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Efficient process using microRNA converts human skin cells into neurons

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The addition of two particular gene snippets to a skin cell's usual genetic material is enough to turn that cell into a fully functional neuron, report researchers from the Stanford University School of Medicine. The finding, to be published online July 13 in *Nature*, is one of just a few recent reports of ways to create human neurons in a lab dish.

The new capability to essentially grow neurons from scratch is a big step for neuroscience research, which has been stymied by the lack of human neurons for study. Unlike skin cells or blood cells, neurons are not something that's easy for a living human to donate for research.

"A major problem in neurobiology has been the lack of a good human model," said senior author Gerald Crabtree, MD, professor of pathology and of developmental biology. "Neurons aren't like blood. They're not something people want to give up."

Generating neurons from easily accessible cells, such as skin cells, makes possible new ways to study neuronal development, model disease processes and test treatments.

It also helps advance the effort, still in its infancy, to replace damaged or dead neurons with new ones.

Before succeeding at turning skin cells straight into neurons, scientists had discovered two years ago that they could get similar results if they transformed the skin cell first into a stem cell and then coaxed the stem

cell into becoming a neuron. But Crabtree's new study and two studies by others show it's possible to go straight from skin cell to neuron without the stem-cell pit stop.

Crabtree's study is unique among the efforts because of the surprising identity of the molecules that nudged the cells to switch — short chains of genetic material called microRNA, best known for their ability to bind to specific genetic transcripts to turn off their activity.

"In this case, though, they're playing an instructive role," Crabtree said.

The discovery of the microRNAs' ability to switch the cells came to light when Andrew Yoo, PhD, then a postdoctoral researcher in Crabtree's lab (now on the faculty of Washington University in St. Louis), was trying to better understand what makes neural stem cells move on to become mature neurons. He found that two microRNAs, miR-9/9* and miR-124, trigger it by controlling a molecular machine (called the BAF chromatin remodeling complex) that shapes chromosomes so they'll direct the cell to remain a stem cell.

"When the microRNAs bind to one subunit of this 13-membered complex they turn this function off, and the cells begin to grow up and connect to one another — that is, they become mature, functioning neurons," said Crabtree. After they published this in *Nature* in 2009, Yoo went on to try to understand how the two microRNAs functioned. One way he did this was to watch what happened when he introduced them into cells that normally lacked them.

At first he didn't believe what he was seeing through the microscope: The cells with the additional microRNAs had started to look like neurons. "It was very weird. We were astounded," said Crabtree, who is also the David Korn, MD, Professor of Pathology.

Yoo, one of the new report's lead authors, continued to study the phenomenon with others at Stanford. They used a virus to carry the snippets into skin cells and investigated whether the resulting cells really were neurons. They found that 2 to 3 percent of the skin cells reliably converted to neurons: The cells generated the electrical signals neurons use to communicate with one another, and they budded off small globules, called synaptic vesicles, just as the adult neurons ordinarily do.

"What we made are neurons that are characteristic of the frontal cortex — actually what you'd imagine would be the most difficult to make. They're the ones we think with, that we use to put two things together and see connections, not the ones involved in evolutionarily older emotional responses," said Crabtree. "We also find inhibitory neurons among the converted cells, whose role is to keep the activity of other neurons at a resting, controlled state."

The team improved the efficiency of the transformation to 20 percent by adding two of the factors used in a similar experiment by colleague Marius Wernig, MD, assistant professor of pathology, in the first published account of converting a human skin cell directly to a neuron. In May this year, Wernig reported in Nature that the combination of four particular proteins can convert skin cells directly into functional neurons with 2 to 4 percent efficiency. (Even more recently, on July 3, *Nature* published a study led by a researcher at the San Raffaele Scientific Institute in Milan, Italy, showing a mix of three other proteins can set off the conversion.)

"It's been a long time in coming to this," said Crabtree. "But science often progresses in leaps and starts, and then all of a sudden many scientists come to the same position at the same time. Now these studies have come out, and more will be coming, all of which are going to say that not only can you can make neurons different ways, but also you can make neurons of different types."

Wernig's study produced the same "thinking" neurons as Crabtree's did, but did not find inhibitory neurons. The Italian study produced neurons that release dopamine, a chemical that affects many behaviors, from moving, to learning, to sleeping.

Among the projects taking off from this finding is an effort to set up a model for Down syndrome. Stanford graduate student Alfred Sun, a co-leader of the study, has obtained skin cells from patients and converted them to neurons. Now he can try to see what's different about them.

"Our belief is there are certain biochemical abnormalities that might be correctable," Crabtree said.

Provided by Stanford University Medical Center