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Protein-based urine test predicts kidney transplant outcomes

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Levels of a protein in the urine of kidney transplant recipients can distinguish those at low risk of developing kidney injury from those at high risk, a study suggests. The results also suggest that low levels of this protein, called CXCL9, can rule out rejection as a cause of kidney injury. The study appears online Aug. 22 in the *American Journal of Transplantation*. The work was funded by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health.

To prevent rejection, kidney transplant recipients typically take immunosuppressive drugs every day. However, these drugs can cause kidney damage and lead to other serious side effects such as cancer, infection and infertility. Even with immunosuppressive therapy, 10 to 15 percent of kidney recipients experience rejection during the first year after transplantation.

Currently, the only definitive way to distinguish rejection from other causes of kidney injury is by performing a biopsy, in which doctors remove a small piece of kidney tissue to look for rejection-associated damage. Although this procedure is generally considered safe, it carries some minor risks for the patient and does not always provide an accurate impression of the overall state of the kidney.

"A noninvasive urine test to accurately monitor the risk of kidney rejection could dramatically reduce the need for biopsies and possibly enable doctors to safely reduce immunosuppressive therapy in some

patients," said NIAID Director Anthony S. Fauci, M.D. "The results of this study support the further development of noninvasive tests for the detection and management of transplant rejection."

In this multicenter Clinical Trials in Organ Transplantation study, doctors periodically collected urine samples from 280 adult and child kidney transplant recipients for two years after transplantation. Investigators led by Peter Heeger, M.D., of the Icahn School of Medicine at Mount Sinai in New York City, and Donald Hricik, M.D., of Case Western Reserve University in Cleveland, measured the urinary levels of molecules that had previously been associated with rejection. These included two proteins and nine messenger RNAs (mRNAs)—intermediary molecules in the construction of proteins from genes. They identified CXCL9 protein and CXCL9 mRNA as potential biomarkers—molecules that indicate the effect or progress of a disease—for the diagnosis of rejection.

After further testing, the researchers found that CXCL9 protein was better at ruling out rejection than any of the mRNAs tested. Low levels of the protein biomarker also could identify patients likely to have stable long-term kidney function. Transplant recipients with low urinary CXCL9 protein six months after transplantation were unlikely to experience rejection or loss of kidney function over the next 18 months. In addition, detection of the protein in the urine of transplant recipients was more straightforward than measuring mRNA levels. While proteins can be measured directly in urine, mRNAs must first be extracted from urine samples. The researchers obtained sufficient mRNA from just 76 percent of samples, highlighting the technical challenges of extraction.

"The relative ease of measuring urinary proteins suggests that developing a protein-based urine test for use in clinical practice would be less complicated than an mRNA test," said Daniel Rotrosen, M.D., director of NIAID's Division of Allergy, Immunology and Transplantation.

"There is strong precedent for the development and use of tests that measure urinary proteins, such as home pregnancy tests."

CXCL9 protein levels also may be useful for predicting and monitoring transplant rejection. The investigators noted that urinary CXCL9 levels began to increase up to 30 days before clinical signs of kidney injury, which could allow doctors to intervene early to potentially avoid rejection-associated kidney damage. The protein levels began to drop after treatment for rejection, suggesting that the urine test could be used to monitor treatment progress.

"Development of noninvasive tests to detect immune activation before kidney damage occurs would help guide the care of kidney transplant recipients," said NIAID Transplantation Branch Chief Nancy Bridges, M.D., a co-author of the paper. "Clinical application of the findings from this study could help avoid unnecessary biopsies and excess immunosuppression."

More information: DE Hricik et al. Multicenter validation of urinary CXCL9 as a risk-stratifying biomarker for kidney transplant injury. *American Journal of Transplantation* (2013). onlinelibrary.wiley.com/doi/10 … 1/ajt.12426/abstract

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