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# Silencing growth inhibitors could help recovery from brain injury

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Silencing natural growth inhibitors may make it possible to regenerate nerves damaged by brain or spinal cord injury, finds a study from Children's Hospital Boston. In a mouse study published in the November 7 issue of *Science*, researchers temporarily silenced genes that prevent mature neurons from regenerating, and caused them to recover and re-grow vigorously after damage.

Because injured neurons cannot regenerate, there is currently no treatment for spinal cord or brain injury, says Zhigang He, PhD, Associate Professor of Neurology at Children's and senior author on the paper. Previous studies that looked at removing inhibitory molecules from the neurons' environment, including some from He's own lab, have found only modest effects on nerve recovery. But now He's team, in collaboration with Mustafa Sahin, MD, PhD, Assistant Professor of Neurology at Children's, demonstrates that re-growth is primarily regulated from within the cells themselves.

"We knew that on completion of development, cells stop growing due to genetic mechanisms that prevent overgrowth," explains He. "We thought that this kind of mechanism might also prevent regeneration after injury."

The key pathway for controlling cell growth in neurons, known as the mTOR pathway, is active in cells during development, but is substantially down-regulated once neurons have matured. Moreover, upon injury, this pathway is almost completely silenced, presumably for

the cell to conserve energy to survive. He and colleagues reasoned that preventing this down-regulation might allow regeneration to occur.

He and his team used genetic techniques to delete two key inhibitory regulators of the mTOR pathway, known as PTEN and TSC1, in the brain cells of mice. After two weeks, the mice were subjected to mechanical damage of the optic nerve. Two weeks post-injury, up to 50 percent of injured neurons in the mice with gene deletions of PTEN or TSC1 survived, compared to about 20 percent of those without the deletions. And of the surviving mutant mice, up to 10 percent showed significant re-growth of axons, the fiber-like projections of neurons that transmit signals, over long distances. This re-growth increased over time.

Although this study used genetic techniques, He notes that it may be possible to accomplish the same re-growth through pharmacologic means. "This is the first time it has been possible to see such significant regeneration by manipulating single molecules," says He. "We believe that these findings have opened up the possibility for making small-molecule drugs or developing other approaches to promote axon regeneration."

While such long-distance regeneration of axons has not been seen before using other techniques, it is still unknown whether these regenerating axons can restore function, He adds.

The research group is now looking at axon regeneration after spinal cord injury and given the current availability of specific PTEN inhibitors, the researchers hope that these and similar small-molecule inhibitors of the mTOR pathway will lead to future neural regeneration therapies.

Source: Children's Hospital Boston