed a "cut-and-paste" model in which an element leaves behind a gap in the DNA when it jumps. The gap has to be filled in, and when that occurs, Engels says, "It looks around the genome for a sequence that matches the ends." The matching sequence is then used as a template to direct the filling in of the gap—and that may lead to the restoration of the P element at its old site.

If a P element jumps after the chromosomes have duplicated but before the cell divides, for example, one of the sister chromatids (as the duplicated chromosomes are called) will still have the P element in its original position. And, according to the cut-and-paste model, this P element, whose ends match those of the gap, may serve as the template for filling the hole left on the other sister chromatid when the P element moved to its new position, which can be anywhere in the genome. The upshot, Engels points out, is that when a P element jumps, the number of elements in the genome may increase by one. The P elements can reproduce faster than the DNA of the fruit fly itself, and their rapid replication helps to explain how they could spread so fast.

Under those circumstances, says Margaret Kidwell of the University of Arizona, Tucson, whose own work includes studies of P element migration, the elements wouldn't have to confer any evolutionary advantage on the organism in order to invade the genome. They might even spread if they had negative effects. Engels notes, however, that human activities—such as importing fruit and the flies that infest it—probably also helped P elements move into new fruit fly populations.

In any event, the next question the Engels group asked was whether the gap left by an absconding P element could be filled, not with a copy of the same P element but with a gene supplied by the researchers. The answer, reported in the current paper, turns out to be yes, providing both direct confirmation of the group's cut-and-paste model as well as the basis of a targeted gene replacement method.

To get targeted gene transfer, the first requirement, Engels says, is to have a P element in or near the gene that is to be replaced. Although that might seem like a drawback, it's not an insurmountable problem. According to Spradling, fruit fly researchers have already made thousands of different P element strains, and more are still being created.



Filling the gap. *The scheme shows how the gap left when a P element jumps out of a gene can be repaired with the foreign sequence a researcher chooses.*

Then the next step is to transfer in the desired replacement gene. This can be readily done with a gene transfer method developed several years ago by Spradling and Gerry Rubin of the University of California, Berkeley. The method uses P elements themselves to insert new genes into the fruit fly genome. But the problem with the older method is, as Engels puts it, that "the gene doesn't go where you want it to go, it goes where the gene wants to jump."

It doesn't matter where the P element with replacement gene goes, however. Wherever it lands, it can still match up with the gap left when the P element jumps from the target gene and serve as the template to fill the gap when it's repaired. By using this approach, Gloor, Engels, and their colleagues were able to replace a defective eye color gene with the normal one in their fruit flies. The frequency of the correction was sufficiently high—it worked in somewhat more than 1% of the fruit flies—to make gene replacement practical, Engels says.

And that could be a real advantage, Spradling points out, because sometimes genes don't work the way they should if they're not in their normal location. What's more, genes longer than about 40 kilobases haven't been sucessfully transferred by the Rubin-Spradling method. But with the newer method it should be possible to alter systematically even very big genes right in their normal locations to see how that affects their function. "The new method will be useful for people like me who are working with big genes that can't be put into flies on a P element," says molecular geneticist Welcome Bender of Harvard University, who is already beginning to use the technique on a developmental control gene whose coding sequences extend over about 75 kilobases.

And finally, the gene replacement technique should be applicable to any organism that has transposons that move the same way P elements do. According to recent work by Ronald Plasterk of the Netherlands Cancer Institute in Amsterdam, this may include the roundworm *Caenorhabditis elegans*, another favorite of molecular geneticists. Expect more than one molecular geneticist to jump on the new gene replacement bandwagon. ■ **J.M.**