MedicalXpress

How human cells 'hold hands'

April 30 2012

University of Iowa biologists have advanced the knowledge of human neurodevelopmental disorders by finding that a lack of a particular group of cell adhesion molecules in the cerebral cortex -- the outermost layer of the brain where language, thought and other higher functions take place -- disrupts the formation of neural circuitry.

Andrew Garrett, former neuroscience graduate student and current postdoctoral fellow at the Jackson Laboratory, Bar Harbor, Maine; Dietmar Schreiner, former postdoctoral fellow currently at the University of Basel, Switzerland; Mark Lobas, current neuroscience graduate student; and Joshua A. Weiner, associate professor in the UI College of Liberal Arts and Sciences Department of Biology, published their findings in the April 26 issue of the journal *Neuron*.

Cell adhesion is the way in which cells "hold hands" -- how one cell binds itself to another cell using specific molecules that protrude from cell membranes and bind each other together. The process is necessary to form all body tissues. The UI researchers studied a clustered family of 22 genes (gamma-protocadherins) that make such cellular hand-holding possible by encoding cell adhesion molecules.

In their previous work, they found that mice lacking the molecules exhibited death of neurons and loss of synapses in the spinal cord. So, they knew the gamma-protocadherins were important for neurons in the spinal cord, but not whether this was true in the cortex. However, in the current study, they found that an absence of the cell adhesion molecules had a significant and much different effect.

"We found that mice lacking the gamma-protocadherins in the cortex do not exhibit the severe loss of synapses and increased neuronal death that we observed in the spinal cord," says Weiner. "Instead, we found that the cortical neurons had severely reduced development of their dendrites, tree-like branched structures that receive input from other neurons.

"We discovered the reason for this: gamma-protocadherins normally inhibit a key signaling pathway within neurons that acts to reduce dendrite branching. In the absence of the gamma-protocadherins, this signaling pathway was hyperactive, leading to defective branching of cortical neuron dendrites," says Weiner.

In their previous work, the researchers showed that these molecules -- the 22 distinct adhesion molecules, the gamma-protocadherins -- are critical for the development of the animal, because when all of the genes are deleted from mice, they die shortly after birth with a variety of neurological defects including loss of connections (synapses) and excessive neuronal cell death in the spinal cord -- an early-developing part of the nervous system.

Because those mutants die so young, the researchers could not assess a role for the gamma-protocadherins in the cerebral cortex. The reason is that the cortex develops only after birth. They used new genetic technologies to remove the gamma-protocadherins only from the cerebral cortex, which allowed the animals to survive to adulthood.

Weiner says that the latest research findings may help researchers to better understand the causes of various human developmental disorders.

"Human neurodevelopmental disorders such as autism, mental retardation, and schizophrenia all involve dysregulation of dendrite branching and synaptogenesis," he says. "Our identification of a large family of 22 cell adhesion molecules -- which we previously showed

interact with each other in very complex and specific ways -- as new regulators of dendrite branching raises the question of whether specific interactions between distinct neuronal groups during development is important for the spreading of dendritic branches. If so, the gamma-protocadherins and/or the signaling pathways they regulate might be disrupted in a variety of human brain disorders."

Now that the researchers have shown that the gamma-protocadherin family, as a whole, is critical for dendrite branching, they plan to become more focused in their research. Next, they plan to ask whether specific interactions between individual members of the family are important for instructing neurons on the location and size of dendrite growth.

Provided by University of Iowa