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Scientists learn how stem cell implants help heal traumatic brain injury

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For years, researchers seeking new therapies for traumatic brain injury have been tantalized by the results of animal experiments with stem cells. In numerous studies, stem cell implantation has substantially improved brain function in experimental animals with brain trauma. But just how these improvements occur has remained a mystery.

Now, an important part of this puzzle has been pieced together by researchers at the University of Texas Medical Branch at Galveston. In experiments with both laboratory rats and an apparatus that enabled them to simulate the impact of trauma on human neurons, they identified key molecular mechanisms by which implanted human neural stem cells — stem cells that are in the process of developing into neurons but have not yet taken their final form — aid recovery from traumatic axonal injury.

A significant component of traumatic brain injury, traumatic axonal injury involves damage to axons and dendrites, the filaments that extend out from the bodies of the neurons. The damage continues after the initial trauma, since the axons and dendrites respond to injury by withdrawing back to the bodies of the neurons.

"Axons and dendrites are the basis of neuron-to-neuron communication, and when they are lost, neuron function is lost," said UTMB professor Ping Wu, lead author of a paper on the research appearing in the *Journal of Neurotrauma*. "In this study, we found that our stem cell transplantation both prevents further axonal injury and promotes axonal

regrowth, through a number of previously unknown molecular mechanisms."

The UTMB researchers began their investigation with a clue from their previous work: they had determined that their neural stem cells secreted a substance called glial derived neurotrophic factor, which seemed to help injured rat brains recover from injury. As a first step toward identifying the processes by which GDNF and neural stem cell transplantation produced their beneficial effects, Wu enlisted UTMB professors Larry Denner, Douglas Dewitt and Dr. Donald Prough to use proteomic techniques to compare injured rat brains with injured rat brains into which neural stem cells had been transplanted.

"We identified about 400 proteins that respond differently after injury and after grafting with neural stem cells," Wu said. "When we grouped them using a state-of-the-art Internet database, we found that a group of cytoskeleton proteins was being changed, and in particular one called alpha-smooth muscle actin, which had never been reported in the neurons before."

Because so many of the proteins that changed were related to axonal structure and function, the UTMB scientists then focused on traumatic axonal injury. Initially working with rats, they confirmed that axons and dendrites suffered damage from trauma; implanted neural stem cells reduced this harm, as well as lowering levels of alpha-smooth muscle actin inside neurons that were raised after trauma.

To probe further into the molecular details of GDNF's role in reducing traumatic axonal injury, the researchers used a system in which human neurons were placed on a flexible membrane that was then suddenly distended with a precisely calibrated puff of gas. Their goal was to simulate the sudden compression and stretching forces exerted on brain cells by a blow to the head.

Initial results from this "rapid stretch injury model" matched those seen in rat experiments, with GDNF protecting axons and dendrites from additional damage in the period after trauma and significantly reducing alpha-smooth muscle actin levels boosted by the simulated injury. In addition, they found evidence linking alpha-smooth muscle actin with RhoA, a small protein that blocks axonal growth after injury. Finally, again taking a cue from their proteomic study, they turned their attention to one component of a protein known as calcineurin, finding that it interacted with GDNF to protect axons and dendrites in the RSI model.

"We're quite excited about these discoveries, because they're highly novel — we now know much more about how GDNF protects axons and dendrites from further injury and promotes their re-growth after trauma," Wu said. "This kind of detailed study is essential to developing safe and effective therapies for traumatic brain injury."

Provided by University of Texas Medical Branch at Galveston