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# Biologists show how brain cells get the message to develop a signaling network

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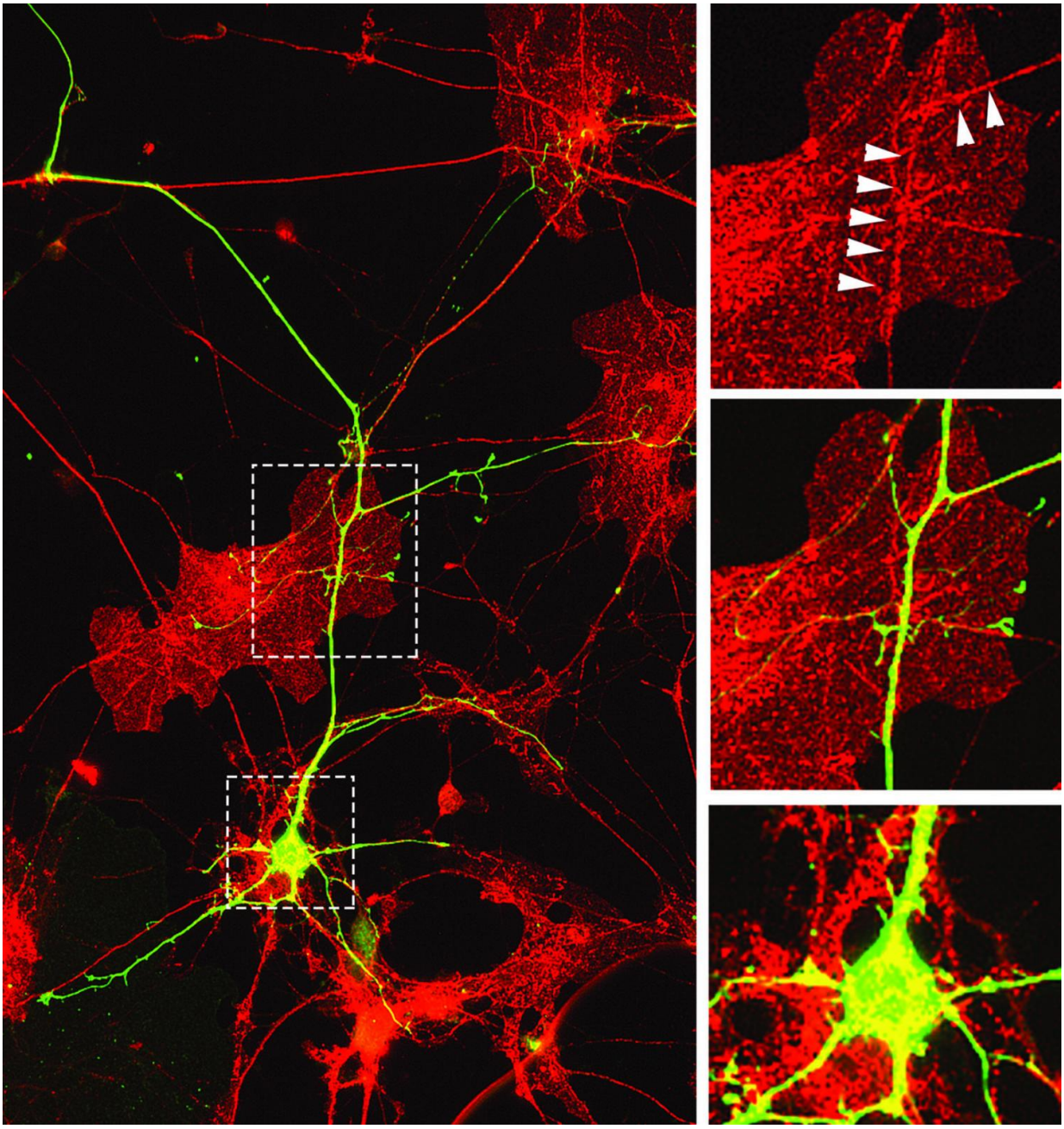

