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Discovery could provide new prevention, treatment option for organ transplant rejection

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An international team led by researchers from the University of Pittsburgh School of Medicine found that targeting certain donor cells lowered the risk of organ rejection in mice that underwent kidney and heart transplants. The study results, published today in *Nature Communications*, could lead to new ways of preventing or treating organ transplant rejection in humans.

"The success of organ transplantation has reached a plateau over the past 10 or 20 years, with a significant proportion of patients still losing their grafts to rejection despite immunosuppressive treatment," said Fadi Lakkis, M.D., Frank & Athena Sarris Chair in Transplantation Biology, professor of surgery, immunology and surgery at the University of Pittsburgh, scientific director of the Thomas E. Starzl Transplantation Institute and co-author of the study. "New methods to tackle rejection are needed, and this discovery is another step toward finding a solution."

Without immunosuppressive treatment, transplanted organs are quickly rejected by the recipient's immune system—in particular, by T cells. Successful engraftment has traditionally relied upon preventing the activation of T cells in the lymph nodes and spleen or in the graft by administering anti-rejection drugs. If T cell activation does occur, stopping rejection becomes increasingly difficult.

To become fully activated, T cells need to make physical contact and

receive help from a highly specialized type of cell called dendritic cells. Post-transplant, the main function of the dendritic cells is to present donor-derived antigens to donor-reactive T cells in lymphoid tissues, causing an immune response in the body.

In the study, researchers found that dendritic cells play a key role in driving rejection of transplanted organs by activated T cells that have already entered the transplanted organ. The donor dendritic cells that accompanied heart or kidney grafts in mice were rapidly replaced by the recipient's dendritic cells, which propagated T lymphocyte activation within the graft and increased the risk of rejection.

"We demonstrated that dendritic cells not only exert a key role as antigen-presenting cells in graft-draining lymphoid organs, but also play a critical function within the transplanted organs," said Adrian E. Morelli, M.D., Ph.D., associate professor of surgery and immunology at the Thomas E. Starzl Transplantation Institute and study co-author. "Our study indicates that eliminating transplant-infiltrating dendritic cells reduces proliferation and survival of T cells within the graft with the consequent prolongation of transplant survival."

"The next step would be to devise methods to specifically target dendritic cells within transplanted organs," Dr. Lakkis said. "Such methods carry the promise of preventing or interrupting rejection without compromising the patient's overall immune defenses."

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