How aging can intensify damage of spinal cord injury

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In the complex environment of a spinal cord injury, researchers have found that immune cells in the central nervous system of elderly mice fail to activate an important signaling pathway, dramatically lowering chances for repair after injury.

These studies were the first to show that spinal cord injuries are more severe in elderly mice than in young adults, corroborating previous anecdotal findings from clinical settings. They also revealed a previously unknown player in the repair of spinal cord injuries in young adults.

A key messenger in that pathway is a receptor on the surface of microglia, immune system cells in the central nervous system that are called into action by the trauma of the spinal cord injury.

In young adult mice, this receptor is activated by microglia to recognize and make use of an inflammation-related signaling chemical that is found in the central nervous system after a spinal cord injury. The microglia in the elderly mice, however, do not activate the receptor at all.

The study showed that the difference in receptor activation has consequences later in the recovery process. The kinds of cells recruited to the injury site in young adult mice appear to have more value in the repair process than do the cells that show up in elderly mice. A host of experiments traced those differing effects back to whether or not microglia activated the receptor.

"The microglia are regulated by several different cell types and different signals, and it appears a lot of those systems change with age," said Jonathan Godbout, associate professor of neuroscience at The Ohio State University and senior author of the study.

"We've shown evidence that this more severe injury occurs in an aging animal, and that the difference in recovery is related to the ability to express the receptor. The consequence is we have a different profile of cells at the injury site, and in aging mice, that environment is less reparative."

These differences at the cellular level were associated with vast differences in the characteristics of injury and recovery. The lesions on the injured spinal cord were 38 percent longer, on average, in elderly mice than in young adult mice. In addition, the older mice were unable to gain movement of their hind limbs by the time most younger mice had regained that mobility.

The research is published in the *Journal of Neuroscience*.

The receptor in question is called the IL-4 alpha receptor, and its job is to "see" the infusion of interleukin-4, or IL-4, in the central nervous system after the spinal injury. IL-4 is a cytokine, a type of protein connected to immune system function. Many cytokines promote inflammation, but IL-4 is associated with curbing inflammation.

Godbout and colleagues observed that IL-4 in the central nervous systems in both young adult and aging mice sent signals to recruit additional repair cells to the injury site – cells called macrophages and monocytes. These are types of white blood cells that originate in the bone marrow and circulate in what is known as the "periphery," via blood and outside the central nervous system. But only in young adult mice were these types of cells contributors to wound healing and clearing

of debris, necessary inflammatory functions that help rather than harm.

"This was surprising to us because aging is typically associated with increased inflammation so we'd expect to see higher levels of inflammatory cytokines in the aged mice," said first author Ashley Fenn, who just received her Ph.D. in neuroscience from Ohio State. "But in the aged mice with a spinal cord injury, we saw reduced levels of some inflammatory signals associated with a failure to reprogram the microglia with IL-4 toward a reparative profile. That's how we figured out the IL-4 is unique in the spinal cord injury paradigm, that it induces an inflammatory response that appears to be beneficial."

The IL-4 in the young adult mice also led to production of arginase, a protein that serves as a biomarker of the injury repair response. Significantly less arginase was detected in the injured elderly mice, another signal that the disabled receptor interfered with IL-4's assistance in injury repair.

The communication among systems has long been a focus of Godbout's research. He is an investigator in Ohio State's Institute for Behavioral Medicine Research (IBMR) and Center for Brain and Spinal Cord Repair.

"There is some level of communication going on between the central nervous system microglia and the peripheral immune system's macrophages. In our model, differences in that communication affected the ability to bring in cells to the site of the injury. Maybe the aging microenvironment brings in cells that are less beneficial," he said.

About 200,000 people are currently living with a spinal cord injury in the United States, and an estimated 12,000 to 20,000 new injuries occur each year, according to the Centers for Disease Control and Prevention.

Though any therapy based on this research would take many years to develop, Godbout and Fenn said that finding a drug that could stimulate expression of the IL-4 alpha receptor in elderly spinal cord injury patients might have potential to improve their outcomes.

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