Transplant experts challenge assumption, describe pathway that leads to organ rejection

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Transplant researchers at the University of Pittsburgh School of Medicine challenge a long-held assumption about how biologic pathways trigger immune system rejection of donor organs in a report published online today in the *Journal of Clinical Investigation*. Their study, sponsored by the National Institutes of Health, suggests a different paradigm is needed to develop better anti-rejection therapies.

Immune system troops called T-cells migrate to transplanted organs, fighting the foreign tissue, explained senior author Fadi Lakkis, M.D., Frank & Athena Sarris Chair in Transplantation Biology, professor of surgery, Pitt School of Medicine, and scientific director of the Thomas E. Starzl Transplantation Institute. Until now, scientists have thought these T-cells were beckoned to the site by chemokines, proteins secreted by cells in the lining of the blood vessels, or endothelium, of the organ when it becomes inflamed.

"The prevailing view was that when the endothelium gets inflamed, it gets a little sticky, so T-cells that are zipping by in the bloodstream begin to slow down and bind to chemokines that trigger their arrest and migration into the affected tissue," Dr. Lakkis said. "We decided to test that hypothesis and found out to everyone's surprise that's not the way it works."

If the chemokine receptors on T-cells were blocked, the researchers

reasoned, the cascade of immune events would not happen, stalling rejection. So two days after mice received a heart or kidney transplant, they received T-cells treated with pertussis toxin, which irreversibly binds to a key molecule in the receptor to inhibit its activity, and presumably prevent the migration of memory and effector T-cells already sensitized to recognize the foreign proteins of the donor tissue.

Using a technique called two-photon microscopy, which allows real-time visualization of living tissue, they found that pertussis-treated T-cells invaded the donor organs just as they did if they were untreated, leading to organ rejection.

"This showed us that chemokines are not necessary to start the rejection response," Dr. Lakkis said. "So then we wondered which cells were sounding the alarm to the immune system."

The sophisticated microscopy technique revealed that the donor kidney's dendritic cells, which identify antigens or foreign proteins and present them on their cell surfaces to be recognized by other immune cells, "stick their feet," as Dr. Lakkis put it, in the bloodstream, thereby exposing donor surface antigens to the recipient's immune system.

"So, anti-rejection therapies that target chemokine responses have very little effect," he said. "But novel drugs that interfere with antigen presentation by the endothelium or the dendritic cells could be very helpful."

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