

AUGUST 24, 2007

## Cellular Outposts Keep Dendrites Strong and Healthy

Although the brain's axons and dendrites are neighbors, they differ in many respects and little is known about how they develop differently. Howard Hughes Medical Institute (HHMI) investigators Yuh-Nung Jan, Lily Jan and their colleagues are employing a systematic strategy that they hope will begin to enlighten researchers about the different developmental steps and cellular machinery used to build axons and dendrites.

We are interested in the basic mechanisms of neural development, said Yuh-Nung Jan. Our strategy is to use the relatively simple *Drosophila* peripheral nervous system to discover the genetic program that controls its development. In doing so, we hope to uncover evolutionarily conserved core programs that control different steps of neural development in animals.

---

"We have established the correlation between Golgi outposts and dendritic growth, so we can now explore how they contribute to that growth."

— Yuh Nung Jan

---

Armed with 3,300 mutant fruitfly lines developed in his lab, Jan and his colleagues are now reporting the first data from their experiments. By employing a methodical screen for fly mutants that grow normal axons but abnormal dendrites, Jan's team has identified eight genes that are involved in dendrite formation. Each of these genes was identified in a mutant fly with abnormally short dendrites, so Jan's group named the genes *dendritic arbor reduction (dar) 1-8*. The experiments suggested that growing dendrites rely on cellular structures known as Golgi outposts that are preferentially present in dendrites.

The Jans, postdoctoral fellow Bing Ye, graduate student Ye Zhang and their colleagues at the University of California, San Francisco, published their findings in the August 24, 2007, issue of the journal *Cell*.

Dendrites are the fine branches on nerve cells that receive information from neighboring nerve cells. Axons are the cable-like structures that project from

the nerve cell and transmit information to other neurons. Axons and dendrites are critical components of the nervous system because they enable neurons to establish precise connections and communicate with other neurons.

To search for genes that only regulate dendritic growth, the researchers created 3,300 strains of mutant fruitflies. Each mutant fly's neurons were fluorescently labeled, which permitted the researchers to identify those with stunted dendritic growth but normal axon development. They identified mutations affecting eight genes that led to shortened dendrites.

We didn't know what kinds of mutants would come out of this screen, but we found that three of the genes are part of the secretory pathway, said Jan. The secretory pathway is a series of steps a cell uses to move proteins to the cell surface or out of the cell. The Golgi apparatus is part of the machinery the secretory pathway uses to package and transport proteins and lipid building materials. All cells possess a central Golgi apparatus — a complex of sac-like vesicles that process and package large molecules for delivery to different destinations in the cell. Golgi outposts are smaller versions of the Golgi apparatus in neuronal dendrites and can be thought of as supply stations for the building blocks needed to construct dendrites. Previously, HHMI investigator Michael Ehlers and colleagues at Duke University showed that dendritic Golgi outposts are engaged in secretory trafficking.

The three *dar* genes identified by Jan's team, called *Sec23*, *Sar1* and *Rab1*, are conserved from yeast to mammals. HHMI investigator Randy Schekman had identified these genes in his earlier pioneering work on the secretory pathway. Of these, *Sar1* plays an early role in forming cargo-carrying vesicles that transport materials in cells. In the *Sar1* mutant, the scientists observed that the Golgi outposts in the fly neurons are defective.

To see if *Sar1* has a similar function in mammalian neurons, the researchers decided to test the effects of knocking down the fly equivalent of *Sar1* in cultured rat neurons. The resulting neurons with reduced *Sar1* activity had normal axons but reduced dendritic branches similar to the *Sar1* mutant neurons in fly. They next traced the flow of fluorescently labeled membrane material in the *Sar1*-deficient neurons and saw that the dendrites were being starved of the supply of membrane material that normally nourishes their growth.

When the researchers imaged Golgi outposts in the developing neurons of normal fly larvae, they could see the outposts advance into dendrites as they grew, and retreat back toward the cell body when they retracted. Damaging the Golgi outposts with a laser beam reduced the highly dynamic extension and retraction of dendrites that characterizes normal development of the finely branched structures.

In an additional set of fruitfly experiments, the researchers blocked the function of a protein that links Golgi to a molecular motor that transports Golgi outposts. When they knocked down this gene, they found a dramatic reduction in dendritic branches.

The researchers' finding highlights a unique role of Golgi outposts in dendrite growth and offers an important new research pathway to explore what has been a largely mysterious process, Jan said.

We have established the correlation between Golgi outposts and dendritic growth, so we can now explore how they contribute to that growth, he said. Are they the source of new membrane material inserted into dendrites, and where is this new material inserted? Do they also have a role in recycling membrane material from dendrites? Do Golgi outposts play a role in the different types of dendritic branching seen in different neurons? These are all questions we are now addressing, he said.