Regenerating damaged nerves with 'Pac-Man' cells

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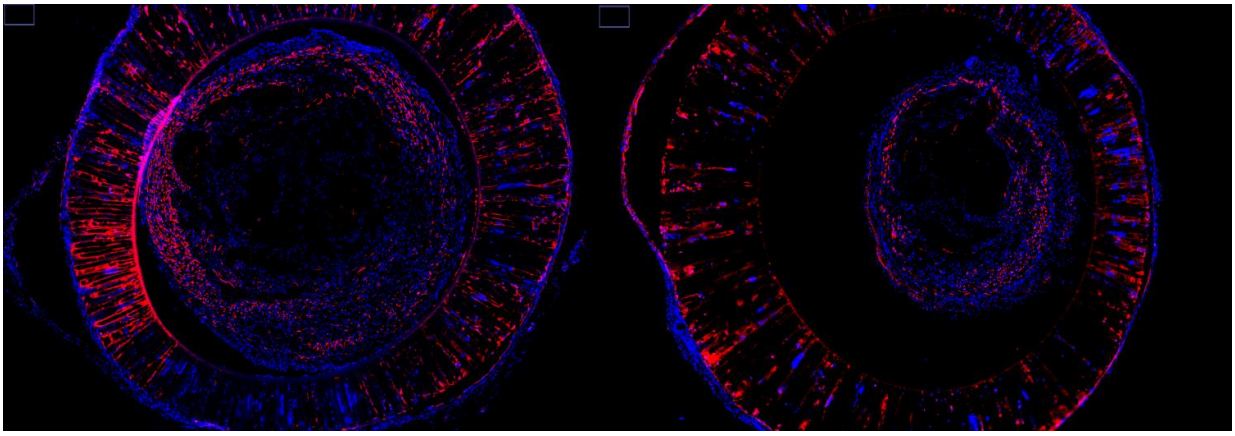

Very small tubes filled with two kinds of growth factors show the regrowth of damaged nerve fibers (central area). On the right is a chemical signal that transforms immune system macrophages into healing cells. On the left is a more robust nerve grown with a signal that recruits undifferentiated cells and makes them specialize as pro-healing macrophages. Credit: Ravi Bellamkonda, Duke University

Biomedical engineers have found an unlikely ally in the struggle to regrow damaged nerves—the foot soldiers of the body's immune system.

Macrophages are known as the Pac-Man of the immune system and form the body's first line of defense against invasion—they indiscriminately engulf and eat most anything deemed a dangerous trespasser, whether it's

a bacterium or cellular debris from deceased tissue. Recent research, however, has shown that some macrophages also promote healing.

In a study appearing online the week of June 12 in the *Proceedings of the National Academy of Sciences*, researchers from Duke University have shown that summoning these pro-healing macrophages can greatly help regrow severed nerves in rats. The approach comes close to equaling the current best treatment—a surgical transplant using a nerve stripped from another part of the patient's body.

"There's been a long-held view that the best way to regrow severed nerves is to provide all sorts of matrix and growth proteins to coax repair," said Ravi Bellamkonda, professor of biomedical engineering and Vinik Dean of the Pratt School of Engineering at Duke. "We've completely shifted that view by finding new players who have remained behind the scenes. We believe this approach will also have a major impact on regenerative medicine, even beyond this specific application."

The peripheral nervous system includes nerves that run from the spinal cord to the rest of the body. It connects and controls movements, the digestive system, heart, lungs and other organs. When these relatively long cells—which can stretch for a meter or more—are damaged or severed, the injury is not easily healed.

The current standard of care, called an autograft, involves surgically removing a less important nerve, like the one running down the back of the calf, and grafting it into the damaged area. But the treatment has several drawbacks. A sensory neuron replacing a motor neuron is not a perfect replacement, painful neuromas can occur at the healing site, the patient loses the function of another nerve and, in the case of extensive injuries, there are only so many semi-disposable nerves in the body to harvest.

Researchers have long been working on an alternative approach using "nerve bridges" to span these gaps. The idea is to introduce a tube filled with growth factors and other goodies across the gap to coax the regrowth of the existing nerve, like luring a dog out of a hiding place with treats. But despite efforts to find the optimal combination of tube material, growth factors, proteins and other helpers, nothing has come close to matching the autograft's success.

Bellamkonda and his group were travelling down this same road until some salamanders lost their tails.

"We saw a study showing that the early presence of macrophages were vital to a salamander's ability to regenerate its tail," said Nassir Mokarram, assistant research professor of biomedical engineering at Duke. "We also knew that rare instances of nerve regeneration were accompanied by a surge of these cells right after the injury occurred. Those two observations gave us the inspiration to see if the same idea could be applied with nerve bridges."

In 2012, Bellamkonda and Mokarram showed that nerve regeneration could be increased in rats by forcing macrophages to become the pro-healing variety that secrete healing compounds. In the new paper, the researchers take their work a step further. Instead of issuing orders to make mature macrophages switch roles, they filled the nerve bridge with a biological signal shown to attract younger, undifferentiated cells destined to become pro-healing macrophages.

"Instead of retraining the demolition and cleanup crew, we hired a new workforce with a future in construction," said Mokarram. "The results were significantly better. This is the closest anyone has ever been to equaling the efficacy of an autograft, and we did it with nothing more than a tube and the recruitment of the body's own immune system."

The researchers next plan to test the approach using a specialized nanofiber material they developed that has already proven better at bridging nerve endings than the tubes used in this proof-of-concept study.

"We're the first group to prove this immunological approach to healing works with nerves in rodents," said Mokarram. "We think this work will open a path to using similar methods in the much more complex and difficult arenas of the spinal cord and brain."

More information: Nassir Mokarram el al., "Immunoengineering nerve repair," *PNAS* (2017). www.pnas.org/cgi/doi/10.1073/pnas.1705757114

Provided by Duke University