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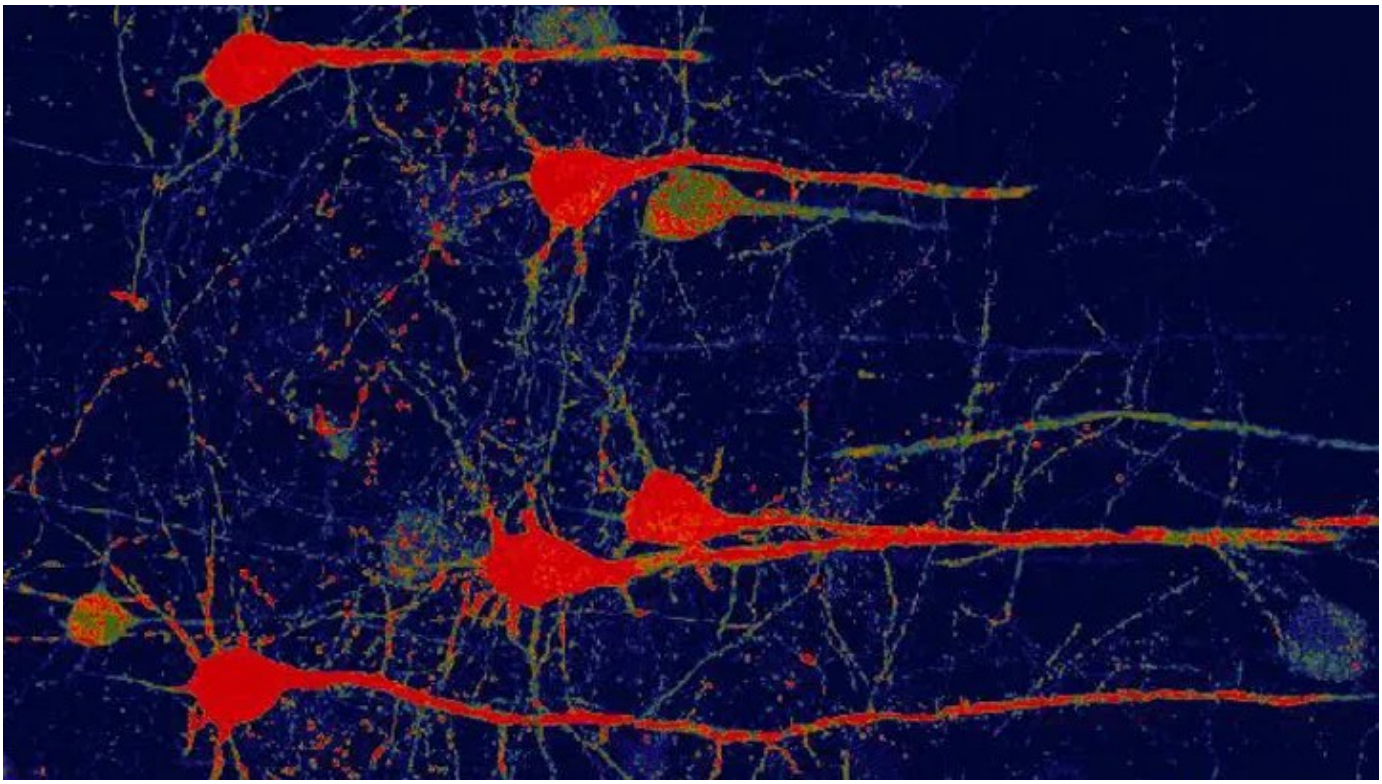
Gene Therapy Shows Promise Repairing Brain Tissue Damaged by Stroke

Posted on September 24th, 2019 by Dr. Francis Collins



Caption: Neurons (red) converted from glial cells using a new NeuroD1-based gene therapy in mice. Credit: Chen Laboratory, Penn State, University Park

It's a race against time when someone suffers a stroke caused by a blockage of a blood vessel supplying the brain. Unless clot-busting treatment is given within a few hours after symptoms appear, vast numbers of the brain's neurons die, often leading to paralysis or other disabilities. It would be great to have a way to replace those lost neurons. Thanks to gene therapy, some encouraging strides are now being made.

