

Discovery highlights promise of new immune system-based therapies

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A new focus on the immune system's ability to both unleash and restrain its attack on disease has led Dana-Farber Cancer Institute scientists to identify cells in mice that prevent the immune system from attacking the animals' own cells, protecting them from autoimmune diseases such as multiple sclerosis, type 1 diabetes, and lupus.

The discovery, reported online on Sept. 16 by the journal *Nature*, may give scientists an effective way of operating the immune system's internal "control panel," leading to improved therapies for a variety of diseases - from vaccines that prompt the immune system to stage a sustained assault on cancers, to treatments that derail the biological onslaught associated with [autoimmune diseases](#). The fact that human immune system cells share key features with those in mice makes the prospect of such advances quite realistic, the study authors say.

"The traditional view of the immune system is of specialized groups of cells poised to attack foreign pathogens [disease-causing agents]," says senior author Harvey Cantor, MD, who is the chair of the Department of [Cancer Immunology](#) and AIDS at Dana-Farber. "While that model is generally correct, we've come to appreciate that the immune system, like other complex biological information systems, includes a counterbalance mechanism - a set of cells programmed to suppress the [immune response](#). Such cells are essential to preventing excessive reactions to pathogens and misguided attacks on the body's own cells."

The search for cells involved in quieting the immune response has

previously focused on [immune system cells](#) known as CD4+ T cells, some of which have been shown to prevent abnormal inflammation in response to disease or infection. In the new study, lead author Hye-Jung Kim, PhD, and her colleagues found that CD8+ T cells (known as killer T cells because of their ability to kill diseased cells) also include a subset that helps dampen the immune response. Instead of reducing inflammation like their CD4 cousins, the CD8+ T regulatory (CD8+Treg) cells ensure that the immune system doesn't produce antibodies that attack normal cells.

The Dana-Farber team discovered how CD8+ Treg accomplish this feat. They mingle with cells known as follicular T-helper cells, which are intermediaries that prompt the immune system's B cells to make disease-fighting antibodies. The meeting with CD8+ Treg cells essentially shuts off the follicular T-helper cells, preventing them from interacting with B cells. No interaction means no production of antibodies, which means no assault on an animal's normal, healthy cells.

The critical point of contact between CD8+ Treg cells and follicular T-helper cells is a protein on the helper cells called Qa-1. When Kim and her colleagues bred a strain of mouse with abnormal Qa-1, the animals developed a form of lupus. The reason: the CD8+ Treg cells couldn't latch onto the defective protein, leaving the follicular cells free to order the B cells to produce antibodies, some of which targeted the animals' own tissue.

The significance of this work is that CD8+ Treg cells represent a new lever for raising or lowering the strength of the immune response. This class of cells, it turns out, depends for its survival on a cytokine (a regulatory compound) called interleukin 15. Increase the supply of CD8+ Treg cells and the immune response is suppressed - a potentially powerful way of dealing with autoimmune diseases. Decrease the amount of such cells and the immune response can be invigorated and

extended - a useful complement to vaccines that unleash the immune system on cancer.

"Experience has shown that vaccines that simply activate or expand the number of T and B cells are not likely to result in a prolonged, robust anti-tumor response," Cantor explains. "The balancing mechanism within the immune system means that when more disease-fighting cells are generated, there's a countervailing increase in the number of immune-suppressing cells that are generated. The key is to break that loop. This work brings that goal closer."

Provided by Dana-Farber Cancer Institute

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