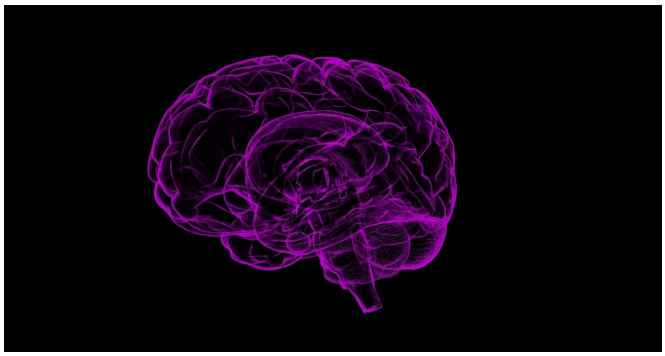
Neurologists identify consistent neuroinflammatory response in ICH patients

22 February 2021



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Understanding how the immune system responds to acute brain hemorrhage could open doors to identifying treatments for this devastating disease. However, up until now, there has been limited information on inflammation in the brain from human patients, especially during the first days after a hemorrhagic stroke.

This led a team of researchers to partner with a large clinical trial of minimally-invasive surgery to tackle defining the human neuroinflammatory response in living patients.

"Our goal was to find out, for the first time, how certain key cells of the immune system are activated when they enter the brain after a hemorrhage and how this may shift over the first week. This is a critical time for our patients," said Lauren Sansing, MD, Academic Chief of Stroke and Vascular Neurology and Associate Professor of Neurology and Immunobiology at Yale.

The study, published in *Science Immunology*, was led by an interdisciplinary team of researchers including Sansing and Michael Askenase, Ph.D., Associate Research Scientist (both of Yale), and MIT scientists Alex Shalek, Ph.D., J. Christopher Love, Ph.D., and Brittany Goods, Ph.D. Using RNA-sequencing, they found that CD14+ macrophages and neutrophils change rapidly in the brain over the first few days after the hemorrhage. They were also able to find signatures in the macrophages that were consistent in patients with good recovery.

According to the American Heart Association, intracerebral hemorrhage (ICH) makes up approximately 13% of all stroke cases. It occurs when a blood vessel bursts and releases blood into the brain, damaging the surrounding brain tissue. The mortality rate is up to 40%, most survivors are left with some disability, and there is no cure.

ICH generates an acute local immune response within and around the hematoma. Researchers have predicted that inhibiting this inflammation may improve patient outcomes, but so far haven't identified cellular and molecular targets that have been effective therapies in patients.

The study's research team partnered with the MISTIE III surgical trial, which implemented a minimally invasive surgery wherein tissue plasminogen activator (tPA) was administered via a small catheter to liquify the clot and allow drainage of blood from the brain over several days. The blood clots were shipped daily from hospitals around the nation to the Sansing Lab.

According to Dr. Askenase, "We used the detailed patient outcome measures collected by MISTIE III to identify key molecular circuits within CD14 monocytes/macrophages that correlated with good neurological outcomes, thereby uncovering potential mechanisms by which these cells may help contribute to patient recovery. In particular, we found that these cells preferentially use glycolytic metabolism to generate a key anti-inflammatory lipid known as prostaglandin E2 that, if it activates the right receptor, may have broad pro-recovery effects not only on neighboring immune cells, but also on brain-resident neurons and glia."

This could allow physicians to target the brain's immune response to ICH and unlock new treatment options for an otherwise deadly form of stroke, although further research is needed to study these pathways.

A study of this breadth demanded collaboration and coordination.

"This project could only be done with great team work across many institutions," said Dr. Sansing.

Dan Hanley, MD and the MISTIE III trial leadership, the coordination with the trial substudies through MTI:M3, the trial investigators and clinical coordinators nationwide who collected the samples and all the scientific collaborators were key to the study success. The investigators thank the patients and families who took part in the study.

"I'm proud to be a part of one of the leading ICH research teams in the country. The ability to learn deeply from surgical samples opens the door for exciting new avenues in ICH research," said Charles Matouk, MD, Chief of Neurovascular Surgery at Yale and the MISTIE III co-site PI and collaborator on the research.

The study serves as a model for future studies to leverage a brain hemorrhage clinical trial to gain significant insight into the fundamental mechanisms of the disease and provide a more targeted approach to treating ICH.

More information: Michael H. Askenase et al, Longitudinal transcriptomics define the stages of myeloid activation in the living human brain after intracerebral hemorrhage, *Science Immunology* (2021). DOI: 10.1126/sciimmunol.abd6279

Provided by Yale University