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## Clever Bacteria Hitch a Ride in the Stem-Cell Niche

Researchers have discovered a new clue to how bacterial parasites are able to produce a long-term infection that can spread through an insect population. They have found that a type of bacteria that infects insects actually hitchhikes in the eggs of fruit flies. This ensures that the bacteria are passed from mother to offspring.

The findings show that in the first stages of infection, *Wolbachia* bacteria home in on stem-cell niches in the fruit fly, where they can continually infect the cells that produce eggs. Stem-cell niches are specialized cellular environments that provide stem cells with the support needed for differentiation and self-renewal.

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The new studies offer the first glimpses of how *Wolbachia* infection, which occurs in a wide range of insects, is passed from one generation to the next. According to the researchers, their experiments with the fruit fly *Drosophila* offer a valuable laboratory model for tracing the machinery bacteria use to infect insects. The basic studies could ultimately help scientists understand the mechanisms underlying insect-borne parasitic diseases that affect humans.

Howard Hughes Medical Institute (HHMI) investigator Eric Wieschaus, first author and HHMI research associate Horacio Frydman, Jennifer Li, and Drew Robson collaborated on the studies. The researchers, who are all at Princeton University, published their findings in the May 25, 2006, issue of the journal *Nature*.

A major question regarding bacterial parasites has been how a new infection can ultimately produce a stable long-term infection that spreads through an

insect population, said Wieschaus. It's obviously important for the bacteria, not just to make it into an insect host, but to somehow exploit that host's biology to ensure that it not only infects that host, but its progeny.

So for the bacterium, targeting the ovary — the source of germ cells for the next generation — is a good strategy. But to our surprise, we found that, although these bacteria do target the eggs, they also find their way into the somatic component surrounding the germ cells — a way station where they can sit and infect germ cells as those cells are producing eggs.

*Wolbachia* are an excellent model for such studies because they infect a wide range of arthropods, said Wieschaus. And the fruit fly *Drosophila* is a standard, easily manipulable laboratory animal, whose genetics and physiology are very well known.

In the experiments, Frydman, Wieschaus and their colleagues first inoculated uninfected fruit flies with *Wolbachia* and followed the movement of the bacteria through multiple tissues and into the structures of the ovary during infection. These studies revealed that the bacteria insinuated themselves into the compartment in the ovary that harbors stem cells.

The scientists next tested whether bacteria in the abdominal cavity could still infect germline cells after an infection had been established in the stem-cell niche. Frydman implanted uninfected germline cell structures — called germaria — into infected flies. We found that even in flies that already have an efficient germline infection, they still continue to show movement of bacteria into these uninfected germaria, said Wieschaus. We don't know quite what that means, but we argue that it may serve to maintain a stable infection even in host germaria that were already infected.

In addition to revealing an unexpected mechanism of infection in insects, the experiments offer a promising new laboratory model for studying the process of infection.

*Wolbachia* is similar to other infections that broadly affect insect populations, said Wieschaus. So, it offers a good opportunity to understand the basic biology of this process. Although this is very basic research, one might imagine that understanding this infective process could enable better understanding of insect vectors of human disease. And perhaps such understanding might enable ways to manipulate or control the disease in those vector populations.

The *Wolbachia-Drosophila* model system could also help researchers answer major questions about the complex relationship between the bacteria and their host. We'd like to understand from an evolutionary standpoint how the bacteria adapt to use the cell biology of their host, he said. And since *Wolbachia* and *Drosophila* seem to be reasonably well adapted to one another, how does the host evolve to adapt to the bacteria? Perhaps the infection even helps the fly in some symbiotic way that we don't understand.

Although the mechanism of transmission of bacteria in insects is far removed from the mechanism in mammals, emphasized Wieschaus, these findings do trigger thoughts about experimental strategies that might be applied to mammalian systems. There might well be cases where bacteria that infect mammals might adopt a strategy of targeting germline cells, or of targeting some particular niche in the infective process, rather than targeting a dividing cell itself, he said.

And while the studies were not aimed at understanding stem cell niches, he said, any studies involving such niches can add insights into their function. For example, knowing how the bacteria recognize the niche might give us a new molecular marker for the niche. Understanding the function of stem cell niches is a major objective of researchers seeking to grow and use stem cells for therapeutic purposes.

Indeed, Wieschaus said his group is planning studies that aim to understand the dynamics and functional relationship between the bacterium and the stem cell niche that enables the bacterium to take advantage of that niche for transmission between generations.