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RESEARCH NEWS

JANUARY 09, 2009

New Protein Family May Explain a Mystery of Insect Olfaction

Howard Hughes Medical Institute investigator Leslie Vosshall dreams of a day when her findings on insect olfaction are used to develop a strategy for blunting an insect's sense of smell. Without smell, blood-thirsty mosquitoes would be blinded to the scent of humans, and medflies would be unable to find their way to citrus crops.

Vosshall and her colleagues at Rockefeller University have been working to understand how the insect olfactory system works, always keeping their eyes on the bigger picture: New knowledge about how insects detect odors and how odors influence their behavior may help researchers identify new ways to fend off pests that transmit diseases like malaria or ravage agricultural crops.

In the January 9, 2009, issue of the journal *Cell*, Vosshall's team reports that it has discovered a novel kind of odor-detecting protein that may explain some of the gaps in researchers' knowledge of how insects detect odors in their environment. Vosshall and her colleagues identified the proteins, which they call ionotropic receptors, in a group of neurons located in the antennae of fruit flies.

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> **- Leslie B. Vosshall**

The majority of Vosshall's research involves insects like the fruit fly and mosquito, which serve as relatively simple models for probing how the brain and nervous system transform olfactory cues into specific behaviors. Fruit flies, like other insects, detect odors with sensory neurons located primarily on their antennae. Since the late 1990s, researchers studying insect olfaction have focused their attention on a set of proteins known odorant receptors, which stipple the surface of most of these olfactory neurons. That work, much of which Vosshall has been involved in herself, has yielded a good deal of information about how odorant receptors detect odors in the environment.

“We know everything about the cells that express the odorant receptor genes, how they map into the brain, and what odors the odorant receptors smell,” Vosshall said. “But we knew that there was still a big, dark secret in fly olfaction.”

At the heart of that “secret” is earlier research that indicated that odorant receptors are found on only about 70 percent of a fruit fly's olfactory neurons--yet all of the neurons have the capacity to detect odors. The big mystery for Vosshall and others in her field was how the other 30 percent of the fly's olfactory neurons sensed odorants. “We know that there are olfactory neurons sitting in the fly antenna that respond to odors but we have no idea how they do it,” Vosshall said.

Although Vosshall and her postdoctoral fellow Richard Benton did not set out to answer that question, they stumbled across a promising lead when they undertook a search for genes that were shared by mosquitoes and fruit flies, but absent in other organisms. They embarked on that search hoping to find clues about which proteins help odorant receptors relay information to an insect's brain.

Their search turned up a large set of genes that were distantly related to the mammalian genes that encode receptors for the neurotransmitter glutamate. Like vertebrates, fruit flies use these receptors, known as ionotropic glutamate receptors, to mediate communication between neurons. But flies have an additional 60 ionotropic receptors (IR) that are not involved in this process. In fact, no one had determined what those 60 IRs did. The extra receptors, Vosshall said, had been “hiding in plain sight. People knew they were there, but they had been completely ignored.”

Vosshall and Benton decided to do experiments to see if any of the 60 additional IR genes were turned on in the fruit fly's “mystery neurons”--those with the unexplained odor-detecting abilities. Their studies showed that the genes were active in sensory neurons in the antenna--but only in neurons that lacked the well-known odorant receptors. By attaching a tiny tungsten needle to the region of the antenna where the receptors were found, they found that certain odors could trigger activity in those nerve cells.

Stronger evidence that the genes functioned in olfaction came when the researchers genetically manipulated the neurons by inserting a particular receptor into a type of nerve cell in which it was not normally found. The neuron that is normally home to a receptor named IR84a is sensitive to a chemical known as phenylacetaldehyde. This molecule has an aroma similar to a combination of honey and grass. When the team put the gene for IR84a into neurons that normally do not respond to phenylacetaldehyde, they began to respond to the chemical, triggering a nerve impulse when it was near. A weaker, but similar, effect was found when they shifted the receptor from ammonia-sensitive cells to new neurons.

Together, the team's findings add up to “tantalizing” evidence that ionotropic glutamate receptors provide fruit flies with an alternative mechanism for detecting odors, Vosshall said.

In 2008, Vossshall's lab published evidence that odorant receptors work as channels that open when an odorant binds to let ions into the cell. The IRs, too, appear to be ion channels that sit in a cell's membrane. But that's where the similarities end, Vosshall said. “Although we think they're both ion channels, they're structurally totally different. And there's already pretty good evidence that they smell mostly non-overlapping smells. So you have embedded in the antennae two different ways to smell mostly non-overlapping odors. That's pretty cool.”

It's not clear yet how odors detected through this alternate method influence behavior--whether, for example, the IRs help hungry mosquitoes locate their next meal. Vosshall says uncovering the link between IRs and behavior will be crucial if researchers hope to stem infectious disease transmission by manipulating insects' ability to smell. “We need to know how important this parallel pathway is. If it's really important, then we can't ignore it,” she said.