Post-transplant combo can replace toxic immune-suppressing drugs in monkeys

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Transplant patients rely on drugs to prevent graft rejection, but at the cost of serious side effects. The class of immunosuppressive drugs known as calcineurin inhibitors (examples are cyclosporine and tacrolimus) can damage patients' kidneys and lead to high blood pressure, among other problems.

A combination of treatments can effectively replace calcineurin inhibitors in preventing graft rejection when kidney transplants are performed on monkeys, scientists at the Emory Transplant Center have shown. The non-human primate research was conducted at the National Institutes of Health and Yerkes National Primate Research Center, Emory University.

The results are published in the July issue of Nature Medicine.

The finding opens the door to less-toxic post-transplant treatment that could be administered once a week rather than a dizzying mound of pills every day, says senior author Allan Kirk, MD, PhD, scientific director of the Emory Transplant Center and a Georgia Research Alliance Eminent Scholar.

"Both of the drugs used in this regimen are already used separately in humans, thus a clinical trial could be developed quickly," Kirk notes.

One key ingredient in the combination is an experimental therapy called a costimulation blocker, designed to interfere with the T cells that cause

graft rejection without affecting other organs. Costimulation refers to one of two signals T cells need from other cells (antigen presenting cells) to become fully activated.

The other key ingredient -- a protein called alefacept -- subdues memory T cells, a variety of T cells that allow the immune system to respond faster and stronger to an infectious agent or vaccine upon second exposure.

Costimulation blockers are sufficient for allowing mice to tolerate a transplanted kidney, but not monkeys or people, Kirk says. Memory cells appear to prevent costimulation blockers from working as well in monkeys as they do in mice.

"One of the big differences we've found between mice and both monkeys and people is that we primates have more exposure to infections that require us to develop immunological memory," he says. "Memory cells are quicker to become activated and don't need costimulation as much, so blocking costimulation doesn't slow them down."

By themselves, neither costimulation blockers (in this case, a molecule called CTLA4-Ig) or alefacept could prevent rejection in monkeys after the eight week treatment period, Kirk and his colleagues found. They had more success by combining costimulation blockers, alefacept and the transplant drug sirolimus. Under this regimen, monkeys could last for months after treatment ended without developing rejection or self-reactive antibodies.

CTLA4-Ig mimics a molecule found on T cells (CTLA4) and acts as a decoy. CTLA4-Ig is now used as an FDA-approved therapy for rheumatoid arthritis.

A similar drug called belatacept is now in phase III kidney transplant clinical trials, but current studies use it in combination with conventional immunosuppressive drugs.

Alefacept targets memory T cells via a molecule on their surfaces called CD2, the authors found. Alefacept was approved by the FDA for treatment of psoriasis in 2003. It is also being tested in a kidney transplant clinical trial in combination with conventional drugs.

Both CTLA4-Ig and alefacept are proteins and must be administered intravenously or possibly subcutaneously. However, their stability means they don't need to be taken every day - once a week is enough, Kirk says.

More information: T.A. Weaver et al. Alefacept promotes costimulation blockade-based allograft survival in primates. *Nature Medicine*. 15, 746-749 (2009)

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