

MAY 04, 2007

Gene Helps Distinguish Self from Non-Self During Neural Development

Like the elegant branching of a tree, the dendritic limbs of developing nerve cells must organize themselves to cover as much space as they can evenly and efficiently. To complicate matters, they must also take care to avoid overlapping with their sister dendrites.

Precisely how these critical branch-like structures grow to avoid such trespassing has been a mystery of neural development. Now, researchers have found that a much-studied gene provides branches of nerve cells the ability to recognize one another and grow apart.

The finding is the result of two independent but converging lines of research. During the past few years, Howard Hughes Medical Institute investigator S. Lawrence Zipursky and his colleagues at the University of California Los Angeles have been investigating the role of a gene known as *Dscam* in nerve cells' recognition of axons and dendrites. In parallel, HHMI investigators Yuh-Nung Jan, Lily Jan, and their colleagues at the University of California San Francisco have been studying a group of sensory neurons in fruit flies known as dendritic arborization neurons as a model for dendrite development.

"When you remove *Dscam* from a single cell and ask what happens to the branching pattern, it is very interesting. The branches don't separate with the same fidelity."

- S. Lawrence Zipursky

In three papers published this week in the journals *Cell* and *Neuron*, three groups of researchers report how a vast assortment of proteins produced by *Dscam* steers sister dendrites away from one another. Wes Grueber at Columbia University and Zipursky led one of the teams, which published its findings in the May 4, 2007, issue of the journal *Cell*. A similar finding, discovered independently by a group led by Yuh-Nung Jan and Lily Jan, is

described in the May 3, 2007, issue of the journal *Neuron*. A third paper from Dietmar Schmucker's lab at Harvard Medical School describes similar findings in the same issue of *Neuron*.

Dendrites gather and route sensory information and signals from other nerve cells. "Dendrites are a critical part of the wiring pattern of animals," Zipursky noted. "They play a crucial role in processing information within the central nervous system and they come in an extraordinary variety of shapes."

In an organ as complicated as the brain of the fruit fly, the model animal in which the new work was conducted, there are millions of connections and circuits that must be choreographed with precision. And different neurons can have very different dendritic patterning.

"If you look at any area of the nervous system, you'll see some areas densely packed with dendrites," Yuh-Nung Jan explained. "Unrelated dendrites can co-exist in a very tight space," but it is critical that dendrite limbs from the same cell not overlap.

If dendritic organization goes awry, the central nervous system does not develop as it should. Scientists believe that there are rules that govern how dendrites organize their intricate branching. Rule number one, says Zipursky, is that nerve cell dendrites avoid sister dendrites, a phenomenon known as self-avoidance. That behavior allows the branches from the same cell to avoid overlap and grow and organize themselves into optimal fields of coverage.

Working in the fruit fly *Drosophila melanogaster*, the three research teams found that cell surface proteins produced by *Dscam* help guide developing dendrites and keep them from bumping into and overlapping with their sister dendrites, thus exhibiting self-avoidance.

The finding is important because it implies *Dscam* may have a central role in helping orchestrate cell interactions in the developing fly nervous system. Humans have an analogous gene, but the fruit fly *Dscam* gene is far more prolific in its ability to produce protein isoforms, slightly different variants of proteins that act as signaling molecules.

The great diversity of these isoforms--totaling 38,016--seems to lend neurons the ability to initiate self-avoidance without the risk of expressing the same isoforms as a neighboring neuron, noted Jan. Engineering the expression of the same shared isoforms of *Dscam* in different classes of neurons prevented their dendrites from sharing the same territory.

"This is a very large family of potential cell recognition molecules," Zipursky said, explaining that each isoform specifically recognizes the same isoform on cell surfaces. Each nerve cell produces a collection of *Dscam* isoforms largely different from those expressed by other nerve cells, and the protein

allows dendrites in the developing fly to recognize sister dendrites and nudge them in different directions.

"When you remove *Dscam* from a single cell and ask what happens to the branching pattern, it is very interesting. The branches don't separate with the same fidelity," said Zipursky.

In short, the molecular diversity encoded by the gene ensures that branches from the same neuron selectively recognize and repel only each other. That specificity is likely to be crucial for the proper patterning of dendrites as the developing brain wires itself.

The fly model used by Zipursky and Jan and their colleagues is a simple two-dimensional model in the peripheral nervous system, the portion of the nervous system outside the brain and the fly equivalent of the spinal cord. Dendrite formation in the central nervous system, said Zipursky, is three dimensional and much more complex. But the role of *Dscam*, the mechanism that helps dendrites recognize and avoid sister dendrites, is very likely the same.

"We would argue that's what is happening in the central nervous system. Dendrites require self-recognition to elaborate these patterns. They have to have *Dscam* to do this," Zipursky said.

What's more, the same strategy for forming the elegant dendritic arbors is probably at work in humans and other vertebrates, Jan and Zipursky argued, albeit with a different gene or genes at work. Thus, the new insight produced by both groups provides a basis for exploration of the same phenomenon in higher animals, including humans.

"The general idea might be the same in vertebrates, but it is likely to be different genes at play," Zipursky said. "It raises the interesting issue of what is the mechanism in vertebrates and is it similar?"

Co-authors of the *Cell* paper include Benjamin J. Matthews, and Michelle E. Kim of Columbia University; John J. Flanagan and Daisuke Hattori of the Howard Hughes Medical Institute at UCLA; and James Clemens of Purdue University.

Co-authors of the *Neuron* paper include Peter Soba, Sijun Zhu, Kazuo Emoto, and Susan Younger, all of UCSF; and Shun-Jen Yang, Hung-Hsiang Yu and Tzumin Lee of the University of Massachusetts.