Researchers identify promising therapeutic target for central nervous system injuries

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Scars can serve as double-edged swords in spinal cord injuries—saving a victim's life, but sealing his or her fate as a paraplegic or quadriplegic. The scar forms a wall around the wound, preventing the injury from spreading, but limiting opportunities for neural regeneration. Cells in the scar release molecules that keep severed nerve fibers from passing the damaged tissue, so they cannot connect with their original targets to restore motor and sensory function.

Now, a team of researchers from Harvard Medical School and Case Western Reserve University has identified where these potent molecules—called chondroitin sulfate proteoglycans (CSPGs)—bind to the surface of neurons, exposing a novel therapeutic target. Their findings appear online in the journal *Science* on Oct. 15.

"The docking station for these molecules has eluded scientists for nearly two decades," says Harvard Medical School Professor John Flanagan, senior author on the study. "Our collaborator Jerry Silver discovered that CSPGs inhibit regeneration of the central nervous system in the early 1990s, but nobody knew how they were keeping neurons at bay."

Now chemists can hunt for small molecules that will block the docking station and explore other approaches to disrupt it.

"This discovery suggests that we might be able to treat central nervous system injuries with a pill in the future," says Silver, who is a professor at Case Western Reserve University. "In reality, we'll probably need a

drug cocktail because CSPGs are not the only barrier to regeneration."

Most scientists had given up on finding a docking station for CSPGs because they suspected such a location did not exist. Like M&Ms, CSPGs are covered in slippery sugar, which coats their sticky interior. The tough sugar coating ruled out the typical interaction with a docking station, or receptor. Flanagan's cell biology lab, however, recently discovered an anomaly—a family of receptors on cells that tolerate and bind to the hard sugar coating itself.

Flanagan wondered if one of these receptors might recognize CSPGs. Motivated by the therapeutic potential of such a discovery, Flanagan lab postdoctoral researcher Yingjie Shen and graduate student Alan Tenney—who are first authors on the study—conducted initial experiments in test tubes and showed that, indeed, CSPGs bind to one of these receptors. Careful follow-up experiments in culture dishes on neurons missing the receptor—called PTP sigma—and studies in mice confirmed the connection.

"When John came up to me at a meeting in February and told me he'd found a receptor for CSPGs, I was shocked," says Silver. "In the regeneration field, we weren't sure how these molecules worked. We had some hypotheses, but we certainly didn't suspect that CSPGs were actually sitting on the surface of the neurons and talking directly to the cellular machinery."

Silver temporarily suspended projects in his lab to help Flanagan explore the significance of his discovery. Silver lab researchers tested how adult mice missing the PTP sigma receptor responded to an injury. They poked a hole into the spine, waited two weeks, and then imaged the growth of neurons in the area to assess regeneration. Neurons sent extensions into the fresh scar tissue surrounding the wound, something they don't do in normal mice.

A paper published online in the journal *Glia* on Sept. 24 helps prove this regeneration isn't a fluke. A team of researchers in Samuel David's lab at McGill University observed unprecedented levels of growth in the neurons of injured mice missing the PTP sigma receptor. In fact, motor neurons sent extensions all the way through the scar and well beyond the wound. The next step is to determine if movement is restored in these animals.

"Sam David probably didn't realize the full significance of this observation in his paper because he was unaware of the CSPG receptor," says Silver. "Taken together, these two papers suggest a new therapeutic approach with significant promise."

Silver and Flanagan caution that teams must find drug candidates that disable PTP sigma for the discovery to be relevant to the clinic. But the identification of a receptor for CSPG is a big step in the right direction.

"It's hard to overcome CSPGs in the human body, but receptors may offer an easier target," says Flanagan, who points out that according to the National Spinal Cord Injury Statistical Center, there are approximately 12,000 new cases of spinal cord injury alone in the United States each year. "This discovery may lead to treatments that help repair spinal cord injury and may be beneficial to patients with brain injury and neurodegenerative diseases such as Alzheimer's, Parkinson's, Lou Gehrig's, multiple sclerosis and stroke."

Source: Harvard Medical School (news : web)