University of Iowa biologists have shown that neurons need exact gene matches to get the signal to grow dendrites, the branches in brain cells that help pass messages from the brain throughout the body. Left: An image of mouse neurons with developed, functioning dendrites (yellow and green), surrounded by other cells called astrocytes (in red). Lower right: A single neuron's nucleus (yellow spot) with dendrites (yellow tendrils). Upper right: Arrows showing sites of contact between a neuron's cell surface and an astrocyte. Middle right: the enlarged area of a neuron-dendritic network. Credit: Joshua Weiner lab/University of Iowa

When you think of a neuron, imagine a tree. A healthy brain cell indeed looks like a tree with a full canopy. There's a trunk, which is the cell's nucleus; there's a root system, embodied in a single axon; and there are the branches, called dendrites.

Neurons in your brain pass signals from one to another like they're playing an elaborate, lightning-quick game of telephone, using axons as the transmitters and dendrites as the receivers. Those signals originate in the brain and are passed throughout the body, culminating in simple actions, such as wiggling a toe, to more complex instructions, such as following through on a thought.

Just as you can judge a healthy tree by its canopy, so too can scientists judge a healthy neuron by its dendritic branches. But it had been unclear what causes dendrites to grow, and where those instructions to grow come from.

Biologists at the University of Iowa have determined a group of genes associated with neurons help regulate dendrites' growth. But there's a catch: These genes, called gamma-protocadherins, must be an exact

match for each neuron for the cells to correctly grow dendrites.

The findings may offer new insight into what causes aggressive or stunted dendrite growth in neurons, which could help explain the biological reasons for some mental-health diseases, as well as help researchers better understand brain development in babies born prematurely.

"Disrupted dendrite arborization is seen in the brains of people with autism and schizophrenia, so processes like the one we have uncovered here may have relevance to human disorders," says Joshua Weiner, a molecular biologist at the UI and corresponding author on the paper, published online this month in the journal *Cell Reports*.

Gamma-protocadherins are called "adhesion molecules" because they stick out from a cell's membrane to bind and hold cells together. The researchers learned about their role by giving a developing brain cell in a mouse the same gamma-protocadherin as in surrounding cells. When they did, the cells grew longer, more complex dendrites. But when the researchers outfitted a mouse neuron with a different gamma-protocadherin than the cells around it, dendritic growth was stunted.

The human brain is filled with neurons. Scientists think adults have 100 billion brain cells, each in close proximity to others and all seeking to make contact through their axons and dendrites. The denser a neuron's dendritic network, the more apt a cell is to be in touch with another and aid in passing signals.

Gamma-protocadherins act like molecular Velcro, binding neurons together and instructing them to grow their dendrites. Weiner and his team figured out their role when they observed paltry dendritic growth in mouse brain cells where the gamma-protocadherins had been silenced.

The researchers went further in the new study. Using mice, they expressed the same type of gamma-protocadherin (labeled either as A1 or C3) in neurons in the cerebral cortex, a region of the brain that processes language and information. After five weeks, the neurons had sizeable dendritic networks, indicative of a healthy, normally functioning brain. Likewise, when they turned on a gamma-protocadherin gene in a neuron different from the gamma-protocadherin gene with the cells surrounding it, the mice had limited dendrite growth after the same time period.

That's important because human neurons carry up to six gamma-protocadherins, meaning there are many combinations potentially in play. Yet, it seems the "grow your dendrite" signal only happens when neurons carrying the the same gamma-protocadherin gene pair up.

"The neurons actually care who they match with," says Weiner, associate professor in the Department of Biology, part of the College of Liberal Arts and Sciences. "It takes what we knew from biochemical studies in a dish and shows that protocadherins really mediate these matching interactions in the developing brain."

The team reports that star-looking cells called astrocytes also play a role in neurons' dendrite development. Astrocytes are glial (Greek for "glue") cells that help to bridge the gap between neurons and speed signals along. When the molecular binding between an astrocyte and neurons is an exact match, the neurons grow fully formed dendrites, the researchers report.

"Our data indicate that g-Pcdhs (gamma-protocadherins) act locally to promote dendrite arborization via homophilic matching and confirm that connectivity in vivo depends on molecular interactions between neurons and between neurons and astrocytes," the authors write.

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