How does the immune system fight off threats to the brain?

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This illustration shows what the researchers found -- that a killer T cell (yellow) in the brain can target an infected or tumor cell (marked with A) and surrounding cells by releasing cytokines (dots) both within the gasket-like immunological synapse between the cells, and into the surrounding area via "leaks." These findings may help advance research on infections, tumors and autoimmune disease. Credit: Lowenstein/Castro lab

Like a police officer calling for backup while also keeping a strong hold on a suspected criminal, immune cells in the brain take a two-tier approach to fighting off a threat, new research from the University of Michigan Health System finds.

For the first time, the scientists managed to capture that reaction in action, showing how certain immune cells locked onto a model of virus-infected brain cells, while also sending signals to neighboring uninfected cells to let them know about the immune attack.

The findings may help research on how the brain fights off viruses and

tumors. It also aids the search for ways to harness the immune response to attack and kill brain tumor cells -- or to calm the overzealous self-attack that occurs in people with certain autoimmune diseases.

Published online today in the *Proceedings of the National Academy of Sciences,* the findings illuminate how cells called CD8+ T cells, or "killer" T cells, carry out their police-like role. Pedro Lowenstein, M.D., Ph.D., professor in the Department of Neurosurgery at the U-M Medical School, led the research team.

He explains that the research yields new insight into the nature of the "gasket" that forms between killer T cells and their target cells, i.e., infected -- or tumor -- cells. Killer T cells go after cells when they detect the presence of foreign proteins, called antigens, on the cell surface.

The gasket-like structure creates an area between the two cells called an immunological synapse -- and has been thought of by some scientists as a tight seal. Studies, including previous ones by Lowenstein's team, have suggested that it allows the killer T cell to lock on to its target and bombard it first with molecules called cytokines, and then with chemicals that break down the infected cell and kill it.

But other scientists have shown that when killer T cells are attacking infected cells, the cytokines they release seem to cause a reaction in many neighboring, uninfected cells – suggesting a very open connection. These latter studies question the role of immunological synapses.

Using a unique live-cell imaging technique developed by the team, the new results show that the gasket connection focuses the T cell attack on the infected cell, but is leaky. This creates a two-tier response when a killer T cell goes after an infection.

"The T cell targets the infected cell preferentially, but it also secretes

cytokines that reach a number of other cells in the neighborhood," says Lowenstein. "The immunological synapse fails to restrict how far cytokines can spread."

The research team, including U-M postdoctoral fellow Nicholas Sanderson, Ph.D., made the finding using a live-cell imaging method they developed that allows them to detect how many cells are exposed to the cytokine interferon gamma.

While the immunological synapse "gasket" ensured that the targeted cell was hit first by cytokines, other cells in the area soon showed signs of having received the same cytokine signal.

What's more, the researchers confirmed that the killer T cell carried out its killer function only on the targeted, infected cell it had attached to – sparing nearby cells.

"This work disproves the idea that T cells secrete cytokines indiscriminately in the brain, but shows that T cell cytokine secretion affects a larger area beyond the targeted cell," says Lowenstein. "This helps settle the quandary of why widespread response to cytokines are seen, even when immune cells form specific immunological synapses only with target cells."

The finding, he adds, will help illuminate at a molecular level how the brain gets rid of infection. But it also hints at how the body's own T cells might mount the misguided attack on normal healthy brain cells in autoimmune diseases. The findings clarify how widespread effects can be obtained in spite of very specific cell-to-cell interactions.

And, significant for the U-M team's work on brain tumor physiology, the new result helps build knowledge that could be used in attempts to attack and kill brain tumor cells while sparing normal cells. "What we want to

know is how T cells work, how they interact with target cells and how we can make this process more efficient," Lowenstein explains.

Such an approach is the goal of the team led by Lowenstein and Maria Castro, Ph.D., who is a co-author on this paper.

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