MedicalXpress

Scientists discover new cause of fatal brain injury from acute viral meningitis

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In a November 16 advance, online publication of the journal *Nature*, the researchers say their discovery revamps common beliefs about how such potentially lethal infections may be ravaging the brain and suggests the possibility of new treatments.

"This is a paradigm shift in how we think about some forms of meningitis and possibly other infections," says the study's lead investigator, Dorian B. McGavern, Ph.D., an associate professor in the Department of Immunology at Scripps Research. "What we thought were the killers are actually immune cells that recruit other accessory cells that then drive the disease. If we can find ways to block recruitment of the cells that actually do the damage into the brain, we may be able to limit the impact of the virus."

Meningitis occurs when the membrane (the meninges) that covers and protects the spinal cord and brain become inflamed, usually due to a bacterial or viral infection. The condition is considered a medical emergency because it can lead to an inflammatory response that results in brain swelling, seizures, blood clotting, epilepsy, or other complications, sometimes resulting in death. Many viruses can cause meningitis.

In this study, investigators looked at what happens in the brain of mice exposed to lymphocytic choriomeningitis virus (LCMV), a virus that can also infect humans, but which does not cause a lot of damage on its own. Instead, the virus pushes an immune response that, in itself, is damaging

because it results in "leaky" blood vessels in the meninges at the blood-brain border.

"We use this mild virus because all the damage produced in the brain is caused by the immune system," McGavern says. "While other viruses are more pathologic, they all produce an immune response."

The researchers developed a unique way to "watch" what happens in the brain of mice infected with LCMV by tagging immune cells known as cytotoxic T lymphocytes (CTLs)—also known as killer T cells—with proteins that shine a fluorescent green. These cells, which the researchers knew reacted to LCMV, are the immune system fighters previously thought to be responsible for battling the virus and damaging the brain in the process.

When the researchers injected the tagged killer T cells into the mice, followed one day later with a dose of the virus, then a dye to visualize blood vessels, the scientist found that they could use two-photon microscopy to see what was happening 300-400 microns below the surface of the skull in the brain. Sure enough, the scientists could see blood vessels breaking down as meningitis developed and progressed, but the tagged killer T cells did not appear to be the direct cause of the vascular damage.

"We thought the disease depended on these killer T cells, but they didn't seem to be associated with any of the damage we were seeing," McGavern says.

The researchers then tagged other populations of immune cells: monocytes, which usually clean up and repair damage, and neutrophils, which may help with antiviral immunity. To their surprise, the scientists saw that these cells flooded the brain after LCMV infection, and were associated with significant damage to blood vessels in the brain's

membrane.

"The vessels just start exploding," McGavern says. "This tells us that killer T cells recruit monocytes and neutrophils that actually produce the pathology we see with meningitis. What we thought were the cells responsible actually only recruit accomplices who commit the crime."

The researchers don't know exactly why monocytes and neutrophils are called to sites of infection by killer T cells, or how they produce such damage in meningitis. They theorize that the breakdown of blood vessels may be the result of these cells' attempts to move quickly out of the blood system into tissue within the confined space of the brain.

Now, however, the scientists do have a new avenue to explore for possible treatments for the deadly disease.

Source: Scripps Research Institute