A new weapon against stroke: Stem cell study uncovers the brain-protective powers of astrocytes

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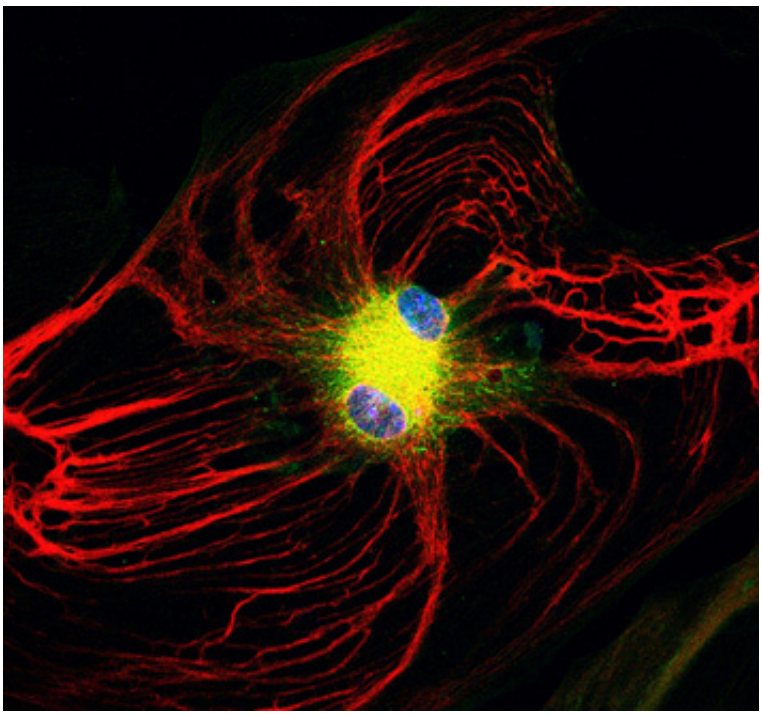

An astrocyte

One of regenerative medicine's greatest goals is to develop new treatments for stroke. So far, stem cell research for the disease has focused on developing therapeutic neurons—the primary movers of electrical impulses in the brain—to repair tissue damaged when oxygen to the brain is limited by a blood clot or break in a vessel. New UC Davis

research, however, shows that other cells may be better suited for the task.

Published July 23 in the journal *Nature Communications*, the large, collaborative study found that astrocytes—neural cells that transport key nutrients and form the blood-brain barrier—can protect brain tissue and reduce disability due to stroke and other ischemic brain disorders.

"Astrocytes are often considered just 'housekeeping' cells because of their supportive roles to neurons, but they're actually much more sophisticated," said Wenbin Deng, associate professor of biochemistry and molecular medicine at UC Davis and senior author of the study. "They are critical to several brain functions and are believed to protect neurons from injury and death. They are not excitable cells like neurons and are easier to harness. We wanted to explore their potential in treating neurological disorders, beginning with stroke."

Deng added that the therapeutic potential of astrocytes has not been investigated in this context, since making them at the purity levels necessary for stem cell therapies is challenging. In addition, the specific types of astrocytes linked with protecting and repairing brain injuries were not well understood.

The team began by using a transcription factor (a protein that turns on genes) known as Olig2 to differentiate human embryonic stem cells into astrocytes. This approach generated a previously undiscovered type of astrocyte called Olig2PC-Astros. More importantly, it produced those astrocytes at almost 100 percent purity.

The researchers then compared the effects of Olig2PC-Astros, another type of astrocyte called NPC-Astros and no treatment whatsoever on three groups of rats with ischemic brain injuries. The rats transplanted with Olig2PC-Astros experienced superior neuroprotection together with

higher levels of brain-derived neurotrophic factor (BDNF), a protein associated with nerve growth and survival. The rats transplanted with NPC-Astros or that received no treatment showed much higher levels of neuronal loss.

To determine whether the astrocytes impacted behavior, the researchers used a water maze to measure the rats' learning and memory. In the maze, the rats were required to use memory rather than vision to reach a destination. When tested 14 days after transplantation, the rats receiving Olig2PC-Astros navigated the maze in significantly less time than the rats that received NPC-Astros or no treatment.

The investigators used cell culture experiments to determine whether the astrocytes could protect neurons from oxidative stress, which plays a significant role in brain injury following stroke. They exposed neurons co-cultured with both types of astrocytes to hydrogen peroxide to replicate oxidative stress. They found that, while both types of astrocytes provided protection, the Olig2PC-Astros had greater antioxidant effects. Further investigation showed that the Olig2PC-Astros had higher levels of the protein Nrf2, which increased antioxidant activity in the mouse neurons.

"We were surprised and delighted to find that the Olig2PC-Astros protected neurons from oxidative stress in addition to rebuilding the neural circuits that improved learning and memory," said Deng.

The investigators also investigated the genetic qualities of the newly identified astrocytes. Global microarray studies showed they were genetically similar to the standard NPC-Astros. The Olig2PC-Astros, however, expressed more genes (such as BDNF and vasoactive endothelial growth factor, or VEGF) associated with neuroprotection. Many of these genes help regulate the formation and function of synapses, which carry signals between neurons.

Additional experiments showed that both the Olig2PC-Astros and NPC-Astros accelerated synapse development in mouse neurons. The Olig2PC-Astros, however, had significantly greater protective effects over the NPC-Astros.

In addition to being therapeutically helpful, the Olig2PC-Astros showed no tumor formation, remained in brain areas where they were transplanted and did not differentiate into other cell types, such as neurons.

"Dr. Deng's team has shown that this new method for deriving astrocytes from embryonic stem cells creates a cell population that is more pure and functionally superior to the standard method for astrocyte derivation," said Jan Nolta, director of the UC Davis Institute for Regenerative Cures. "The functional improvement seen in the brain injury models is impressive, as are the higher levels of BDNF. I will be excited to see this work extended to other brain disease models such as Huntington's disease and others, where it is known that BDNF has a positive effect."

Deng added that the results could lead to stem cell treatments for many neurodegenerative diseases.

"By creating a highly purified population of astrocytes and showing both their therapeutic benefits and safety, we open up the possibility of using these cells to restore brain function for conditions such as Alzheimer's disease, epilepsy, traumatic brain disorder, cerebral palsy and spinal cord injury," said Deng.

More information: *Nature Communications* Doi: 10.1038/ncomms3196

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