Dine or dash? Genes help decide when to look for new food

March 16 2011

For worms, choosing when to search for a new dinner spot depends on many factors, both internal and external: how hungry they are, for example, how much oxygen is in the air, and how many other worms are around. A new study demonstrates this all-important decision is also influenced by the worm's genetic make-up.

In the simple Caenorhabditis elegans nematode, the researchers found that natural variations in several genes influence how quickly a worm will leave a lawn of bacteria on which it's feeding. One of the genes, called tyra-3, produces a receptor activated by adrenaline—a chemical messenger involved in the 'fight-or-flight' response. The findings appeared online March 16, 2011, in the journal *Nature*.

"What's encouraging to us about this story is that molecules related to adrenaline are implicated in arousal systems and in decision-making across a lot of different animals, including humans," says Howard Hughes Medical Institute investigator Cornelia Bargmann of Rockefeller University in New York, who mentored the work of graduate student Andres Bendesky. These parallels between diverse species suggest that aspects of our decision-making abilities have ancient evolutionary roots.

C. elegans thrive in agricultural settings, such as orchards and crop lands, feeding on bacteria from rotting fruits and vegetables. But eating in this environment is tricky: the worms encounter many bacterial species that are difficult to digest or even toxic. "The worms need to somehow evaluate a whole spectrum of conditions to decide whether they want to

try this food source or go out and look for a better one," Bargmann says.

The great scientific advantage of using *C. elegans* to study complicated behavioral processes such as decision-making is that the worms have only 302 neurons, and the connections between all those neurons have all been precisely mapped. In contrast, the human brain has billions of neurons. What's more, most of the worm's 20,000 genes have equivalents in the human genome. "Behavior includes the action of genes, their function in neurons, and the neurons' assembly into circuits," Bargmann says. "Studying *C. elegans* gives you an exceptional ability to make connections between those levels."

Over the past decade, her lab has probed several of these levels. In 2004, they reported that *C. elegans* sense precise oxygen concentrations in soil, which helps steer them toward their favorite meal: oxygen-consuming bacteria. Three years later, they investigated what neurons do with chemosensory information, finding that odor-sensing neurons can switch on other cells that control crawling and turning behaviors.

In the new study, Bendesky and Bargmann went one level deeper, investigating how genetic tweaks can change a worm's behavior in particular circumstances. To do their experiments, the researchers placed hundreds of different strains of *C. elegans* onto Petri dishes lined with a circular "lawn" of bacteria and calculated the rate at which worms left the lawn. "Lawn-leaving is something that occurs abruptly, in an all-or-none way. It's very striking," Bargmann says.

To find the genes that affect the behavior, they collaborated with HHMI investigator Leonid Kruglyak and his postdoc Matt Rockman to use a technique called quantitative trait locus analysis, they then analyzed the precise genetic make-up of each strain and correlated it with how frequently each strain left its lawn. In the end, the researchers could pinpoint particular genetic blips associated with moving away from a

food source.

One of those blips crops up in a gene called npr-1, which had already been associated with foraging behaviors and immunity in the worm. The npr-1 variant is a special case, however, because it evolved in laboratory strains of *C. elegans* and is not known to exist in the wild.

In a more exciting development, the researchers also found a natural genetic variation in tyra-3 that is associated with lawn-leaving. This gene encodes a receptor protein that responds to tyramine, an adrenaline–like hormones derived from the amino acid tyrosine. Like adrenaline, tyramine is an internal signal that regulates the function of neurons expressing its various receptors.

To find out where in the brain the tyra-3 gene is turned on, the researchers engineered strains of worms in which they could observe production of tyra-3. By attaching a fluorescent green marker to the tyra-3 protein, they could easily observe whenever the protein was made. They then traced where the green fluorescence appeared inside the worms and discovered that the tyra-3 receptor is produced in a place that makes intuitive sense: sensory neurons. In these neurons, external cues, such as oxygen levels, can be integrated with internal states, such as hunger. "It's the result you would have gotten if you made it up," Bargmann says, laughing.

The findings show that particular genetic variants lead to specific behaviors in the real world—but how, exactly, they do this is still mysterious. "We don't have a fix on when tyramine is being made, where it's released, and how it's working to change behavior," Bargmann says.

Figuring that out is the obvious next step. The trouble is, the tools for tracking the brain's chemical messengers in real time don't exist yet. "We'll just have to put our heads down and develop some," she says.

Provided by Howard Hughes Medical Institute