Researchers disclose key advance in treating spinal cord injuries

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Researchers in Rochester, N.Y., and Colorado have shown that manipulating stem cells prior to transplantation may hold the key to overcoming a critical obstacle to using stem cell technology to repair spinal cord injuries.

Research from a team of scientists from the University of Rochester Medical Center and the University of Colorado Denver School of Medicine, published today in the online *Journal of Biology*, may lead to improved spinal cord repair methods that pave the way for victims of paralysis to recover the use of their bodies without the risk of transplant-induced pain syndromes.

The research focuses on a major support cell in the central nervous system called astrocytes. When nerve fibers are injured in the spinal cord, the severed ends of the nerve fibers fail to regenerate and reconnect with the nervous system circuitry beyond the site of the injury. During early development, astrocytes are highly supportive of nerve fiber growth, and scientists believe that if properly directed, these cells could play a key role in regenerating damaged nerves in the spinal cord.

The Rochester team – which consists of biomedical geneticists Chris Proschel, Ph.D., Margot Mayer-Proschel, Ph.D., and Mark Noble, Ph.D. – are pioneers in manipulating stem cells to generate nervous system cells that can be used for therapeutic treatments. Rather than transplanting naïve stem cells, the team has adopted an approach of pre-differentiating stem cells into better defined populations of brain cells.

These are then selected for their ability to promote recovery. Here glial restricted precursor (GRP) cells – a population of stem cells that can give rise to several different types of brain cell – were induced to make two different astrocyte sub-types using different growth factors that promote cell formation during normal development. Although these astrocytes are made from the same stem cell population, they apparently have very distinct characteristics and functions

"These studies are particularly exciting in addressing two of the most significant challenges to the field of stem cell medicine – defining the optimal cell for repair and identifying means by which inadequately characterized stem cell approaches may actually cause harm," said Noble, who is also co-director of the New State Center of Research Excellence in Spinal Cord Injury, one of the primary funders of the research.

The research team in Colorado, which consisted of Stephen Davies, Ph.D. and Jeannette Davies, Ph.D., transplanted the two types of astrocytes into the injured spinal cords of rats and found dramatically different outcomes. One type of astrocyte was remarkably effective at promoting nerve regeneration and functional recovery, with transplanted animals showing very high levels of new cell growth and survival, as well as recovery of limb function. However, the other type of astrocyte 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 the beneficial astrocytes. Moreover, transplantation of the precursor cells themselves, without first turning them into astrocytes, also caused pain syndromes without promoting regeneration.

"To our knowledge, this is the first time that two distinct sub-types of astrocytic support cells generated from a common stem cell-like precursor have been shown to have robustly different effects when transplanted into the injured adult nervous system," said Mayer-

Proschel.

"It has long been a concern that therapies that promote growth of nerve fibers in the injured spinal cord would also cause sprouting in pain circuits," said Stephen Davies. "However by using the right astrocytes to repair spinal cord injuries we can have all the gains without the pain, while these other cell types appear to provide the opposite – pain but no gain."

"These results emphasize the importance of astrocytes in controlling the outcome of neurological disease processes," said Proschel. "In addition, because transplants of undifferentiated stem cells harbor the risk of making deleterious astrocytes, it is important to understand their properties and how they might form. By being able to study different types of astrocytes derived from a common neural precursor, we are now underway to finding means of preventing the formation of the deleterious astrocyte type in the first place."

The research teams in Denver and Rochester consider the dramatically dissimilar outcomes between the different astrocyte transplants a development that can change the way stem cell technologies are used to repair spinal cord injuries. To that end, the researchers are in the process of developing a safe, efficient and cost-effective way to use this approach to better define the optimal human astrocytes with an eye toward use for clinical trials.

Source: University of Rochester