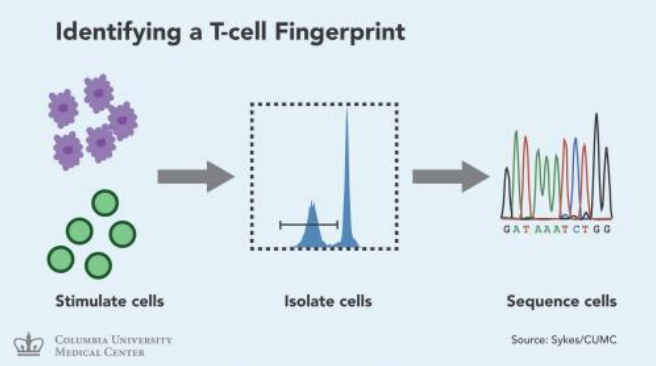
Kidney transplant tolerance mechanism identified

16 March 2015



A new technique for identifying of patient-specific T cells that react to donor tissue. The method could help predict rejection and tolerance in different types of transplant patients. Credit: Laboratory of Megan Sykes/Columbia University Medical Center

Columbia University Medical Center (CUMC) researchers have pinpointed the immune system mechanism that allows a kidney transplant to be accepted without lifelong immunosuppressive drugs, a significant step toward reducing or eliminating the need for costly and potentially toxic immunosuppressant drugs and improving long-term transplant success. The findings were published in the Jan. 28 online issue of *Science Translational Medicine*.

Using a new technique for identifying and tracking specific cells, combined with advanced genetic sequencing, the researchers found a set of patient-specific T cells that react to the donor tissue, increasing in number in patients who reject the organ but gradually disappearing in patients who accept the organ without immunosuppression and are therefore considered to be immunologically "tolerant" of their donors.

"This new technique provides a window into the fate of these T cells and has potential as an individualized biomarker for predicting and identifying rejection and tolerance in different types of transplant patients," said study leader Megan Sykes, MD, the Michael J. Friedlander Professor of Medicine, professor of microbiology & immunology and surgical sciences (in surgery), and director of the Columbia Center for Translational Immunology at CUMC.

When a patient receives a transplant, a unique population of lymphocytes, donor-reactive T cells, emerges to reject the foreign organ. Immunosuppressive medication is almost always required to prevent rejection of the donor tissue. "Previously, it had not been possible in humans to identify these specific T cells because of their vast number and diversity," said Dr. Sykes. "Furthermore, they are unpredictable and distinct for each transplant patient and donor."

Earlier studies suggested that a unique subset of T cells, called regulatory cells, play a role in initially inducing tolerance, but they seemed not to be involved in maintaining tolerance later on. Therefore, other explanations for long-term tolerance were needed. It was unclear whether the large number of donor-reactive T cells actually disappeared or was still present but inactive in long-term tolerant recipients. To learn more, the CUMC team devised a new technique for identifying and tracking these cells.

The researchers used the technique on blood samples taken from six kidney-transplant patients. Two of the patients had undergone conventional kidney transplants. The other four had received combined kidney and bone marrow transplantation (CKBMT) in a clinical trial and stopped taking immunosuppressants eight months after surgery. CKBMT, an experimental therapy, is known to produce an immune state that combines elements of both the recipient's and donor's immune systems. "Our studies have shown that CKBMT induces tolerance of the transplanted organ without

the need for long-term immunosuppressants. But we didn't understand the mechanism behind this tolerance," said Dr. Sykes, who helped develop CKBMT in the early 2000s, as part of a Harvard University-Massachusetts General Hospital team.

In the current study, the CUMC researchers identified the donor-reactive T cells in each patient's blood before transplant and repeated the test after transplant at three intervals (six, 12, and 18 months). Three of the four patients who underwent CKBMT showed a decrease in donor-reactive T cells from pre-transplant to post-transplant. All three tolerated the transplant. In the fourth CKBMT patient, the donor-reactive cells did not significantly decline over time, and the patient, unlike the others, rejected the donor kidney. The two patients who had the kidney transplant alone had an increase in donor-reactive T cell receptors.

"Our findings suggest that deletion of a specific set of donor-reactive T cells is a major mechanism governing tolerance of donor tissue," said Dr. Sykes. "The study also supports the approach of combining kidney transplants with bone marrow transplants, with its resultant elimination of donor-reactive T cells. This approach needs further study, but so far, all signs indicate that it could eliminate the need for lifelong immunosuppression."

Although immunosuppressant drugs have dramatically increased transplant success, they have notable drawbacks, including significant side effects and increased risk of cancer, opportunistic infections, hypertension, elevated cholesterol, and other conditions. "On top of all that, the transplants often do not survive permanently because of the drugs and the constant attacks of the recipient's immune system," said Dr. Sykes.

The team is currently planning a trial of CKBMT at CUMC.

More information: Tracking donor-reactive T cells: Evidence for clonal deletion in tolerant kidney transplant patients, stm.sciencemag.org/content/7/272/272ra10.abstract

Provided by Columbia University Medical Center