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Genetic marker may help predict success of kidney transplants

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Kidneys donated by people born with a small variation in the code of a key gene may be more likely, once in the transplant recipient, to accumulate scar tissue that contributes to kidney failure, according to a study led by researchers at the Icahn School of Medicine at Mount Sinai and published today in the *Journal of Clinical Investigation*.

If further studies prove the variation to cause fibrosis (scarring) in the kidneys of transplant recipients, researchers may be able to use it to better screen potential donors and improve transplant outcomes. Furthermore, uncovering the protein pathways that trigger kidney fibrosis may help researchers design drugs that prevent this disease process in kidney transplant recipients, and perhaps in all patients with chronic kidney disease.

"It is critically important that we identify new therapeutic targets to prevent scarring within transplanted kidneys, and our study has linked a genetic marker, and related protein pathways, to poor outcomes in kidney transplantation," said Barbara Murphy, MD, Chair, Department of Medicine, Murray M. Rosenberg Professor of Medicine (Nephrology) and Dean for Clinical Integration and Population Health at the Icahn School of Medicine at Mount Sinai. "Drug designers may soon be able to target these mechanisms."

A commonly used study type in years, the genome-wide association study (GWAS) looks at differences at many points in the genetic code to see if, across a population, any given variation in the genetic code is

found more often in those with a given trait; in the case of the current study, with increased fibrosis in recipients of donated kidneys.

Even the smallest genetic variations, called single nucleotide polymorphisms (SNPs), can have a major impact on a trait by swapping just one of 3.2 billion "letters" making up the human DNA code. The current study found a statistically significant association between SNP identified as rs17319721 in the gene SHROOM3 and progressive kidney scarring (fibrosis) and function loss in a group of kidney donors, mostly of European descent. In many cases, certain SNPs will be more common in families or ethnic groups.

The kidneys filter the blood to remove extra blood sugar and waste products that trickle down the kidney tubes to become urine, while re-absorbing key nutrients. The build-up of scar tissue in these delicate structures over time interferes with proper renal function.

Chronic kidney disease already affects 10 percent of US adults and its prevalence is increasing. Along with leading to kidney failure in many cases, chronic kidney disease increases the risk of cardiovascular disease. Fibrosis in kidney tubules is a common pathogenic process for many types of chronic kidney disease, and a central part of chronic disease in donated kidneys (chronic allograft nephropathy, or CAN).

CAN comes with a steady, gradual loss of function in the donated kidneys. A significant percentage of patients with chronic kidney disease and fibrosis in their kidney tubules will eventually progress to renal failure that requires dialysis or transplantation of kidneys, with demand far higher that supply. To date, there is no effective therapy to prevent the progression of kidney disease.

Researchers and clinicians have made great gains in preventing transplant rejection during the first few years by selectively suppressing

the immune system, but long term damage and disease remain a major challenge. The eventual development of an assay to predict whether a donor's kidney, once transplanted, would be more susceptible to inflammation or scarring may help overcome this challenge.

Newfound Pathways Reveal Drug Targets

The *Journal of Clinical Investigation* study found that the SNP rs17319721 in the gene SHROOM3, when present in the donor of kidney, correlates with increased expression of the SHROOM3 genes, and a greater quantity of SHROOM3 protein in the organ once transplanted. More SHROOM3 turns on more transcription factor 7-like 2 (TCF7L2). This, in turn, turns on several genes with many functions in cells. TCF7L2 is a member of the Wnt signaling pathway, and ultimately results in increased signaling by transforming growth factor beta 1 (TGF-β1) and increased COL1A1 expression.

TGF-β1 signals for the building of connective tissue (scar tissue), which normally restores tissue architecture as part of healing, but may also drive fibrosis in the wrong context. COL1A1 (Collagen, type I, alpha 1) is the gene that codes for the major component in type I collagen, the major protein component of connective tissues (e.g. bone. cartilage) and of scar tissue that forms as wounds heal. Together, these factors contribute to excess tissue fibrosis.

While SHROOM3 had been associated with chronic kidney disease by earlier work, the specific role of and mechanisms by which SHROOM3 contributed to transplant injury and kidney fibrosis was unknown going into this study.

The current study results proceed from an ongoing NIH-sponsored study in kidney transplant recipients [Genomics of Chronic Allograft Rejection (GOCAR) study]. The research team performed biopsies of

transplanted kidneys at pre-specified time points after transplantation and matched gene activation (expression) levels in the transplanted kidneys 3 months after transplantation to indices of transplant dysfunction at 12 months.

The link between the SHROOM3 gene, related protein pathways and fibrosis detected in the GWAS was confirmed in studies of mice engineered to be models of human kidney disease.

"Further work is needed before a clinical application of the study can be introduced," said Dr. Murphy. "However, our results are a crucial and optimistic step towards improving treatment of chronic kidney disease."

Provided by The Mount Sinai Hospital