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Breakthrough could help heal spinal cord injuries without pain

AURORA, Colo. (Sept. 19, 2008) – Researchers at the University of Colorado Denver School of Medicine say manipulating embryo-derived stem cell precursors prior to transplanting them holds the key to using stem cell technologies for repairing spinal cord injuries in humans.

In the online Journal of Biology, Dr. Stephen Davies, an associate professor of neurosurgery reports his research team has produced two types of spinal cord support cells called astrocytes (“star” cells) from the same embryo-derived stem cell-like cells called Glial Restricted Precursor cells (GRPs) that have remarkable effects on the injured spinal cord.

Astrocytes carry out many important functions within the brain and spinal cord and account for roughly 70 percent of the total cells in the central nervous system. “To our knowledge, this is the first time that two distinct sub-types of astrocyte support cells generated from a common stem cell-like precursor cell have been shown to have robustly different effects when transplanted into the injured adult nervous system,” Davies explains.

When nerve fibers are injured in the adult spinal cord, their severed ends fail to regenerate and re-connect with nervous system circuits beyond the injury site. Inflammation at sites of injury not only promotes the formation of scar tissue that inhibits the re-growth of nerve fibers but is also thought to play a major role in the onset of neuropathic pain syndromes that are a common side effect of severe and even relatively mild spinal cord injuries. These pain syndromes can be so severe that the touch of a finger feels like the stab of a knife.

In the embryonic spinal cord however injured nerve fibers are able to regenerate past sites of injury and reform functional connections. It is widely believed that early astrocytes within the embryonic spinal cord help support this regeneration. As the embryonic spinal cord does not form a scar or develop pain syndromes after injury, Davies and co-workers hoped therefore that embryonic GRP-derived astrocytes (GDAs) would confer the striking repair capabilities of the embryonic spinal cord on the injured adult spinal cord.

Using signal molecules that are known to be involved in the generation of embryonic astrocytes during spinal cord development, Davies and co-workers were able to make pure cultures of two different types of astrocytes from the stem cell-like GRP cells.

One type of astrocyte - GDAsBMP – so called because they are derived from glial restricted precursor cells treated with bone morphogenetic protein, are remarkably effective at promoting nerve regeneration and functional recovery. Adult spinal cord injured rats treated with these cells showed ~40% nerve fiber regeneration in just 8 days and had returned to pre- injury scores in a test of coordinated limb movement by two weeks after treatment. In addition the GDAsBMP were also able to protect injured neurons in the brain from undergoing atrophy.

The other type of astrocyte cell generated by Davies and co-workers by treating GRP cells with

ciliary neurotrophic factor -GDAsCNTF - however not only failed to promote nerve fiber regeneration or functional recovery but also caused neuropathic pain, a severe side effect that was not seen in rats treated with GDAsBMP. When the research team transplanted naïve GRP cells into adult spinal cord injuries in rats without first instructing them to turn into GDAsBMP, the GRP cells also turned in astrocytes that promoted neuropathic pain.

“Controlling the development of embryonic stem cells immediately before transplanting them into injured spinal cords is essential,” says Davies, “because doctors cannot rely on the injured tissues of the body to create the right types of cells from ‘naïve’ embryonic stem cells.” “In order to use stem cell technologies like GRP cells for repairing the injured spinal cord, scientists and physicians (and not the injured spinal cord) must control what the GRP cells turn into” Davies commented. “By giving the GRP cells the right signal molecules such as BMPs, we have been able to make desirable cells such as GDAsBMP, rather than allowing the injured spinal cord to turn the transplanted GRP cells into highly undesirable cells such as GDAsCNTF. When we analyzed scar tissue in untreated spinal cord injuries we found adult astrocytes that closely resemble GDAsCNTF that promote pain and no recovery.”

Davies’ and his team, including his wife, Jeannette Davies, an assistant professor of neurosurgery at UC Denver, consider the distinction between GDAsBMP and GDAsCNTF a breakthrough that can change the way stem cell technologies are used to repair spinal cord injuries.

“Our study shows that different types of immature astrocytes can have opposite effects on the injured spinal cord and that not all cells that can be made by naïve embryo derived stem cells are necessarily beneficial for repairing the injured spinal cord,” Davies says. “It has long been a concern that therapies that promote growth of nerve fibers in the injured spinal cord would also cause sprouting of pain circuits. However by using GDAsBMP to repair spinal cord injuries we can have all the gains without the pain.”

To that end, Davies and his collaborators, Drs Margot Mayer-Proschel and Christoph Proschel at University of Rochester, NY, are developing a safe, efficient and cost-effective way to make human GDAsBMP with an eye toward testing this new cell replacement technology in humans. The eventual result of all his research, Davies hopes, will be a fast, relatively pain-free spinal cord recovery process that paves the way for victims of paralysis to recover the use of their bodies.

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