Specialized regulatory T cell stifles antibody production centers

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A regulatory T cell that expresses three specific genes shuts down the mass production of antibodies launched by the immune system to attack invaders, a team led by scientists at The University of Texas MD Anderson Cancer Center reported online in the journal *Nature Medicine*.

"Regulatory T cells prevent unwanted or exaggerated immune system responses, but the mechanism by which they accomplish this has been unclear," said paper senior author Chen Dong, Ph.D., professor in MD Anderson's Department of Immunology and director of the Center for Inflammation and Cancer.

"We've identified a molecular pathway that creates a specialized regulatory T cell, which suppresses the reaction of structures called germinal centers. This is where immune system T cells and B cells interact to swiftly produce large quantities of antibodies," Dong said.

The discovery of the germinal center off-switch, which comes two years after Dong and colleagues identified the mechanisms underlying a helper T cell that activates the centers, has potential implications for cancer and autoimmune diseases.

"In some types of cancer, the presence of many regulatory T cells is associated with poor prognosis," Dong said. "The theory is those cells suppress an immune system response in the tumor's microenvironment that otherwise might have attacked the cancer."

However, in B cell lymphomas, overproliferation and mutation of B cells are the problems, Dong said. Hitting the regulatory T cell off-switch might help against lymphomas and autoimmune diseases, while blocking it could permit an immune response against other cancers.

Antibody production central

Germinal centers are found in the lymph nodes and the spleen. They serve as gathering points for B and T cell lymphocytes, infection-fighting white blood cells.

When the adaptive immune system detects an invading bacterium or virus, B cells present a piece of the invader, an antigen, to T cells. The antigen converts a naïve T cell to a helper T cell that secretes cytokines, which help the B cells expand and differentiate into specialized antibodies to destroy the intruder.

"Germinal centers have mostly B cells with a few helper T cells to regulate them. The B cells mutate to make high-affinity antibodies and memory B cells for long-term immunity. The cell population in the germinal center structures replicates in an average of several hours, one of the fastest rates of cell replication known in mammals," Dong said.

Tracking down specialized T cell

In the Nature Medicine paper, Dong and colleagues found that a subgroup of regulatory T cells that expresses two genes, Bcl-6 and CXCR5, moves into germinal centers in both mice and humans, where they have access to B cells.

(Bcl-6 produces a protein called a transcription factor, which moves into the cell nucleus to regulate other genes. CXCR5 is a receptor protein for a signaling molecule called CXCL13.)

They also found that the Bcl-6/CXCR5 T cells aren't produced in the thymus, with other T cells, but are generated by regulatory T cell precursor cells that express Foxp3, another transcription factor.

Knocking out the regulatory T cells that express all three proteins in mice resulted in increased germinal center production of antibodies. They named this key T cell the T follicular regulatory cell, or Tfr.

In a 2009 paper in the journal *Science*, the researchers found that naïve T cells that expressed Bcl-6 and CXCR5 also gathered in the B cell zone of germinal centers. Expression of Bcl6 converted the T cell into a T follicular helper (Tfh) cell that launches antibody production in the germinal centers.

With Tfr turning germinal centers off and Tfh turning them on, we could potentially regulate antibody production, Dong noted. Increasing Tfr production could be a new approach to treating autoimmune inflammatory disorders, such as lupus and rheumatoid arthritis.

Provided by University of Texas M. D. Anderson Cancer Center