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New clues found to preventing lung transplant rejection

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Organ transplant patients routinely receive drugs that stop their immune systems from attacking newly implanted hearts, livers, kidneys or lungs, which the body sees as foreign.

But new research at Washington University School of Medicine in St. Louis suggests that broadly dampening the immune response, long considered crucial to transplant success, may encourage lung transplant rejection.

In a surprising discovery, the researchers found that newly transplanted lungs in mice were more likely to be rejected if key immune cells were missing, a situation that simulates what happens when patients take immunosuppressive drugs.

These long-lived memory T cells are primed to "remember" pathogens that infiltrate the body and quickly trigger an immune response during subsequent encounters. In heart, liver and kidney transplants, knocking down memory T cells with immunosuppressive drugs helps to ensure that the immune system recognizes a new organ as the body's own.

But not so in lung transplants, according to the new research published online Feb. 24 in the *Journal of Clinical Investigation*.

"In mice, memory T cells are critical for a lung transplant to have a good outcome," said co-corresponding author Daniel Kreisel, MD, PhD, a Washington University lung transplant surgeon at Barnes-Jewish

Hospital. "A lot of transplant recipients receive drugs that indiscriminately deplete many different T cells. But in lung transplants, this strategy may contribute to organ rejection."

In light of the new findings, the researchers think current immune-suppression strategies should be re-evaluated in lung transplantation.

"Most immunosuppressive drugs were adopted for use in lung transplants based on their results in other solid organ transplants, without an appreciation that the lung is different," Kreisel said.

The research also may help explain, in part, why the success of lung transplants in people lags far behind other solid organ transplants.

Five years after lung transplantation, fewer than half of the transplanted lungs are still functioning, according to the U.S. Organ Procurement and Transplantation Network. This compares with five-year organ survival rates of about 70 percent for heart, kidney and liver transplants.

The poorer outcomes after lung transplantation are related largely to higher rejection rates, the researchers said. About 1,800 lung transplants are performed each year in the United States.

"The high failure rate of lung transplants is a major problem," said co-corresponding author Alexander Krupnick, MD, a Washington University lung transplant surgeon at Barnes-Jewish Hospital. "Lungs are unique. Unlike other organs, they are continually exposed to bacteria, viruses and everything else in the environment, and we think this increases the risk of chronic rejection and the eventual failure of the organ."

Memory T cells regularly patrol the lungs, where they distinguish harmless challenges like cat dander or tree pollen from more serious

insults like respiratory viruses or pathogenic bacteria. Without these cells, the immune system recognizes a newly transplanted lung as harmful and mounts an attack that eventually can lead to rejection of the organ.

As part of the study, the researchers performed lung transplants in mice. When memory T cells were absent in these mice, the newly transplanted lungs underwent rejection. The researchers found evidence of severe inflammation in the lungs, an indicator that the immune system had instigated an aggressive attack against the foreign organ.

However, when the scientists infused memory T cells into the lung recipients, they could reduce inflammation and prevent rejection. Further, they defined the molecular pathway by which memory T cells naturally dampen the body's response to lung transplants. Rather than attacking the lungs, memory T cells unleash a cascade of signaling molecules that encourage the immune system to see the transplanted lung as the body's own.

Based on their findings, the researchers want to find ways to selectively target immunosuppression in lung transplants, to encourage memory T cells to thrive while eliminating other T cells that harm transplanted lungs.

"We really need to develop immune suppression strategies just for lung transplants that boost the ability of memory T cells to do their job," Krupnick said. "This may give newly transplanted lungs a much better chance of surviving long after the transplant is over."

Provided by Washington University School of Medicine