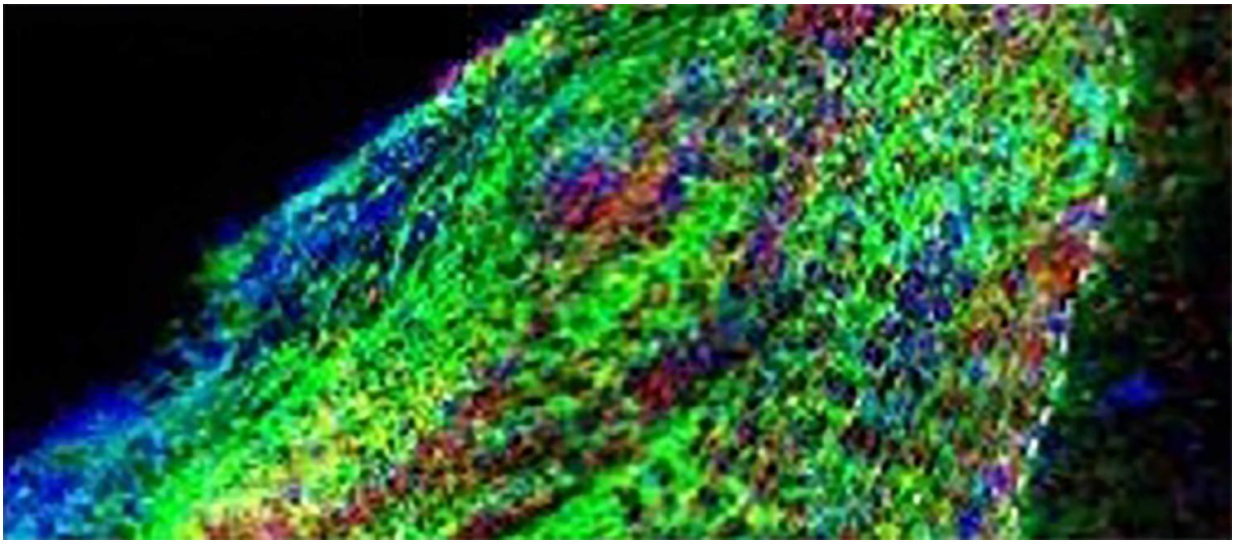
MedicalXpress

Stem cell therapy heals injured mouse brain

August 22 2016



Giving a compound called 3K3A-APC to mice with stroke-induced brain damage dramatically increased the production of new neurons (labeled in red) from neural stem cells implanted next to the injured area. Credit: Berislav Zlokovic, M.D., Ph.D., University of Southern California

Permanent brain damage from a stroke may be reversible thanks to a developing therapeutic technique, a USC-led study has found.

The novel approach combines transplanted human stem cells with a special protein that the U.S. Food and Drug Administration already approved for clinical studies in new stroke patients.

"This USC-led animal study could pave the way for a potential breakthrough in how we treat people who have experienced a stroke," said Jim Koenig, a program director at the National Institute of Neurological Disorders and Stroke, which funded the research. "If the therapy works in humans, it could markedly accelerate the recovery of these patients."

Berislav Zlokovic, senior author of the Aug. 22 *Nature Medicine* study, and his colleagues identified a protein that spurs neural stem cells to become functional neurons: 3K3A-APC, a variant of the human protein "activated protein C."

The created compound is being tested as a neuroprotectant. Researchers in a National Institutes of Health-funded Phase II clinical trial administer 3K3A-APC to patients who have very recently (within a few hours) suffered from an ischemic stroke, when a clot blocks blood from reaching the brain. About 87 percent of all strokes are ischemic, according to the Centers for Disease Control and Prevention.

However, Zlokovic, director of the Zilkha Neurogenetic Institute at the Keck School of Medicine of USC, said he and his colleagues are the first to use 3K3A-APC to produce neurons from human stem cells grafted into the stroke-damaged mouse brain.

