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Libyan International Medical University

Faculty of Basic Medical Science

Endangered Axolotl Offers Clues on Healing Spinal Cord Injury

Submitted by: Fatema Jalal 1509, 2nd year medical student

Supervised by: Dr. Asma Alfarsi

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**Abstract:**

One of the most vexing problems with spinal cord injuries is that the human body does not rebuild nerves once they have been damaged. Other animals, on the other hand, seem to have no problem repairing broken neurons. Although the Mexican salamander or axolotl share many of the same genes with humans, it can successfully regenerate neurons while humans instead form scar tissue. Humans have very limited capacity for regeneration, while other species like axolotl have the remarkable ability to functionally regenerate limbs, heart tissue and even the spinal cord after injury. This knowledge could be used to design new therapeutic targets for treating spinal cord injury or other neurodegenerative diseases.

**Introduction:**

All spinal cord injuries are divided into two broad categories; incomplete and complete. In Incomplete spinal cord injuries the cord is only partially severed, allowing the injured person to retain some function. In these cases, the degree of function depends on the extent of the injuries. Incomplete spinal cord injuries like Anterior cord syndrome, Central cord syndrome, and Brown-Sequard syndrome. In complete spinal cord injuries they occur when the spinal cord is fully severed, eliminating function. Though, with treatment and physical therapy, it may be possible to regain some function. There are layers which usually protect the spinal cord from injuries, those layers are like myelin, which surrounds nerve fibers called axons, plays a complex role after spinal cord injury. It must be restored to axons that remain, yet it contains molecules that discourage axon regeneration. (1)

**Discussion:**

For many years researchers have been looking for treatments of some spinal cord injuries, one promising combination, reported in the Journal of Neuroscience by an international team of researchers anchored by Damien Pearse at The Miami Project to Cure Paralysis, used an enzyme that counteracts inhibitory signals together with two types of nervous system cells to act as structural support and guide nerve fiber regrowth in the right direction. This three-pronged strategy achieved significant improvements in several measures of movement ability and motor coordination when tested in adult rats with completely severed spinal cords. Although preliminary, the results provide important direction for researchers developing combined treatment regimens for spinal cord injury in humans, according to the authors. A second experimental treatment combined stem cells with gene therapy to remyelinate nerve fibers in rats with spinal cord injuries, effectively improving the animals’ ability to walk, according to work reported in the Journal of Neuroscience by Scott Whittemore and colleagues.3 The therapy teamed stem cells called glial-restricted precursor cells, which have “committed” to becoming central nervous system support cells, with gene therapy designed to mimic the effects of two types of nerve growth factors. The combination promoted the growth of myelin and enhanced nerve signal transmission along the resheathed nerve fibers, which corresponded with improved motor function. The study provided the best demonstration to date that boosting myelin growth can lead to functional improvements, according to a statement from the National Institute of Neurological Disorders and Stroke, which funded the research.(2)

Another study, from the biotech firm Biogen Idec, combined an “old” drug with known anti-inflammatory action, methylprednisolone, with an experimental “Nogo blocker,” a drug that is being investigated for its ability to block inhibitory signals that restrict nerve growth (via a receptor called Nogo-66).4 Tested in rats with spinal cord injury, the co mbination had a more pronounced effect on recovery of movement and coordination and on axonal growth than either treatment alone, suggesting that each may work through different mechanisms. Slowly but surely, scientists are making progress in learning how best to harness stem cells, in all their variations, for the goal of spinal cord repair. In 2005, a number of researchers inched toward this goal, including two separate groups at the University of California at Irvine. Hans Keirstead and colleagues restored myelin in rats with spinal cord injuries and improved their capacity to move around by transplanting glial support cells called oligodendrocytes, which they had successfully developed from human embryonic stem cells grown in culture dishes.11 In research reported in the Journal of Neuroscience, the team saw benefits when the cells were transplanted seven days after the injury, but not when the transplant took place 10 months after the surgery, suggesting an early therapeutic window of opportunity. The second study, reported in Proceedings of the National Academy of Sciences by Brian Cummings and colleagues, used adult neural stem cells from humans to regenerate myelin and improve mobility in mice with spinal cord injuries.12 When the cells were transplanted nine days after an injury, they developed into oligodendrocytes that restored the insulating myelin sheath around nerve fibers, and the mice showed improved mobility. (2)

One of the most vexing problems with spinal cord injuries is that the human body does not rebuild nerves once they have been damaged. Other animals, on the other hand, seem to have no problem repairing broken neurons. A new study takes a comparative approach to pinpoint what happens differently in humans versus other animals to explain why they can successfully regenerate neurons while we instead form scar tissue. By learning from the similarities and differences, researchers hope to find new leads in the treatment of spinal cord injury. "Humans have very limited capacity for regeneration, while other species like salamanders have the remarkable ability to functionally regenerate limbs, heart tissue and even the spinal cord after injury," said lead researcher Karen Echeverri, PhD, assistant professor in the department of genetics, cell biology and development at the University of Minnesota. "We have discovered that despite this difference in response to injury, these animals share many of the same genes with humans. This knowledge could be used to design new therapeutic targets for treating spinal cord injury or other neurodegenerative diseases."(3)

Although the Mexican salamander—or axolotl—share many of the same genes with humans, it can successfully regenerate neurons while humans instead form scar tissue. When an axolotl suffers a spinal cord injury, nearby cells called glial cells proliferate rapidly and reposition themselves to rebuild the connections between nerves and reconnect the injured spinal cord. By contrast, when a human suffers a spinal cord injury, the glial cells form scar tissue, which blocks nerves from ever reconnecting with one another.

In their study, the release continues, Echeverri and her team traced the molecular mechanisms at work in each case. They found a particular protein called c-Fos, which affects gene expression, is essential to the processes axolotls use to repair injured nerves. While humans also have c-Fos, in humans the protein functions in concert with other proteins, in the JUN family, that cause cells to undergo reactive gliosis, which leads to scar formation. In axolotls, this molecular circuitry is carefully regulated to direct axolotl glial cells toward a regenerative response instead.

“Our approach allows us to identify not just the mechanisms necessary to drive regeneration in salamanders but what is happening differently in humans in reposes to injury,” said Echeverri, adding that the work has implications for other types of injury, as well. “In addition to spinal cord regeneration, our work also focuses on other forms of regeneration including scar-free wound healing and limb regeneration.”(4)

**Conclusion:**

Axolotl, are some of the few vertebrates fortunate in their ability to regenerate diverse structures after injury. Unlike mammals they are able to regenerate a fully functional spinal cord after injury. However, the molecular circuitry required to initiate a pro-regenerative response after spinal cord injury is not well understood. More studies needed to understand this mechanism and using the axolotl to improve it for spinal cord injury healing in human.

**References:**

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