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# Study seeks new way to enhance neuron repair in spinal cord injury

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If researchers could determine how to send signals to cells responding to a spinal cord injury, they might be able to stop one type of cell from doing additional damage at the injury site and instead, coax it into helping nerve cells grow.

That is the theory behind new research at Ohio State University, where scientists are trying to determine how to simultaneously stop damage and promote neuron growth with a single, targeted signal.

The cells in question are macrophages, a type of white blood cell found in injured tissue. After a spinal cord injury, macrophages travel to the injury site from at least three known locations in the body as part of an intense inflammatory response. After several days, these cells promote inflammation and toxicity, which can exacerbate effects of the original injury. But these same cells might also offer hope for restoration of function in people with injured spinal cords.

Scientists determined in previous research that macrophages receive signals at the site of a spinal cord injury that cause them to both promote the growth of axons – extensions that allow for communication among nerve cells – as well as cause tissue damage. This new study suggests that there could be a way to manipulate these signals to silence the damaging effects while enhancing the repair function.

"We know a single population of macrophages has both capabilities," said John Gensel, a postdoctoral researcher in neuroscience at Ohio State

and lead author of the work. "But we've also found that there are some specific receptors we can target that reduce the pathological potential of macrophages while retaining their regenerative characteristics."

Gensel presented the research during a mini-symposium today (11/15) at the Society for Neuroscience meeting in San Diego.

Ohio State researchers consider manipulation of the immune response after spinal cord injury a potential therapy approach for these devastating traumas, for which no federally approved treatments currently exist. An estimated 1.3 million people in the United States are living with a spinal cord injury, experiencing paralysis and complications that include bladder, bowel and sexual dysfunction and chronic pain.

Using a synthetic molecule to stimulate macrophages, the researchers previously showed that multiple receptors on these cells were involved in their activation, and that the receptors dictate how the macrophages behave. If more than one receptor is stimulated, the macrophage has the potential to either kill a nerve cell, stimulate it to grow, or both.

"What we're trying to do is split the activation switch, so there could be two switches and you can keep one off and turn the other one on," said Phillip Popovich, professor of neuroscience, director of Ohio State's Center for Brain and Spinal Cord Repair and senior co-author of the study. "We think we have learned how to do that, at least with regard to one signaling pathway."

There are actually thousands of potential activators present in these complex injuries, Gensel noted. By exploring signals that control the cells' behavior at a specific time point in the injury, he and colleagues are getting closer to zeroing in on which receptor on the cell surface to target to promote repair.

Two receptors, known as TLR-2 and dectin-1, have been identified in this most recent work as critical in this environment. When both are activated, the macrophages perform damaging and reparative functions simultaneously in the spinal cord. But when only TLR-2 was stimulated, the cells retained their regenerative effect without creating a toxic environment. In contrast, when only dectin-1 was stimulated, nerve cells died.

An experimental compound used in the study was able to activate the TLR-2 receptor alone in cell cultures, enhancing growth of axons without causing cell death. When introduced to the spinal cords of rats, the compound caused inflammation, but little tissue damage.

More investigation is needed, as it remains unknown exactly what starts this signaling process in the injured spinal cord.

"Now we have to go into the cell to figure out what part of that signaling process we can manipulate and if that manipulation can stop the toxicity," Gensel said.

Ultimately, the scientists hope to identify a precise target for drug therapy that could alter the immune response after the devastating effects of the injury and tip the balance of macrophage activity toward nerve cell repair.

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