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Molecule Awakens and Maintains Neural Connections

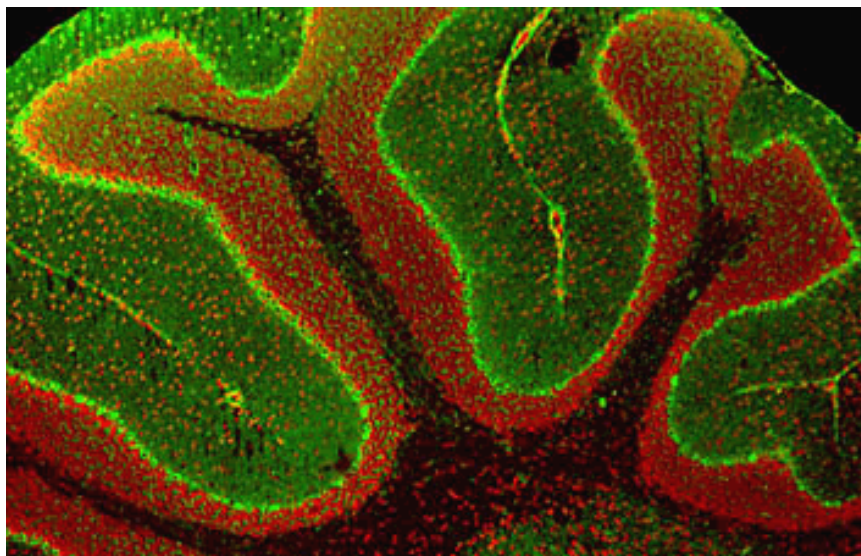


Image Title: A neuron from the brain in which DNA has been stained red and the Dasm1 protein, which controls mammalian dendrite development, has been stained green. Dasm1 is abundantly expressed in the dendrites of neurons, but not in the axons. - Cover, *PNAS*, September 7, 2004. Copyright 2004, National Academy of Sciences, U.S.A.

Researchers have discovered a critical protein that regulates the growth and activation of neural connections in the brain. The protein functions in the developing brain, where it controls the sprouting of new connections and stimulates otherwise silent connections among immature neurons, and potentially in the mature brain as well, where it may play a role in memory formation.

The researchers published their discovery of the protein, called dendrite arborization and synapse maturation 1, or Dasm1, in two papers in the September 7, 2004, issue of the *Proceedings of the National Academy of Sciences*. They were led by Howard Hughes Medical Institute investigators Yuh Nung Jan and Lily Yeh Jan. The first author on both papers was Song-Hai Shi in the Jans' laboratory at the University of California, San Francisco.

"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."

— **Yuh Nung Jan**

Dendritic spines are mushroom-shaped protuberances that extend from the surface of the cable-like axon of a neuron. Dendrites receive chemical signals that trigger nerve impulses in the form of neurotransmitters launched from neighboring neurons. Growth of new dendrites can therefore increase the connection between neurons. Changes in the strength of connections, known as long-term potentiation, allow the brain to create memories.

In exploring the growth and development of dendritic spines, Shi, the Jans, and their colleagues first identified a gene in the fruit fly *Drosophila* that appears to play a role in regulating dendrite growth, or "arborization." In comparing the fruit fly gene with databases of vertebrate genomes, they identified a similar homologue in mice, which they named Dasm1.

Their initial studies revealed that the gene was highly expressed in the brains of embryonic mice. "A major reason we became interested in this molecule is that 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," said 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."

When the researchers blocked the activity of the version of the Dasm1 gene found in rats, they found dendrite arborization to be drastically reduced in cultured brain cells.

The researchers also studied the effects of Dasm1 on the maturation of neuronal connections, or synapses. Newly formed, immature synapses are silent, meaning they lack a type of receptor called AMPA receptors, which receive neurotransmitter molecules. However, these neurons do have other receptors, called NMDA receptors, which are associated with long-term changes in the strength of neuronal signaling. During maturation, dendrites acquire active AMPA receptors, and it was not known whether this process depended on Dasm1.

Shi, the Jans, and their colleagues found that interfering with Dasm1 function drastically decreased AMPA receptor function. Their experiments also revealed that Dasm1 was responsible for "awakening" silent synapses and promoting the maturation of the neuronal connections, a process that depends on dendrite development.

"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," Yuh Nung Jan said.

According to Lily Yeh Jan, the finding of a single control molecule for both maturation and arborization is significant. "It's known that the ratio of AMPA to NMDA receptors increases during development, and it also increases during long-term potentiation," she said. "So, Song-Hai's identification of a molecule that is likely to be important for dendrite arborization and also to control synapse maturation is quite important."

While the function of Dasm1 is not yet known, said Lily Yeh Jan, the protein's structure hints that it is a receptor molecule. "The Dasm1 molecule has a large extracellular domain, a single transmembrane domain and a large cytoplasmic domain," she said. "So that is characteristic of receptor molecules." This suggests that, like other receptors, Dasm1 nestles in the cell membrane, 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 - rendering it unable to interact with Dasm1's usual partners inside the cell. This treatment impaired dendrite growth, "which gives us hints that there is a signaling pathway within the cell activated by Dasm1 that we need to explore," she said.

The next step, the researchers say, is to knock out the Dasm1 gene in mice to see whether the observations they have made in isolated brain tissue and cultured cells can be extended to neural development *in vivo*.