Researchers discover how brain circuits can become miswired during development

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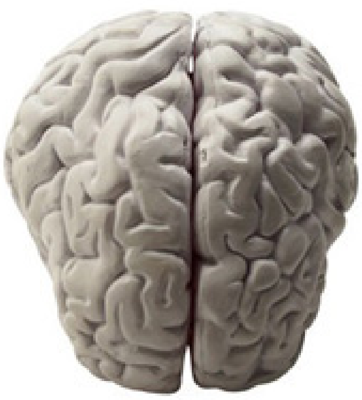

Researchers at Weill Cornell Medical College have uncovered a mechanism that guides the exquisite wiring of neural circuits in a developing brain—gaining unprecedented insight into the faulty circuits that may lead to brain disorders ranging from autism to mental retardation.

In the journal *Cell*, the researchers describe, for the first time, that faulty wiring occurs when RNA molecules embedded in a growing axon are not degraded after they give instructions that help steer the nerve cell. So, for example, the signal that tells the axon to turn—which should disappear after the turn is made—remains active, interfering with new signals meant to guide the axon in other directions.

The scientists say that there may be a way to use this new knowledge to fix the circuits.

"Understanding the basis of brain miswiring can help scientists come up with new therapies and strategies to correct the problem," says the study's senior author, Dr. Samie Jaffrey, a professor in the Department of Pharmacology.

"The brain is quite 'plastic' and changeable in the very young, and if we know why circuits are miswired, it may be possible to correct those pathways, allowing the brain to build new, functional wiring," he says.

Disorders associated with faulty neuronal circuits include epilepsy, autism, schizophrenia, mental retardation and spasticity and movement disorders, among others.

In their study, the scientists describe a process of brain wiring that is much more dynamic than was previously known—and thus more prone to error.

Proteins Sense the Environment to Steer the Axon

During brain development, neurons have to connect to each other, which they do by extending their long axons to touch one another. Ultimately, these neurons form a circuit between the brain and the target tissue through which chemical and electrical signals are relayed. In this study, researchers investigated neurons that travel up the spinal cord into the brain. "It is very critical that axons are precisely positioned in the spinal cord," Dr. Jaffrey says. "If they are improperly positioned, they will form the wrong connections, which can lead to signals being sent to the wrong target cells in the brain."

The way that an axon guides and finds its proper target is through socalled growth cones located at the tips of axons. "These growth cones have the ability to sense the environment, determine where the targets are and navigate toward them. The question has always been—how do they know how to do this? Where do the instructions come from that tell them how to find their proper target?" Dr. Jaffrey says. The team found that RNA molecules embedded in the growth cone are responsible for instructing the axon to move left or right, up or down. These RNAs are translated in growth cones to produce antenna-like proteins that steer the axon like a self-guided missile.

"As a circuit is being built, RNAs in the neuron's growth cones are mostly silent. We found that specific RNAs are only read at precise stages in order to produce the right protein needed to steer the axon at the right time. After the protein is produced, we saw that the RNA instruction is degraded and disappears," he says.

"If these RNAs do not disappear when they should, the axon does not position itself properly—it may go right instead of left—and the wiring will be incorrect and the circuit may be faulty," Dr. Jaffrey says.

RNAs Have Tremendous Power Over Brain Development

The research finding answers a long-standing puzzle in the quest to understand brain wiring, says Dr. Dilek Colak, a postdoctoral associate in Dr. Jaffrey's laboratory.

"There have been a series of discoveries over the last five years showing that proteins that control RNA degradation are very important for brain development and, when they are mutated, you can have spasticity or other movement disorders," Dr. Colak says. "That has raised a major question—why would RNA degradation pathways be so critical for properly creating brain circuits?

"What we show here is that not only does RNA need to be present in growth cones to give instructions, it then also needs to be removed from the growth cones to take away those instructions at the right time," she says. "Both those processes are critical and it may explain why there are so many different brain disorders associated with ineffective RNA regulation."

"The idea that control of brain wiring is located in these RNA molecules that are constantly being dynamically turned over is something that we didn't anticipate," Dr. Jaffrey adds. "This tells us that regulating these RNA degradation pathways could have a tremendous impact on brain development. Now we know where to look to tease apart this process when it goes awry, and to think about how we can repair it."

Provided by Weill Cornell Medical College