Strategy for mismatched stem cell transplants triggers protection against graft-vs.-host disease

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A new technique being tested in stem-cell transplants from imperfectly matched donors has revealed a striking, unforeseen response that can suppress graft-versus-host disease, a common and dangerous complication of mismatched transplants, report scientists from Dana-Farber Cancer Institute.

Analysis of blood samples from a small number of clinical trial patients showed that the novel method -- which inactivates specific immune cells from the donor that would attack the recipient's body -- also unleashes a surge of T-cells that further dampen the immune reaction.

The previously unrecognized specificity of these regulatory T-cells (also called Tregs) helps explain why the patients treated with the new strategy -- known as "co-stimulatory blockade" -- have shown a gratifyingly low level of graft-vs-host disease, according to the report published online by the new journal Science Translational Medicine.

The findings also suggest that optimizing the activity of Tregs in this manner might prove valuable in transplants of kidneys and other solid organs, as well as in treating autoimmune disease, say the scientists, led by Eva Guinan, MD, senior author, of Dana-Farber and Children's Hospital Boston, and Jeff Davies, MD, PhD, first author, of Dana-Farber. Both are also on the Harvard Medical School faculty.

The innovative method for improving mismatched bone-marrow and stem-cell transplants was first described clinically 10 years ago in the New England Journal of Medicine by Guinan, Lee Nadler, MD, also at Dana-Farber and a co-author on the new publication, and others. They employed a technique called "co-stimulatory blockade" to prevent certain T-cells in the donor material from recognizing and attacking cells in the patient's body, causing graft-vs-host inflammatory reactions that can affect the gastrointestinal system, skin, and other organs. The need for techniques that can reduce complications in mismatched transplants is great; the odds of a patient having a perfectly matched sibling for a donor are only about 25 percent.

"Originally we thought that using this method to specifically block the harmful response by donor T-cells explained the decrease in graft-vs-host disease and the rapid recovery of immune function we have seen in the clinical trials," said Guinan. "Now we learn that there is another powerful mechanism that is induced -- the generation and rapid expansion of Treg cells in the three months following the transplant."

Regulatory T-cells are a special population of T-cells that suppress immunity. They have two important functions: Turning off immune reactions following a successful defense against infectious organisms, and preventing immune cells from attacking the body's own tissues, which are identified by distinctive "self-antigen" markers.

In the past five years or so, scientists have used new tools to study Tregs and consider ways they could be harnessed for therapy in transplantation and autoimmune disease. In 2008, Davies and Guinan reported low levels of graft-vs-host disease in a small number of mismatched transplants using co-stimulatory blockade, which not only neutralized the T-cells that cause the harmful graft-vs-host response but also led to rapid reconstitution of the patients' bone marrow.

The researchers then designed experiments to learn more molecular details about how the blockade strategy had reduced graft-vs-host complications. Based on few reports in the literature, "We wondered whether Tregs were playing an additional role," said Davies.

Davies analyzed frozen blood samples taken from five patients and donors at various intervals after the transplants. The analysis showed that during the first three months, the level of Tregs in the patients rapidly rose to very high levels, which helped explain why the recipients experienced only mild graft-vs-host symptoms. The Tregs, they confirmed, were generated from the donated T-cells - not remnants of the recipient's immune system.

"We found there was something about co-stimulatory blockade that caused this rapid expansion of Tregs," said Davies, adding that further studies are exploring this question.

Importantly, the researchers noted, the Tregs acted in a highly specific fashion: They turned off only the donor T-cells that would have triggered the immune attack on the recipient's tissues -- other T-cells that help the patients fight off infections were spared. This specificity appears to have developed in the recipient's body, where the Tregs were "educated" to respond only to a harmful T-cell reaction.

As a result, said Guinan, this technique "creates a good balance of effects -- inactivating the T-cells that cause graft-vs-host disease (GVHD), revving up the Tregs to turn off any incipient GVHD, while bringing about a rapid reconstitution of the recipient's immune system."

The scientists expect the new findings to influence the design of further clinical tests of the co-stimulatory blockade technique. And, they said, it opens a window on other potential applications of co-stimulatory blockade, which is already being used clinically to treat rheumatoid

arthritis (an autoimmune disease) and is being tested in mismatched kidney transplants.

Source: Dana-Farber Cancer Institute