Immune system 'atlas' will speed detection of kidney transplant

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Scientists at the Stanford University School of Medicine and Lucile Packard Children's Hospital have devised a new way to decode the immune signals that cause slow, chronic rejection of all transplanted kidneys. They've created an immune-system "atlas" that will improve doctors' ability to monitor transplanted organs and shed light on the mechanisms of gradual, cumulative kidney malfunction after transplant.

"The reason chronic injury occurs in transplanted organs is really a mystery," said senior study author Minnie Sarwal, MD, PhD, professor of pediatrics at the School of Medicine and a nephrologist at Packard Children's Hospital. "Even patients who receive an organ from an identical twin develop chronic rejection."

The findings will be published online Feb. 23 in the *Proceedings of the National Academy of Sciences*.

Before an organ transplant, doctors check for compatibility between the donor's and recipient's immune systems, Sarwal said. They examine the genes encoding small proteins, called human leukocyte antigens, that label the exterior of every cell. These proteins are the immune system's main mechanism for distinguishing "self" from "non-self" tissues. Only identical twins have perfectly matched human leukocyte antigens; for other organ recipients, doctors use a donor with the closest match they can find. After transplant, an organ recipient receives strong drugs that reduce the body's ability to crank out antibodies — immune "search-and-destroy" markers — against the donated kidney.

But the fact that chronic organ rejection occurs even between twins suggests the immune system is doing more than keeping tabs on human leukocyte antigens.

The Stanford team set out to find what that was. The researchers devised a first-of-its-kind method to catalog every one of the antibodies attacking donated kidneys after transplant. They tracked evidence of all types of immune system attack by comprehensively comparing antibody levels in 18 kidney recipients before and after transplant. To do this, they melded two biological sleuthing systems, first comparing all proteins in the subjects' blood to an array of more than 5,000 human proteins, then running the results from that analysis through a genetic database that showed which blood proteins were antibodies designed to attack the donated kidney.

"This is pretty revolutionary," Sarwal said. "It opens the door to a lot of exciting work to personalize how we monitor these patients." The new findings will allow inexpensive, noninvasive blood tests that show whether a donated kidney is infected, undergoing acute rejection or accruing chronic injuries that could cause long-term malfunction, she said.

"An individual's antibody profile is a new aspect of human physiology that can now be surveyed in an unbiased way, the same way genes can," said co-senior author Atul Butte, MD, PhD, assistant professor of medical informatics and of pediatrics. "That's very exciting." Butte is also a member of the Stanford Cancer Center. Unlike genes, the body's antibodies change over time, a factor that could improve the effectiveness of personalized medicine, Butte said.

The team's raw data on antibody profiles is now publicly available to other scientists through the Gene Expression Omnibus database maintained by the National Center for Biotechnology Information, a division of the National Library of Medicine.

In addition to improving patient monitoring, the team's comprehensive list of anti-kidney antibodies will spur research on the mechanisms of chronic kidney rejection. For example, the study establishes for the first time what part of the kidney

causes the largest immune response after transplant.

"To our great surprise, the most immunogenic region of the kidney is the renal pelvis," Sarwal said. The renal pelvis is the cavity deep inside the organ that collects urine and funnels it toward the bladder. The next-largest immune responses were observed at the cortex and glomerulus, regions of the kidney with large blood supplies and extensive exposure to the recipient's immune system. The next step in understanding chronic organ rejection will be to identify which specific anti-kidney antibodies are the most reliable harbingers of renal malfunction, Sarwal said.

"If we can correlate these antibodies with clinical events in the organ, we'll have the tools to extend the life of kidney transplants," Sarwal concluded.

Source: Stanford University Medical Center