Medical Xpress

Damaging inflammatory response could hinder spinal cord repair

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(PhysOrg.com) -- The inflammatory response following a spinal cord injury appears to be set up to cause extra tissue damage instead of promoting healing, new research suggests.

Scientists analyzing this inflammatory response in mice discovered that the types of cells recruited to the site of the injury are dominated within a week by those that promote inflammation. When chronic, inflammation can prevent healing, and these inflammatory cells are believed to remain at the injury site indefinitely.

Meanwhile, similar cells that are typically involved in a later phase of injury repair and that are anti-inflammatory were found to promote effective growth of axons that connect nerve cells. However, these cells disappear shortly after an injury, making it unlikely that they get a chance to complete their work under naturally occurring circumstances.

All of the responding cells in question are macrophages, but the study revealed that they have slightly different characteristics that define their functions. The research suggests that changing the balance of how these cells are activated in favor of the anti-inflammatory macrophages could be a potential treatment strategy for spinal cord injury.

Currently, no Food and Drug Administration-approved treatment exists for spinal cord injury, and scientists have not discovered a way to repair nerve cells that are damaged or killed when the spinal cord is injured. An estimated 1.3 million people in the United States are living with a spinal

cord injury, experiencing paralysis and complications that include bladder, bowel and sexual dysfunction and chronic pain.

"If these pro-inflammatory macrophages are a big part of the reason cells are dying, and we can figure out how to shut off that death cascade that they start, we might be able to minimize the amount of tissue damage," said senior study author Phillip Popovich, a professor of neuroscience and molecular virology, immunology and medical genetics at Ohio State University.

"If that could be achieved by injecting a drug or giving a patient a pill for a set number of days after injury, that could improve a lot of function and quality of life for people who suffer a spinal cord injury."

The research was presented Wednesday during a poster session at the Society for Neuroscience annual meeting in Chicago.

Popovich has known about the presence of macrophages after spinal cord injury for a long time. What he didn't know was exactly what they did, or how they did it, or whether there could be more than one function among these cells.

"I've always been of the mind that if nature requires these cells to be there, we must figure out if it's advantageous or disadvantageous for spinal cord function," said Popovich, also director of Ohio State's Center for Brain and Spinal Cord Repair.

"If what they do is disadvantageous, how can we change that without completely removing them? Because if we remove them, it will probably change a lot of other things and that is not going to be beneficial."

In this study, he and colleagues compared the spinal cords of mice with injury to the spinal cords of uninjured mice. The mouse injuries

resembled the most common contusion/compression spinal cord damage in humans that occurs when a vertebral bone or a disc bumps into the cord, causing a lesion and bleeding.

The researchers used chemicals to stain the spinal cords with markers that would indicate what types of cells were active at the injury site. They named the pro-inflammatory macrophages M1 cells and anti-inflammatory macrophages M2 cells.

Immediately after the injury, the researchers observed an intermingling of M1 and M2 cells at the site of the spinal cord injury. In just a few days, all of the anti-inflammatory M2 cells had disappeared. The pro-inflammatory M1 population persisted for a month after injury - the longest period scientists have ever observed.

Popovich said he and colleagues used recent principles learned by others in models of repair of injured heart muscle to predict how the inflammatory response to spinal cord injury would occur. After the heart is damaged, macrophages migrate to the site to clean up debris and protect against any invading bacteria or other pathogens. Signals are eventually sent out to initiate a next phase, which prepares the site for repair. Then new cells are recruited, blood vessels grow and other macrophages facilitate closure of the wound.

In the spinal cord, the long-term presence of pro-inflammatory M1 cells appears to prevent the shift into a repair phase.

"What we've done is overly simplistic, but it's an advance conceptually from where we were because we're saying that even though it looks like a homogeneous response, not all macrophages are created equal," Popovich said.

Once they knew how M1 and M2 cells were distributed at an injury site,

the researchers sought to determine what those two types of macrophages could do.

They created in vitro models - essentially, test tube experiments - in which they examined the effects of M1 and M2 macrophages on neurons, the cells that make up most of the spinal cord and brain.

The M1 macrophages killed neurons or stimulated a sprouting type of growth among their axons, which function as arms on neurons that reach out to connect with other cells or to send and receive signals. This type of sprouting of axons is associated with misguided circuits and can actually cause chronic pain.

The M2 cells, on the other hand, promoted long-distance axon growth without causing toxicity. This is the kind of axon growth required to regenerate spinal cord tissue and is the type of axon growth that is normally inhibited by proteins and cells that accumulate in the spinal cord after injury.

Popovich speculates that the immune system normally inhibits axon regeneration because its primary goal is to keep the injured spinal cord free from infection.

"The injury opens tissue to the external environment, increasing the potential to be exposed to pathogens. The immune system doesn't care that the spinal cord is damaged - it just wants to keep the organism alive," he said. "And neurons want to regrow, but when they try to grow their axons, they hit a wall of inflammatory cells that they can't get past or that are working against them."

One class of drugs - PPARgamma agonists, used to treat diabetes - is known to promote recruitment of M2 macrophages and has appeared in previous research to protect neurons in models of spinal cord injury,

Popovich said. But before pursuing drug therapies, researchers must determine whether changing the balance of macrophages in an injured spinal cord to favor the activation of M2 cells would actually be beneficial in a human body.

"The only benefits we've shown so far were in vitro," he said. "There's a chance we'll never be able to figure out how to regenerate an axon. But if we could minimize damage caused by inflammation, that would be helpful. Each axon that dies gets you closer to a threshold where you lose function. If we could just keep axons and neurons alive, we may have a better chance at promoting recovery."

Source: The Ohio State University (news : web)