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Hope for spinal cord injuries: Coaxing damaged nerve cells to grow, send messages to the brain again

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"An ailment not to be treated," read the prescription for a spinal cord injury on an Egyptian papyrus in 1,700 B.C. Not much has changed in the intervening millennia. Despite decades of research, modern medicine has made little headway in its quest to reverse damage to the central nervous system.

That is not to say, however, that there isn't a glimmer of hope. Laura Wong, an M.D./Ph.D. student in Professor Eric Frank's molecular physiology lab at the Sackler School, has been able to coax damaged nerve cells known as sensory neurons to regenerate, growing as much as 10 times longer than previously documented. What's more, the new neurons make organized connections with their counterparts inside the spinal cord and brain stem, ensuring information from the outside world paints an accurate picture inside the brain.

"All the regeneration in the world isn't going to make any difference if they don't reconnect. You're still not going to get any function," says Wong, who has worked since 2010 in Frank's lab, which is trying to develop therapies for spinal cord injuries.

Her findings, which she presented at the annual meeting of the Society for Neuroscience in 2011 and 2012, shed light on the complex processes behind nerve cell growth and regeneration. If those results can be replicated in patients, it could prevent certain types of nerve damage and

improve quality of life for some.

Going the distance

Unlike tissues such as skin and bone, the cells of the central nervous system in an adult are notoriously resistant to healing. Not only does the supply of natural growth stimulants decline as we age, but the body also produces chemicals that discourage nerve cells from regenerating. Worse, the scar tissue that starts to form immediately after a spinal cord injury also contains compounds that hinder nerve cell growth.

Researchers in Frank's lab have been seeking ways to either stimulate growth or block the mechanisms that inhibit nerve cell growth—or both—since 2005. Wong's predecessor in the lab, Pamela Harvey, a 2009 graduate of the Sackler School, tested a synthetic version of a nerve cell growth factor, called artemin, on crushed sensory neurons that relay information from the hands, arms and shoulders to the brain.

The damage mimics a common injury called Erb's palsy, which can occur when a baby's shoulder gets caught behind the mother's pelvis during labor and delivery, creating undue strain on nerves in the newborn's neck. Riders thrown head first off a motorcycle or snowmobile can suffer similar injuries.

"Anytime the shoulder goes one way and the head and neck go the other, that's when you see these injuries," Wong says.

In earlier experiments, Harvey and Frank found that treating with artemin did indeed stimulate the sensory nerve fibers to regenerate and grow back into the spinal cord over the course of about six weeks. In her follow-up experiments, Wong showed that artemin could induce those nerve fibers to grow the 3- to 4-centimeter distance from there up to the brainstem, where the brain and the spinal cord meet. That's a little more

than an inch—or roughly 10 times longer than any other researchers have been able to demonstrate with artemin or any other growth factor.

"A lot of other researchers just haven't seen this length," notes Wong, who saw the artemin-induced growth occur over a period of three to six months.

That's important, because while axons only have to grow across microscopic distances in a developing embryo, they would have to bridge much wider gaps—depending on the site of the injury—to heal a neural injury in an adult, Wong says. Nerves that extend from the spine to the foot or toe can reach lengths of about 60 centimeters, she adds.

But Wong's artemin-treated nerve fibers achieved more than unprecedented growth. They also reestablished connections with correct regions in the brain stem, just as Harvey had seen the nerve cells do in the spinal cord. That is, the axons essentially plugged themselves back in just as they were prior to the injury, and, like an old-fashioned telephone switchboard, they sent the right messages to the right parts of the brain.

That's crucial because should the sensory nerves that relay pain signals become crossed, for example, it could result in a patient feeling phantom pain or the sensation of pain from something that shouldn't cause discomfort at all.

"With some other growth-promoting compounds you get regeneration, but you see those axons growing kind of willy-nilly," says Wong. "You can see where it would be just as detrimental to have things wired incorrectly as it would be to have things not wired at all."

Just a start

Artemin isn't a panacea for spinal cord injuries, Wong and Frank stress.

To work its cellular magic, the compound must be administered within a day or two, and the sooner the better. Also, artemin promotes growth only in sensory neurons—and so far, only in rats—which means such growth wouldn't improve motor function for someone who had been paralyzed by a spinal cord injury, for example.

But if the findings, which Wong presented at the Society for Neuroscience meetings in 2011 and 2012, prove applicable to humans, restoring sensation alone could still improve quality of life, even for those living with paralysis. Giving these people the ability to sense heat, cold and pain could help them avoid other accidental injuries, says Frank.

Wong hopes her work with sensory neurons will help unlock the secrets to promoting regeneration of other, more obstinate types of neurons in the brainstem and spinal cord. While she demonstrated that the sensory nerves plugged themselves back into the spinal cord precisely where they should have, it's not clear how they did that.

Frank speculates that chemical cues guided the cells back into place. Should researchers be able to identify those cues, they potentially could use that knowledge to spark regeneration of other classes of neurons, such as motor neurons.

"There is hope—not proof—that even in humans these guidance molecules will persist into adulthood," says Frank. "That means if we are able to get neurons to regenerate in patients, we might be able to make them go back to the right place. These experiments suggest we have some reason to believe it may work."

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