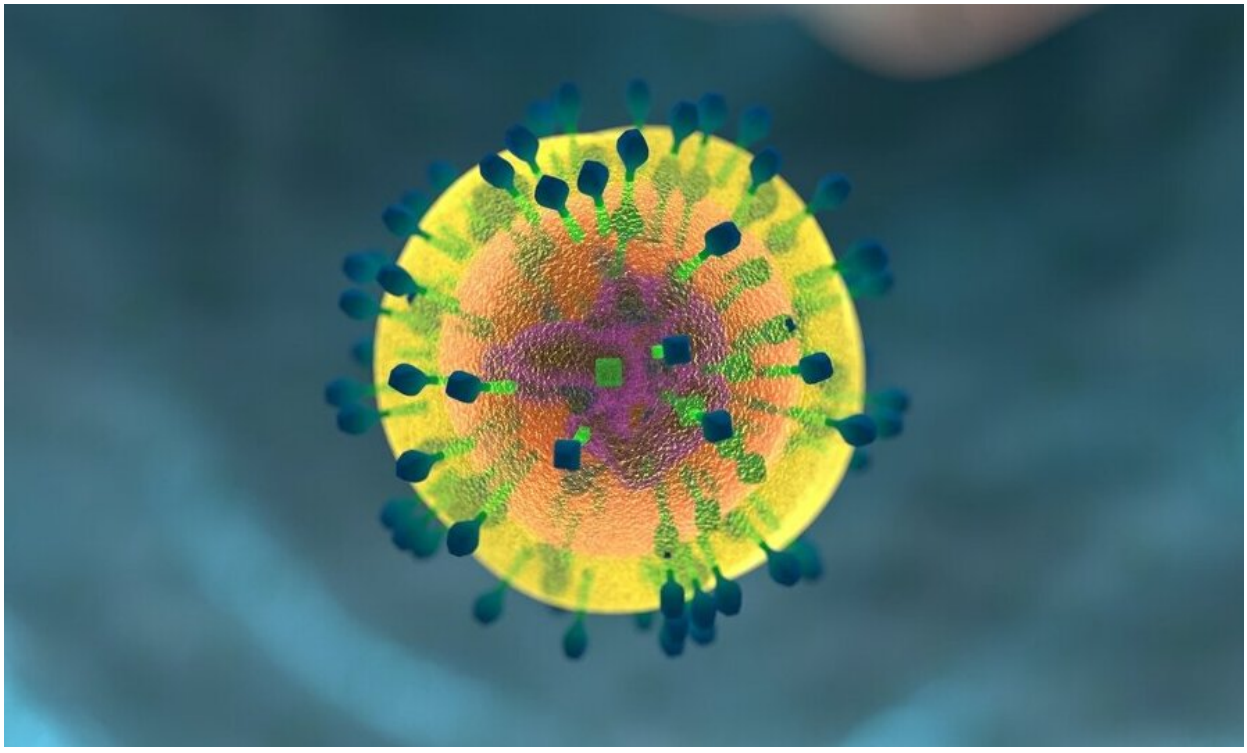
MedicalXpress

Newly identified immune cell switch could control inflammation

July 24 2024, by Krishna Ramanujan



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Cornell researchers have identified a switch that regulates inflammation caused by an immune response, a finding that could one day help clinicians control inflammation-related conditions such as autoimmune, cardiovascular and neurodegenerative diseases.

When an antigen—a toxin or foreign substance that induces an immune response—enters the body, depending on the context, naive immune system T-cells (which have never been exposed to an antigen) become stimulated and can differentiate into one of two cell types that will dictate the type of immune response that will occur. At that point, these immature T-cells can differentiate into different T cell types. Two of the T cell types are T_H17 cells, which induce inflammation, or T_{reg} cells, which are anti-inflammatory.

A new study, published July 23 in the journal *Science Signaling*, has identified the roles played by kinase ITK, an enzyme, and calcium, in controlling a switch in the development of these inflammatory or anti-inflammatory T cell types, that is, whether T cells promote or suppress inflammation.

"The more we understand about how inflammation develops, the more potential we have to be able to develop ways to suppress it," said Avery August, professor of immunology in the College of Veterinary Medicine (CVM) and deputy provost, the paper's senior author.

"The fact that we can switch these cells from being inflammatory to being suppressive suggests that maybe we can use this approach in cases where we don't want an inflammatory response, but we actually want to suppress inflammation and the immune system, such as in autoimmune disease," he said.

The study used an engineered mouse strain with T cells marked by a fluorescent protein that glows green if they become T_H17 cells and red when they turn into T_{reg} cells. Another mouse strain allowed them to inhibit only the kinase ITK and no other kinases, as well as a small molecule chemical inhibitor to inhibit the kinase ITK.

They found that when they removed the activity of the kinase ITK,

either using the mouse model via genetic means or with the chemical inhibitor, naive T cells became T_{reg} cells, which suppress inflammation, instead of becoming inflammatory T_H17 cells.

"We're switching what the cells actually do by inhibiting the kinase activity, and we can do this in a dose-dependent way," August said.

The researchers used RNA sequencing and other techniques to confirm that even though naive T cells were receiving signals to become inflammatory T_H17 cells, they in fact became T_{reg} suppressor cells.

Also, the researchers knew that when kinase ITK activates a naive T cell, calcium floods inside the cell. But when they inhibited kinase ITK and yet still increased intracellular calcium, naive T cells no longer behaved as if the kinase was inhibited and were instead activated to produce T_H17 cells and an inflammatory response. The finding showed that kinase ITK's ability to tune the cell differentiation process could be sidestepped with calcium to switch between inflammatory T_H17 cells and suppressing T_{reg} cells.

Orchi Anannya, Ph.D. '23, former doctoral student in August's lab, is the paper's first author. Weishan Huang, Ph.D. '14, also a former doctoral student in August's lab, currently an associate professor at Louisiana State University, is a co-author.

More information: Orchi Anannya et al, The kinase ITK controls a Ca 2+ -mediated switch that balances T_H17 and T_{reg} cell differentiation, *Science Signaling* (2024). DOI: 10.1126/scisignal.adh2381

Provided by Cornell University