

## Helping the Brain to Make Connections

*Newly discovered protein awakens, maintains neural connections.*

**R**esearchers have discovered a critical protein that regulates the growth and activation of neural connections in the brain. The protein—called dendrite arborization and synapse maturation 1, or *Dasm1*—functions in the developing brain, where it controls the sprouting of new dendritic connections and stimulates existing synaptic connections among immature neurons. *Dasm1* is potentially active

in the mature brain as well, where it may play a role in memory formation.

The researchers—HHMI investigators Yuh Nung Jan and Lily Jan, lead author Song-Hai Shi, and colleagues, all at the University of California, San Francisco—published their findings in two papers in the September 7, 2004, issue of the *Proceedings of the National Academy of Sciences*.

***Yuh Nung Jan and his wife and collaborator, Lily Y. Jan, have discovered a protein that is critical to the growth and activation of neural connections in the brain and acts in ways that are "quite surprising."***



Dendrites are tree-like filaments that deliver “input” information to the nerve cell body. Dendritic spines are mushroom-shaped protrusions that extend from the surface of dendrites and receive chemical signals emitted by neighboring neurons. In response, the dendrites trigger an electrical impulse from the cell body and down the cable-like axon, which then passes its message to the dendrites of other neurons in the form of neurotransmitters. Growth of new dendrites therefore can increase the number of connections between neurons, and changes in the strength of the signals allow the brain to create memories.

In exploring the growth and development of dendritic spines, the Jan team first identified a gene in the fruit fly *Drosophila* that appears to play a role in “arborization” (dendrite growth). Then, by comparing the fruit fly gene with databases of vertebrate genomes, they identified a homologous gene in mice, which they named *Dasm1*.

Initial studies revealed that the gene was highly expressed in the brains of embryonic mice. “When we used antibody markers to look at the distribution of the protein, we saw it primarily in the dendrites, with very little in the axons,” says Yuh Nung Jan. “If you look at areas of the hippocampus rich in dendrites, they just light up, whereas in axonal areas there is very little evidence for the presence of this protein.”

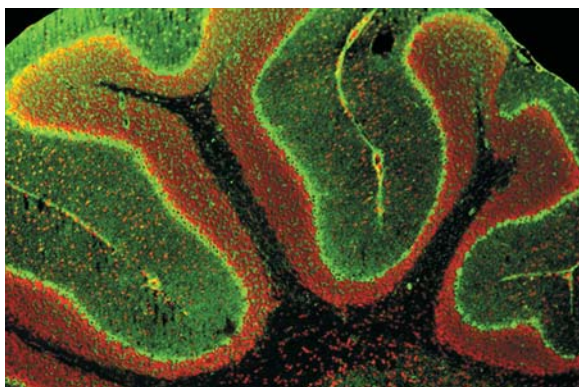
Consequently, when the researchers blocked the activity of the version of the *Dasm1* gene found in rats, they found dendrite growth to be drastically reduced in cultured brain cells.

They also studied the effects of the *Dasm1* protein on the maturation of neuronal connections, or synapses. Newly formed, immature synapses are silent, meaning they lack a type of cellular structure, known as AMPA ( $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors, which receive neurotransmitter molecules. However, these neurons have other receptors, called NMDA (*N*-methyl-D-aspartate) receptors, which are associated with long-term changes in the strength of neuronal signaling. Although dendrites (which influence the development of neuronal connections) do acquire active AMPA receptors during maturation, it was not known whether this process depends on *Dasm1*.

Shi, the Jans, and their colleagues found that interfering with Dasm1 function drastically decreased AMPA receptor function. “While we expected that Dasm1 would contribute to dendrite arborization, the finding that reducing its activity caused a dysfunction in synaptic maturation was quite surprising,” says Yuh Nung Jan.

“It’s known that the ratio of AMPA to NMDA receptors increases during development, and it also increases during long-term potentiation,” says Lily Jan, but Shi’s “identification of a molecule that [controls both] dendrite arborization and synapse maturation is quite important.” The team’s experiments also revealed that Dasm1 was responsible for “awakening” silent synapses.

The mechanism of Dasm1 is not yet known, she adds, but the protein’s structure hints that it is a receptor molecule. “The Dasm1



**A neuron from the brain in which DNA has been stained red and the Dasm1 protein, which controls mammalian dendrite development, has been stained green.**

molecule has a large extracellular domain, a single transmembrane domain, and a large cytoplasmic domain,” all of which are “characteristic of receptor molecules.” This suggests that, like other receptors, Dasm1 nestles in the cell mem-

brane, receiving chemical signals that activate cellular processes.

Further evidence that Dasm1 is a receptor comes from an experiment in which Shi treated neurons with a molecule that mimicked Dasm1, but in which the portion of the molecule that extends into the cell had been replaced by a segment from another protein. This treatment rendered the protein unable to interact with Dasm1’s usual partners inside the cell, and dendrite growth was impaired. The result “gives us hints that there is a signaling pathway within the cell activated by Dasm1 that we need to explore,” says Lily Jan.

The next step, according to the researchers, is to knock out the *Dasm1* gene in mice. In that way, they may see whether their observations in isolated brain tissue and cultured cells can be extended to neural development in vivo.

—DENNIS MEREDITH

## Speed Reader

*A search engine called Textpresso mines the scientific literature to give researchers faster access to critical information.*

**W**hen Paul W. Sternberg first studied the genome of the worm *Caenorhabditis elegans* as an MIT graduate student in 1979, there were perhaps three papers he felt he had to read that year to stay current. Twenty-five years later, the literature has mushroomed to more than 9,000 papers and 20,000 scientific abstracts on just the tiny nematode alone—and that doesn’t count the vast library of research on the genes it shares with other organisms, which expands the universe of papers by orders of magnitude.

“I don’t know if I have 30,000 or 300,000 papers I’m responsible for, but it’s more than I can do,” says Sternberg, an HHMI investigator at the California Institute of Technology.

Scientists, of course, don’t want to miss critical information—perhaps published by a researcher thousands of miles away—that could influence their thinking, lead them to

design their experiments differently, and perhaps save many hours of labor. But how can one sort through reams of text quickly and efficiently to retrieve such key documents?

Enter Textpresso, a new text-mining system for scientific literature that is said to be more precise than Google or even Medline and is almost as accurate as human curators in identifying relevant information. Developed by Sternberg and two colleagues, Hans-Michael Müller and Eimear E. Kenny, the search engine is designed to specifically retrieve information about *C. elegans* from papers.

And it assists in supplementing Wormbase, the genetic database for *C. elegans* and more than 20 other nematode species, which is curated in Sternberg’s laboratory. Importantly, the basic software can serve as the scaffolding of search engines for genomic information on other organisms, such as yeast or fruit flies.

Textpresso, whose apt name evokes the stimulation of caffeine in the context of appealing flavor, has two essential elements: the full texts of scientific articles, which are split into sentences that can be individually accessed; and entire categories, rather than just key words, that contain the terms to be used in searches, making retrieval more precise.

Sternberg, Müller, and Kenny got started by reading through some 500 papers to cull a list of key words, concepts, and relationships, which were then organized into the categories that now form the backbone of the search engine. They

