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New strategy prevents rheumatoid arthritis in mice

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Dana-Farber Cancer Institute scientists have demonstrated a new strategy for treating autoimmune disease that successfully blocked the development of rheumatoid arthritis in a mouse model. They say it holds promise for improved treatment of arthritis and other autoimmune disorders in people.

The scientists report in the Journal of Clinical Investigation that infusing a highly specific type of cell that regulates immune responses into arthritis-prone mice shut down the cascade of inflammation that damages tissues and joints.

The method worked best when the infusions of CD8+ Treg cells were given at the same time that the animals were injected with a protein that triggered the arthritis-causing autoimmune reaction. "We found we could almost completely inhibit the disease in this setting," said Harvey Cantor, MD, chair of the Department of Cancer Immunology and AIDS at Dana-Farber and the study's senior author.

Even when administered weeks after the disease was initiated, CD8+ Treg infusions combined with low doses of methotrexate – a commonly used drug for rheumatoid arthritis – were able to significantly slow the arthritis process, the scientists reported.

The new strategy also blocked disease progression when the scientists injected peptide antigens to expand the rodents' own pool of CD8+ Tregs, rather than infusing them from outside. Overall, the results

"suggest that [these] strategies represent a promising therapeutic approach to autoimmune disorders," the researchers wrote.

The human immune system is a network of cells, tissues, and organs that, when functioning normally, attacks and destroys infections, viruses, parasites, and other foreign "invaders."

In autoimmune disorders, however, parts of the immune system attack the individual's own healthy cells and tissues – the result of the immune forces failing to recognize "self" identifying tags on the body's cells.

An estimated 50 million American suffer from autoimmune disorders, which include rheumatoid arthritis, lupus, type 1 diabetes, multiple sclerosis, and celiac disease. At least 100 different autoimmune diseases have been identified, and are more common among women. The incidence of these diseases is rising in the United States for unknown reasons.

Rheumatoid arthritis is caused by inflammation throughout the body, attacking many tissues, especially the joints, frequently causing painful and deformed fingers and hands. About 1.5 million Americans are afflicted with rheumatoid arthritis. Drugs of several types, including corticosteroids, are given to reduce inflammation and slow the disease. The newest treatments are biologic agents, which block secreted chemicals called cytokines that carry out the misguided attacks. However, even with these agents – which can have serious side effects – rheumatoid arthritis treatment is often not optimal, said Cantor.

In contrast to these "downstream" players in the complex autoimmune cascade, the strategy described in the new report is aimed "upstream," where the attacks begins with overactive immune fighters, called T follicular helper cells, that mistakenly respond to "self" markers on healthy cells. These T cells can become chronically overactivated,

spurring a continuous attack by antibodies on the body's tissues.

"Current treatment strategies that inhibit cytokines such as TNF or IL-1 production spare the upstream initiating events that continuously induce new effector T cells and cytokine secretion," noted Cantor. "We believe that targeting the CD4 T cells that initiate this cascade may be a more effective approach to rheumatoid arthritis therapy."

T regulatory cells, or Tregs, play an important role in turning off an immune response when it's no longer needed, such as after the body has repelled viral or bacterial invaders. Cantor previously found that certain Tregs, known as CD8+ Tregs, can recognize and eliminate overactive CD4 T helper cells that display a marker called Qa-1 in mice; the human equivalent is HLA-E.

In the new experiments, Cantor's team showed that these Qa-1-recognizing CD8+ Tregs could be recruited to kill off the subset of the harmful T helper cells causing arthritis "and exert strong inhibitory effects on disease progression." They found that CD8+ Tregs that recognized an Hsp60 molecule on the Qa-1 T helper cells were the most effective in eliminating the overreacting T cells. The researchers showed that administering the Hsp60 antigen to the mice triggered expansion of the CD8+ Tregs already present in the animals and slowed or stopped disease development.

Moving closer to clinical relevance, the researchers will test this approach in mice carrying human immune cells that provoke an autoimmune response.

Cantor said they are also studying the possibility of using nanoparticles coated with Qa-1/Hsp60 molecules to expand CD8+ Tregs as a more practical method that might be used someday for human therapeutic tests.

More information: Amelioration of arthritis through mobilization of peptide-specific CD8+ regulatory T-cells, *J Clin Invest.* doi:10.1172/JCI66938.