Rare B cells regulate immune responses, may offer novel treatment for autoimmune diseases

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Reproducing a rare type of B cell in the laboratory and infusing it back into the body may provide an effective treatment for severe autoimmune diseases such as multiple sclerosis or rheumatoid arthritis, according to researchers at Duke University Medical Center.

The findings, which were demonstrated in mice, highlight the unique properties of a subset of B cells that normally controls immune responses and limits autoimmunity, in which an organism mistakenly attacks its own healthy tissue. The work appears Oct. 14, 2012, in the journal *Nature*.

B cells are the component of the immune system that creates antibodies, which fight pathogens like bacteria and viruses. However, a small subset of B cells, called regulatory B cells, works to suppress immune responses. These B cells are characterized by a cell-signaling protein called interleukin-10 (IL-10), giving these regulatory B cells the name B10 cells.

While B10 cells are small in number, they are important for controlling inflammation and autoimmunity. B10 cells can also limit normal immune responses during infections, reducing inadvertent damage to healthy body tissue.

"Regulatory B cells are a fairly new finding that we're just beginning to

understand," said Thomas F. Tedder, PhD, professor of immunology at Duke and study author. "B10 cells are important because they make sure an immune response doesn't get carried away, resulting in autoimmunity or pathology. This study shows for the first time that there is a highly controlled process that determines when and where these cells produce IL-10."

Tedder and his colleagues studied the process of IL-10 production in the B10 cells of mice. Creating IL-10 requires physical interactions between B10 cells and T cells, which play a role in turning on the immune system.

The researchers found that B10 cells only respond to very specific antigens. Recognizing these antigens drives the function of B10 cells, causing them to turn off certain T cells when they bind the same antigen to prevent them from harming healthy tissue.

With this understanding of B10 cells, researchers set out to learn whether B10 cells could be harnessed as a cellular therapy, given their ability to regulate immune responses and autoimmunity.

"Since B10 cells are extremely rare, it was important that we find a feasible solution to reproduce these cells outside the body to make them available," Tedder said.

The researchers learned that the B10 cells could be isolated from the body and would maintain their ability to regulate immune responses. Moreover, they could be reproduced in large numbers.

"Normal B cells usually die quickly when cultured, but we have learned how to expand their numbers by about 25,000-fold. However, the rare B10 cells in the cultures expand their numbers by four-million-fold, which is remarkable. Now, we can take the B10 cells from one mouse and increase them in culture over nine days to where we can effectively

treat 8,000 mice with autoimmune disease," said Tedder.

When a small amount of B10 cells were introduced into mice with multiple sclerosis-like autoimmune disease, their symptoms were significantly reduced, essentially turning off the disease.

"B10 cells will only shut off what they are programmed to shut off. If you have rheumatoid arthritis, you would want cells that would only go after your rheumatoid arthritis," continued Tedder. "This research shows that we may have the potential to unharness regulatory cells, make millions of copies, and introduce them back into someone with autoimmune disease to shut down the disease. This may also treat transplanted organ rejection."

Additional research is needed to learn how to expand human B10 cells and determine how B10 cells behave in humans, building on the study's insights into the mechanisms behind their function and autoimmunity.

"Autoimmune diseases are very complicated, so creating a single therapy that allows us to go after multiple disease targets without causing immunosuppression has proven to be difficult." Tedder said. "Here, we're hoping to take what Mother Nature has already created, improve on it by expanding the cells outside of the body, and then put them back in to let Mother Nature go back to work."

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