Targeted Molecules Play Only Minor Role in Axon Repair

Discovery underscores difficulties in developing regenerative spinal cord injury therapies

June 8, 2010

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Neuroscientists at the University of California, San Diego School of Medicine have found that removing three key inhibitory molecules from myelin - the insulating material that surrounds nerve cell fibers - does not significantly boost the ability of injured spinal axons to regenerate and restore themselves to full function.

"I think this just shows how incredibly complicated the challenge is to induce axon regeneration and functional recovery after central nervous system (CNS) injuries," said Binhai Zheng, PhD, assistant professor of neurosciences at UC San Diego School of Medicine and principal investigator of the study. "It's not going to be one gene or one approach that proves to be the answer. Successful regeneration will likely require a combination of many approaches and techniques."

The findings, to be published by Zheng and colleagues in the June 10 issue of the journal *Neuron,* run contrary to a popular and enduring hypothesis that the elimination of key inhibitory molecules in myelin should measurably boost axon regeneration in CNS injuries. The idea has spurred much research in recent years and, in fact, underlies a current clinical trial in Europe testing the safety and efficacy of neutralizing one of three known myelin-associated inhibitors.

In lower animal species, such as fish and tailed amphibians, damaged spinal axons are capable of self-repair and regeneration. This is not true, however, in humans and other mammals. While the mammalian peripheral nervous system (such as nerves in the arms and legs) can repair damage and grow new connections, the central nervous system cannot. Serious trauma to the brain and spinal cord tends to be permanent, and often catastrophic.

The reason why the CNS cannot repair itself remains a fundamental mystery, but researchers have developed a handful of hypotheses, among them: the suppressive nature of scarring after the injury; insufficient growth-promoting factors or tissue bridges at the CNS injury site; the lack of intrinsic growth potential in neurons and myelin-associated molecules that inhibit neuronal growth.

"There is work in all of these areas, but inhibitory molecules, especially those from myelin, have been the basis of the dominant theory for the last 20 years," said Zheng.

Myelin is a fatty material that sheathes the axons or connecting nerve fibers of neurons, insulating them from the surrounding environment. Though it is vital to the health and functioning of neurons, it also contains at least three molecules believed to inhibit new axon growth after injury in adult mammals. "The theory is that these molecules help stabilize growth after initial neuron development," said Zheng.

The three identified inhibitory molecules are Nogo, myelin-associated glycoprotein (MAG) and oligodendrocyte myelin glycoprotein (OMgp). Some scientists have argued that if these molecules could be effectively countered

or removed, a major obstacle to the regeneration of damaged spinal axons might disappear and a door opened to potential new therapies capable of restoring CNS functions.

The UCSD research, however, found that the absence of Nogo, MAG and OMgp did not significantly affect or improve regeneration in damaged axons in mouse models of spinal cord injury. Deleting any one of the inhibitory molecules did enhance compensatory sprouting in undamaged axons, but the sprouting did not result in associated behavioral improvements in the mice. Deleting all three inhibitors produced no synergistic effect at all.

Contrarily, recently published experiments elsewhere have reported some axonal growth and neurological recovery in a different mouse model lacking all three inhibitory molecules. Some regeneration was also noted in Nogo-deficient mice, but none in mice whose myelin lacked MAG or OMgp.

Jae K. Lee, PhD, lead author of the UCSD study and a postdoctoral fellow in Zheng's lab, said the different findings were not unusual for this kind of research, not completely surprising and might be explained by differences in experimental models and laboratory techniques. He said it remains possible, perhaps even likely, that myelin-associated inhibitory molecules contribute to inhibiting regeneration, but that it was also clear that targeting theses molecules alone is insufficient.

"Neutralizing these molecules won't be enough to promote functional regeneration," said Lee. "They are part of a much bigger and more complicated process. By better understanding their role, we get closer to understanding the entire mechanism of regeneration. Sometimes you have to eliminate parts of the process to get to the point where you can focus on the parts that can really effect change."

Co-authors of the *Neuron* paper with Zheng and Lee are Cedric Geoffrey, Andrea Chan, Kristine Tolentino, Michael Crawford, Marisa Leal and Brian Kang, all in the Department of Neurosciences at the UC San Diego School of Medicine.

The work was supported by grants from the National Institute of Neurological Disorders and Stroke (part of the National Institutes of Health), the Roman Reed Spinal Cord Injury Research Fund of California, the Christopher and Dana Reeve Foundation, the Dana Foundation and the International Spinal Research Trust.

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