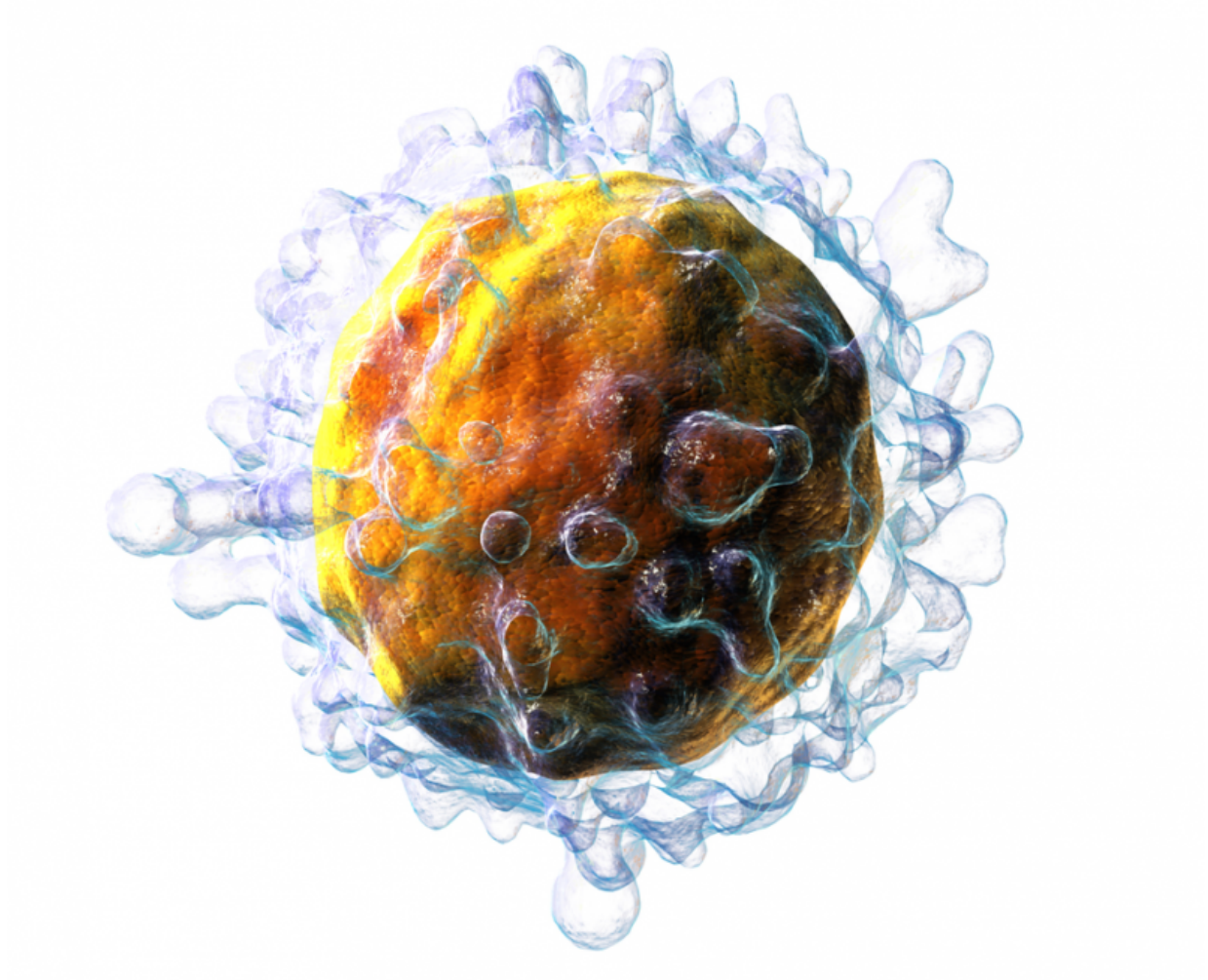
Team finds early inflammatory response paralyzes T cells

August 18 2015



3D rendering of a T cell. Credit: CC BY 3.0, Blausen.com staff. "Blausen gallery 2014". Wikiversity Journal of Medicine. DOI:10.15347/wjm/2014.010. ISSN 20018762.

In a discovery that is likely to rewrite immunology text books, researchers at UC Davis have found that early exposure to inflammatory cytokines, such as interleukin 2, can "paralyze" CD4 T cells, immune components that help orchestrate the body's response to pathogens and other invaders.

This mechanism may act as a firewall, shutting down the immune response before it gets out of hand. However, from a clinical standpoint, this discovery could lead to more effective cancer immunotherapies, better drugs for autoimmune conditions and new ways to expedite recovery from sepsis. The research, online July 28, appears in today's print edition of the journal *Immunity*.

"There's a three-signal process to activate T cells of which each component is essential for proper activation," said first author Gail Sckisel, a post-doctoral fellow. "But no one had really looked at what happens if they are delivered out of sequence. If the third signal - cytokines - is given prematurely, it basically paralyzes CD4 T cells."

To be activated, T cells must first recognize an antigen, receive appropriate costimulatory signals, and then encounter inflammatory cytokines to expand the immune response. Until now, no one realized that sending the third signal early - as is done with some immunotherapies - could actually hamper overall immunity.

"These stimulatory immunotherapies are designed to activate the immune system," said Sckisel, "but considering how T cells respond, that approach could damage a patient's ability to fight off pathogens. While immunotherapies might fight cancer, they may also open the door to opportunistic infections."

This was shown in mice which, after receiving systemic immunotherapy, had trouble mounting a primary T-cell response. The finding was

confirmed in samples from patients receiving high-dose interleukin 2 therapy to treat metastatic melanoma.

"We need to be very careful because immunotherapy could be generating both short-term gain and long-term loss," noted lead author William Murphy, professor and acting chair in the UC Davis Department of Dermatology. "The patients who were receiving immunotherapy were totally shut down, which shows how profoundly we were suppressing the immune system."

In addition to illuminating how T cells respond to cancer immunotherapy, the study also provides insights into autoimmune disorders. The researchers believe this CD4 paralysis mechanism could play a role in preventing autoimmunity, a hypothesis they supported by testing immunotherapy in a multiple sclerosis model.

By shutting down CD4 T cells, immune stimulation prevented an autoimmune response. This offers the potential to paralyze the immune system to prevent autoimmunity or modulate it to accept transplanted cells or entire organs.

"Transplant patients go on immunosuppressants for the rest of their lives, but if we could safely induce paralysis just prior to surgery, it's possible that patients could develop tolerance," said Sckisel.

CD4 paralysis may also be co-opted by pathogens, such as HIV, which could use this chronic inflammation response to disable the immune system.

"This really highlights the importance of CD4 T cells," said Murphy. "The fact that they're regulated and suppressed means they are definitely the orchestrators we need to take into account. It also shows how smart HIV is. The virus has been telling us CD4 T cells are critical because

that's what it attacks."

The team's next step is to continue this research in older mice. Age can bring a measurable loss in immune function, and inflammation may play a role in that process.

"For elderly people who have flu or pneumonia, their immune systems are activated, but maybe they can't fight anything else," said Murphy. "This could change how we treat people who are very sick. If we can block pathways that suppress the immune response, we may be able to better fight infection."

Provided by UC Davis