Autoimmune disease strategy emerges from immune cell discovery

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Scientists from UC San Francisco have identified a new way to manipulate the immune system that may keep it from attacking the body's own molecules in autoimmune diseases such as type 1 diabetes, rheumatoid arthritis and multiple sclerosis.

The researchers, led by immunologist Mark Anderson, MD, PhD, a professor with the UCSF Diabetes Center, have discovered a distinctive type of immune cell called an eTAC, which puts a damper on immune responses.

Anderson's research team found that eTACs reside in lymph nodes and spleen in both humans and mice, and determined that they could be manipulated to stop the destruction of the pancreas in a mouse model of diabetes. The study appears in the September issue of the journal *Immunity*.

Using green fluorescent protein (GFP) to highlight a key regulatory protein called AIRE, Anderson's research team tracked down the rare eTACs and their role in a phenomenon known as peripheral tolerance, which helps prevent autoimmune disease throughout the body.

The newly described immune cells are of a type known as dendritic cells, which make up less than 3 percent of the cells in the immune system. ETAC cells account for a small fraction of all dendritic cells, Anderson said.

Dendritic cells already have been the focus of new cell therapies to treat cancer. These therapies, which include treatments evaluated in clinical trials at UCSF, have been used to prod dendritic cells to rev up a complementary class of immune cells, called T cells. Treatment causes the T cells to target cancer cells, which, despite being abnormal, would not otherwise be subjected to vigorous attack in the same way as foreign microbial invaders.

However, eTAC cells have the opposite effect. Instead of priming T cells to do battle, eTACs counteract the overactive immune response in autoimmune diseases. Anderson's team took advantage of this property to demonstrate that eTACs could prevent autoimmune diabetes in mice.

By displaying "self" molecules to T cells that target them, and turning off these T cells for good, eTACs help the immune system tolerate the molecules naturally present within us, Anderson said.

"The mouse model we are working with involves using T cells that normally attack the islet cells of the pancreas, specifically by recognizing a molecule called chromagranin A that is present on islet cells," Anderson said. "But if the eTACs can get to the T cells first and display chromagranin A, they can prevent T cells from attacking the islets."

Anderson aims to exploit eTACs therapeutically by finding out how to grow them in large numbers outside the body. "We need to figure out how to grow a lot of these cells, to load them up with whatever molecule it is that we want to induce tolerance to, and then to load them back into a patient," he said. "Such a strategy could help selectively shut down an unwanted immune response, such as the anti-islet immune response in type 1 diabetes."

Dendritic cells work with T cells a bit like a sheriff working with a bloodhound. Dendritic cells present not an article of clothing, but rather a specific molecule. If the molecule displayed by the dendritic cell matches the one the T cell was born to target, then that T cell would be activated to expand its numbers and to attack cells or tissues where the molecule is present.

When the interaction is between eTACs and T cells, however, the targeted T cell instead is turned off forever, and never seeks its molecular prey, Anderson said.

The first signal required for activation of a T cell is the display and recognition of the targeted molecule. But a second signal also is required, and eTACs are unable to deliver it, Anderson and colleagues discovered. They lack the molecular arms—molecules called B7-1 and B7-2—needed to hand off the activating message, which are present on other dendritic cells.

The eTACs arise in the bone marrow from adult stem cells that generate the entire blood system, including immune cells, Anderson said. Compared to using pluripotent stem cells of nearly unlimited potential, it should be easier to figure out how to guide the development of eTACs from bone marrow stem cells, he said.

Anderson's search for an immune cell that turns off T cells began with the AIRE protein. Anderson helped discover its function more than a decade ago for specialized cells in the thymus. In the thymus, AIRE plays a key role in central tolerance, the phenomenon whereby immune cells in thymus learn to tolerate the body's naturally occurring molecules shortly after birth. Peripheral tolerance complements central tolerance, and its failure often is responsible for autoimmune diseases that arise long after birth.

Many UCSF faculty members are experts on immune tolerance and autoimmune disease. Another strategy for manipulating the immune system to fight autoimmune disease, pioneered by Jeffrey Bluestone, PhD, the A.W. and Mary Clausen Distinguished Professor of Medicine, Pathology, Microbiology & Immunology at UCSF, already has led to a new treatment being evaluated in a clinical trial for type 1 diabetes. The treatment is based on a type of T cell called the regulatory T cell, which plays a natural role in ending immune responses when infection ends.

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