Scientists infuse rat spinal cords with brain-derived human stem cells

April 19 2005

Unveiling a delivery method that may one day help surgeons treat the deadly neurodegenerative disease amyotrophic lateral sclerosis (ALS), researchers at the UW-Madison have inserted engineered human stem cells into the spinal cords of ALS-afflicted rats.

Reporting their work today in the journal Human Gene Therapy, the scientists directed certain types of neural stem cells to secrete a neuron-protecting protein before injecting them into the rat spinal cord where motor neurons reside. Motor neurons dictate muscle movement by relaying messages from the spinal cord and brain to the rest of the body. ALS causes the neurons to progressively decay and die.

Notably, the UW-Madison stem cell researchers did not work with human embryonic stem cells, blank-slate cells that arise during the earliest stages of development and can develop into any of the 220 tissue and cell types in humans. Scientists have long regarded these cells as a crucial ingredient in the quest to cure spinal injuries and neurodegenerative disease.

Rather, the scientists worked with more specialized neural stem cells - known as neural progenitor cells - that arise from primitive stem cells during the first few weeks of human brain development. Unlike embryonic stem cells, they can only develop into neural tissue and they are incapable of living forever, as embryonic stem cells can. But the neural progenitor cells are much more appropriate for clinical use because, unlike embryonic stem cells, they can grow in the absence of

animal derivatives that are considered a potential source of contamination, says co-author Clive Svendsen, a professor of anatomy based at the university's Waisman Center, and a leading authority on neural progenitor cells.

"This is the first study that shows that certain types of stem cells can survive and release powerful protective proteins in the spinal cord of rats with a genetic form of ALS," says Svendsen.

Once inside the brain or spinal cord, neural progenitor cells grow into neuron-supporting stem cells called astrocytes. Some researchers believe that ALS causes astrocyte malfunction, which in turn causes motor neurons to degenerate and eventually die.

Several research groups around the world are trying to unleash the therapeutic potential of neural progenitor cells. But the UW-Madison work is the first "double whammy," says Svendsen, because the injected neural progenitor cells develop into astrocyte-like cells and simultaneously secrete glial cell-line derived neurotrophic factor (GDNF), a naturally occurring protein that preserves motor neurons during development. The twofold approach has a better chance of protecting healthy neurons that haven't already succumbed to ALS, he says.

Approximately 5,600 people in the United States are annually diagnosed with ALS. Also known as Lou Gehrig's disease, ALS is not well understood, though mutations in the SOD-1 gene - or superoxide dismutase-1 - are known to play a role. ALS attacks nerve cells in the brain and spinal cord, and as motor neurons progressively die, the brain can no longer initiate and control muscle movement.

The UW-Madison researchers tackled several technical barriers trying to ensure that the progenitor cells correctly gather near the motor neurons

in the spinal cord, while continuing to pump GDNF once there, says Sandra Klein, lead author of the study and a UW-Madison doctoral researcher.

But making GDNF-emitting stem cells was the first puzzle to grapple with. Svendsen and his team approached the problem using a genetically engineered viral structure known as a lentivirus. Collaborating with Patrick Aebischer, a researcher in Switzerland, the scientists manipulated the lentivirus' genetic machinery, directing it to secrete GDNF. The team then infected neural progenitor cells with the GDNF-pumping lentivirus. Once the cells were infected, the scientists washed the virus away, leaving self-sustaining colonies of GDNF-producing progenitor cells.

The next problem was actually getting the cells into the right location of the ALS rat spinal cord.

"Nobody had shown that human progenitors could be delivered right into the region of the dying motor neurons," says Klein, who chose to work with rats because they have a larger spinal cord.

Klein bore into the base of the rat spine, using a micro-pipette, or tiny dropping device, to deliver the progenitor cells into the bottom region of the spinal cord where motor neurons are located. After months of trial and error, Klein finally ascertained through staining tests that the progenitor cells were indeed gathering near the neurons and releasing GDNF in the area.

Svendsen says the approach could be regarded as a novel form of gene therapy where progenitor cells are used as "mini pumps" to deliver protein.

It is crucial now to see whether greater numbers of GDNF-bearing

progenitor cells can actually prolong the life of an ALS-ridden rat, says Svendsen. If so, he aims to plan a human safety trial with a small group of patients. Ordinarily, the researchers would first test the work in primates, but good ALS primate models do not exist due to the ravaging nature of the disease, he says.

Compared to small rats, humans will most likely require more extensive spinal cord transplants, the researchers predict. If successful, a similar progenitor cell protein delivery method could radically help to combat several other ailments, including Huntington's disease, Parkinson's disease and stroke.

Source: UW-Madison