"We showed that 3K3A-APC helps the grafted stem cells convert into neurons and make structural and functional connections with the host's nervous system," said Zlokovic, a scientific founder of ZZ Biotech, a company devoted to developing therapeutics using variants of activated protein C. "No one in the stroke field has ever shown this, so I believe this is going to be the gold standard for future studies."

Although other researchers have experimented with grafting stem cells into injured brain areas, they have met with limited success—partially

because transplanted stem cells diminish with time. The therapeutic compound stops that from happening.

Every year more than 795,000 people in the United States have a stroke, according to the CDC. These debilitating seizures reduce mobility in more than half of stroke survivors age 65 and older.

More than 70 percent of stroke survivors live with substantial neurological symptoms such as muscle weakness or paralysis, according to Yaoming Wang, co-lead author of the study and a senior research associate at the Zilkha Neurogenetic Institute at the Keck School.

"The need for an efficacious, practical and late treatment of stroke remains unmet," Wang said. "Regenerative medicine with stem cells holds great promise for the treatment of stroke."

How combination therapy works

A week—the equivalent of several months in humans—after scientists induced a stroke in mice, the researchers placed human neural stem cells next to damaged brain tissue. Then they administered the immunosuppressant cyclosporine and four doses of 3K3A-APC or a placebo solution over a span of seven days.

The transplanted stem cells matured into neurons and other brain cells. Mice treated with the special compound had 16 times more human stem cell-derived neurons than those who were treated with the placebo.

"Functional deficit after five weeks of stroke were minimized, and the mice were almost back to normal in terms of motor and sensorimotor functions," Zlokovic said. "Synapses formed between transplanted cells and host cells, so there is functional activation and cooperation of transplanted cells in the host circuitry."

To test whether the injected stem cells caused the observed motor and sensorimotor improvements, USC researchers used an assassin toxin to exterminate neurons that developed from human stem cells. They found that these mice lost improvements in motor or sensory tests, suggesting the neurons that grew from implanted stem cells were necessary for recovery from stroke-induced disability.

The motor and sensory tests

Researchers tested motor functions by having mice walk forward on a rotating rod without falling off. They tested sensory and motor function by placing tape on the mouse's forepaw and observed how long it took the mice to remove the adhesive.

Rodents given human stem cells and treated with 3K3A-APC performed much better on these performance tests, said Zhen Zhao, co-lead author and an assistant professor of research physiology and biophysics at the Zilkha Neurogenetic Institute.

Functional integration

To test the brain's circuitry after the stroke, researchers labeled stem cells with an indicator of neuronal activity and then stimulated the paws of the mice with a mechanical vibration. They noted the injured area in 3K3A-APC-treated mice was activated much more than in mice treated with the placebo. Moreover, the response time was much closer to that of uninjured mice.

These results suggest that neurons which grew from the stem cells are functionally integrated into the host's brain circuitry.

The future of stem cell therapy

In June, Stanford University researchers drilled a hole into the skulls of people whose motor and sensory abilities had been compromised because of stroke. Then they injected stem cells harvested from the bone marrow of adult donors. Although the study involved only 18 patients, researchers noted meaningful recovery, such as the ability to walk again. Stanford researchers said the stem cells seemed to trigger a biochemical process that enhanced the brain's ability to regenerate neurons. The transplanted stem cells themselves did not become neurons.

In contrast, researchers in the USC-led study were able to stimulate transplanted stem cells to becoming neurons in a mouse study.

Zlokovic and his team now hope to pursue a new Phase II clinical trial to test whether their combination therapy that stimulated the growth of neurons in mice can be replicated in human stroke patients. If the trial succeeds, they plan to extend the neural stem cell grafts and 3K3A-APC treatment to other neurological conditions, such as spinal cord injuries.

More information: Wang et al. 3K3A-activated protein C stimulates postischemic neuronal repair by human neural stem cells in mice. *Nature Medicine*. August 22, 2016. DOI: 10.1038/nm.4154

Provided by National Institutes of Health