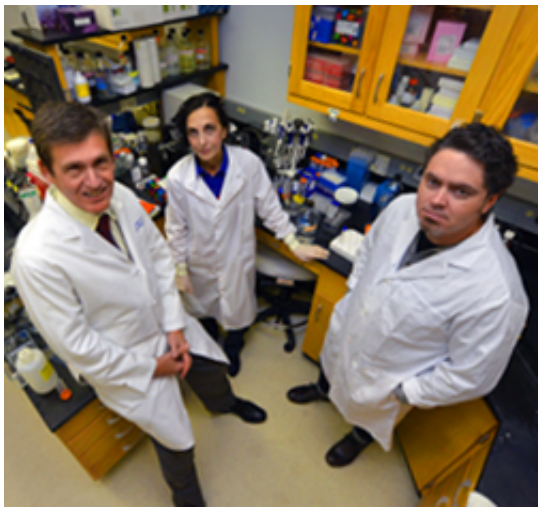
Methods to repair kidney cells, assess kidney function on the horizon

16 April 2013



Drs. Michael P. Madaio (from left), Nino Kvirkvelia and Tracy L. McGaha may have found a way to block kidney-destroying inflammation and help damaged kidney cells recover. Credit: Phil Jones, Georgia Regents University

Researchers may have found a way to block kidney-destroying inflammation and help damaged kidney cells recover.

In a related study, they report progress on a non-invasive method to assess how much kidney function has survived a serious bout of inflammation or a chronic problem like high blood pressure.

The diagnostic tool could help physicians make hard choices about whether a patient has enough kidney function left to benefit from treatment or whether dialysis or a transplant is in their future, said Dr. Michael P. Madaio, nephrologist and Chairman of the Department of Medicine at the Medical College of Georgia at Georgia Regents University.

If the kidneys can be saved, this approach could also aid optimal delivery of drugs directly to ailing kidney filters.

Significant infections, an oxygen-depriving critical illness or injury, diabetes and uncontrolled hypertension all can take a serious or deadly toll on the kidneys.

In an effort to better protect them, researchers induced acute kidney inflammation, or nephritis, in mice then gave them prostaglandin E2 . The kidneys' filtering units promptly recovered. "The cells got better, the kidneys got better," said Madaio, corresponding author of the study in the *American Journal of Physiology-Renal Physiology*.

While prostaglandins are better known as natural pro-inflammatory lipid compounds, prostaglandin E2 has an anti-inflammatory effect. The researchers suspected – and found – it also had the bonus regenerative properties.

"We've already got numerous ways to block inflammation, but what we hope is the magic here is the ability to also help injured kidney cells recover," Madaio said.

In the related study, they found what appears to be a good indicator of kidney function that could help physicians and patients optimize treatment. "It's hard to determine the extent of disease from the current ways we measure kidney function," Madaio said. If it seems like treatment should be tried regardless, current regimes such as immunosuppressive drugs that block inflammation, for example, have serious side effects, including leaving patients vulnerable for additional infections.

In the search for a better way, researchers put a fluorescent tag on a human monoclonal antibody for a collagen found only in the kidney, lungs, and ears; injected it in mice with active kidney disease; then looked for antibody-binding in the kidney, said Dr. Tracy L. McGaha, MCG immunologist and co-corresponding author of the study in *Kidney*

International.

This collagen is part of the base structure of kidney filters and its triple-helix configuration means the collagen molecules must hook together to work. The antibody the researchers used recognizes the stalks where collagen molecules connect, so it only binds when that bond is broken, an early indicator of kidney damage and lost function.

"When you have inflammation in the kidneys, the ends break apart, expose that little domain and the antibody can recognize it," McGaha said. The tagging system worked in the mice as well as tissue taken from patients with various kidney diseases.

This affinity for kidney filters means the antibody also could be used to directly deliver therapy to the filters, enhancing efficacy while reducing side effects. Similar approaches already are being used in cancer, McGaha said. Prostaglandin E2 may one day be one of those targeted therapies, he and Madaio noted.

Unfortunately, there are typically no early signs of kidney injury. When physicians suspect it, they look in the blood for levels of substances such as creatinine, a byproduct of metabolism which kidneys normally eliminate, and/or look to see if the normally fist-sized organs have shrunk, a sign of scarring. By the time either occurs, serious kidney damage has been done, Madaio said. Kidney biopsies, which provide a limited sample size and have their own set of complications, provide limited information as well.

At least in this early stage, the tagged antibody seems to have the current methods beat. "Before you see increases in protein excretion in the urine, before you see changes in the blood chemistry, you see this exposure," McGaha said.

To translate to humans, the labeled antibodies likely would need to be paired with powerful imaging technology such as the PET scanner to enable a full assessment of both kidneys, McGaha said. Antibodies, which are part of the normal immune response, also will have to be engineered so they only bind to their target, and don't also drive more inflammation, which is their usual role.

Every day, the kidneys filter about a quarter of the blood in the body, deciding what to keep, such as nutrients, and what to flush, such as excess sodium or a toxin. This aggressive job makes the kidneys particularly vulnerable to changes in blood pressure, increased inflammation and or toxins circulating in the body.

Provided by Medical College of Georgia