In a recent study in *Molecular Therapy*, researchers reported that, in their mouse and rat models of ischemic stroke, gene therapy could actually convert the brain's support cells into new, fully functional neurons [1]. Even better, after gaining the new neurons, the animals had improved

motor and memory skills.

For the team led by Gong Chen, Penn State, University Park, the quest to replace lost neurons in the brain began about a decade ago. While searching for the right approach, Chen noticed other groups had learned to reprogram fibroblasts into stem cells and make replacement neural cells.

As innovative as this work was at the time, it was performed mostly in lab Petri dishes. Chen and his colleagues thought, why not reprogram cells already in the brain?

They turned their attention to the brain's billions of supportive glial cells. Unlike neurons, glial cells divide and replicate. They also are known to survive and activate following a brain injury, remaining at the wound and ultimately forming a scar. This same process had also been observed in the brain following many types of injury, including stroke and neurodegenerative conditions such as Alzheimer's disease.

To Chen's NIH-supported team, it looked like glial cells might be a perfect target for gene therapies to replace lost neurons. As reported about five years ago, the researchers were on the right track [2].

The Chen team showed it was possible to reprogram glial cells in the brain into functional neurons. They succeeded using a genetically engineered retrovirus that delivered a single protein called NeuroD1. It's a neural transcription factor that switches genes on and off in neural cells and helps to determine their cell fate. The newly generated neurons were also capable of integrating into brain circuits to repair damaged tissue.

There was one major hitch: the NeuroD1 retroviral vector only reprogrammed actively dividing glial cells. That suggested their strategy likely couldn't generate the large numbers of new cells needed to repair damaged brain tissue following a stroke.

Fast-forward a couple of years, and improved adeno-associated viral vectors (AAV) have emerged as a major alternative to retroviruses for gene therapy applications. This was exactly the breakthrough that the Chen team needed. The AAVs can reprogram glial cells whether they are dividing or not.

In the new study, Chen's team, led by post-doc Yu-Chen Chen, put this new gene therapy system to work, and the results are quite remarkable. In a mouse model of ischemic stroke, the researchers showed the treatment could regenerate about a third of the total lost neurons by preferentially targeting reactive, scar-forming glial cells. The conversion of those reactive glial cells into neurons also protected another third of the neurons from injury.

Studies in brain slices showed that the replacement neurons were fully functional and appeared to have made the needed neural connections in the brain. Importantly, their studies also showed that the NeuroD1 gene therapy led to marked improvements in the functional recovery of the mice after a stroke.

In fact, several tests of their ability to make fine movements with their forelimbs showed about a 60 percent improvement within 20 to 60 days of receiving the NeuroD1 therapy. Together with study collaborator and NIH grantee Gregory Quirk, University of Puerto Rico, San Juan, they went on to show similar improvements in the ability of rats to recover from stroke-related deficits in memory.

While further study is needed, the findings in rodents offer encouraging evidence that treatments to repair the brain after a stroke or other injury may be on the horizon. In the meantime, the best strategy for limiting the number of neurons lost due to stroke is to recognize the signs and get to a well-equipped hospital or call 911 right away if you or a loved one experience them. Those signs

include: sudden numbness or weakness of one side of the body; confusion; difficulty speaking, seeing, or walking; and a sudden, severe headache with unknown causes. Getting treatment for this kind of "brain attack" within four hours of the onset of symptoms can make all the difference in recovery.

References:

[1] A NeuroD1 AAV-Based gene therapy for functional brain repair after ischemic injury through in vivo astrocyte-to-neuron conversion. Chen Y-C et al. Molecular Therapy. Published online September 6, 2019.

[2] In vivo direct reprogramming of reactive glial cells into functional neurons after brain injury and in an Alzheimer's disease model. Guo Z, Zhang L, Wu Z, Chen Y, Wang F, Chen G. Cell Stem Cell. 2014 Feb 6;14(2):188-202.

Links:

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***MKF* says:**
September 24, 2019 at 10:43 am
I was in the United States Air Force from 1978-2008 where due to my coworkers and my hard head I rose from a poor female to the highest rank-Chief Master Sergeant. I worked in a very challenging career field – Bioenvironmental Engineering where the team traveled world wide. 11 months after I retired I had an ischemic stroke. Through dedication I am able to walk about 400 feet, as of now. The stroke affected my right side (to include my right arm