Traumatic brain injury interferes with immune system cells' recycling process in brain cells, finds study

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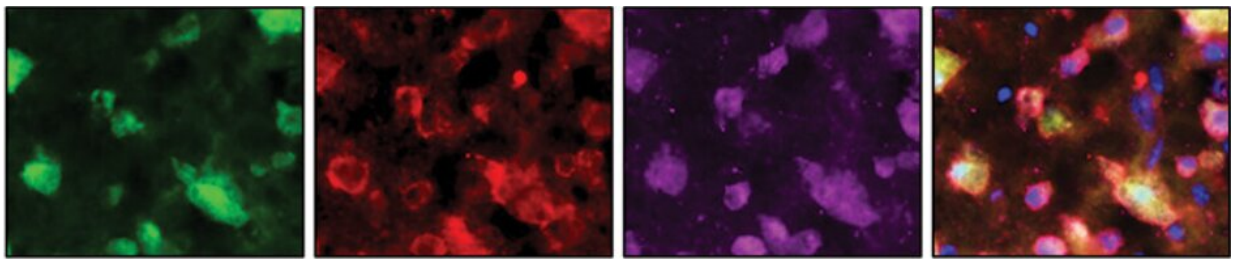

Markers of inflammation (red) and autophagy (purple) appear in brain cells 3 days after traumatic brain injury. Credit: Marta Lipinski in *Autophagy* (2023). DOI: 10.1080/15548627.2023.2167689

Each year about 1.5 million people in the U.S. survive a traumatic brain injury due to a fall, car accident, or a sports injury, which can cause immediate and long-term disability.

University of Maryland School of Medicine (UMSOM) researchers wanted to better understand what happens in the brain during injury, so they conducted a study in mice to determine how different types of brain cells in mice react to severe trauma. In a new study published in the January issue of *Autophagy*, they found that after traumatic brain injury, the brain's immune system cells' internal recycling function slowed dramatically, allowing waste products to build up and interfere with

recovery from injury.

The researchers also found that treating mice that had traumatic brain injury with a drug to promote cellular recycling improved the mice's ability to recover from injury and solve a water maze, a measure of memory function in mice.

"Many drugs and potential solutions have been proposed to treat traumatic brain injury, but none have ever worked in practice," said lead researcher Marta Lipinski, Ph.D., Associate Professor of Anesthesiology and Anatomy & Neurobiology at UMSOM and a member of the Shock, Trauma, and Anesthesiology Research (STAR) Center at the University of Maryland Medical Center (UMMC). "It could be that designing drugs for patients that promote this cellular recycling might reverse or prevent damage from traumatic brain injury as we saw in our animal studies. We are continuing to learn more about the molecular and cell biology mechanisms in trauma, so we can use a more guided approach for developing solutions."

The body's cells regularly recycle their own worn-out or damaged parts that accrue through normal wear and tear, infection, or injury in a process known as autophagy. Most cells in the brain use that process for cleaning up their own waste and recycling it on a smaller scale. In a previous study, Dr. Lipinski's group showed that traumatic brain injury reduced the ability of neurons—the cells that send electrical impulses—to recycle their own damaged parts, which then led to these neurons dying off. However, some cells in the brain can perform greater feats of recycling, such as the resident immune cells in the brain known as microglia, which can engulf, digest, and recycle entire damaged or dead cells in the tissue.

After a traumatic brain injury, white blood cells—normally excluded by the blood-brain barrier—can also get into the brain and work alongside

the microglia cells to eat and remove damaged cells. For this new study, Dr. Lipinski's team focused on the immune cells—microglia and white blood cells—in the brain after traumatic brain injury and found that like the neurons, their recycling function was also suppressed.

"Dr. Lipinski's discovery of the recycling function suppression in both neurons and immune cells demonstrates how important it is for neuroscientists to fully understand the complex system involved in a traumatic brain injury," said Dean Mark Gladwin, MD, who is Vice President for Medical Affairs at the University of Maryland, Baltimore, and the John Z. and Akiko K. Bowers Distinguished Professor at UMSOM. "Developing effective drugs for traumatic brain injury treatment requires a deeper understanding of these cell-to-cell interactions and what impact each cell type has on the brain's ecosystem."

To demonstrate the full impact of the recycling process on traumatic brain injury and recovery, Dr. Lipinski and her team blocked one of the essential proteins needed to carry out the immune cell's recycling function in the brains of mice with a brain injury. These mice experienced an even greater suppression of their cell recycling processes, resulting in more inflammation in their brain. They even performed worse, as measured by their ability to solve the water maze, than the mice with only brain injury. These findings suggested that the recycling function of the immune cells in the brain is essential for recovery after brain trauma. Conversely, boosting it may possibly lessen the impact of the trauma.

To test that, the researchers used a drug, rapamycin (normally used as a cancer drug or to prevent organ rejection), to promote cellular recycling in the brains of mice who had traumatic brain injury. The researchers found that with the treatment, the mice had lower levels of inflammation in the brain and these mice did better in navigating the water maze.

"The drug we used in our study blocks a set of proteins that are important for regenerating the body's cells, so it cannot be used for extended time periods," said Dr. Lipinski. "We need to continue this line of research to identify the exact mechanism of how autophagy protects against neurological damage in order to find more targeted drugs that increase this process without targeting the vital proteins needed by the brain to regenerate."

More information: Nivedita Hegdekar et al, Inhibition of autophagy in microglia and macrophages exacerbates innate immune responses and worsens brain injury outcomes, *Autophagy* (2023). DOI: 10.1080/15548627.2023.2167689

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