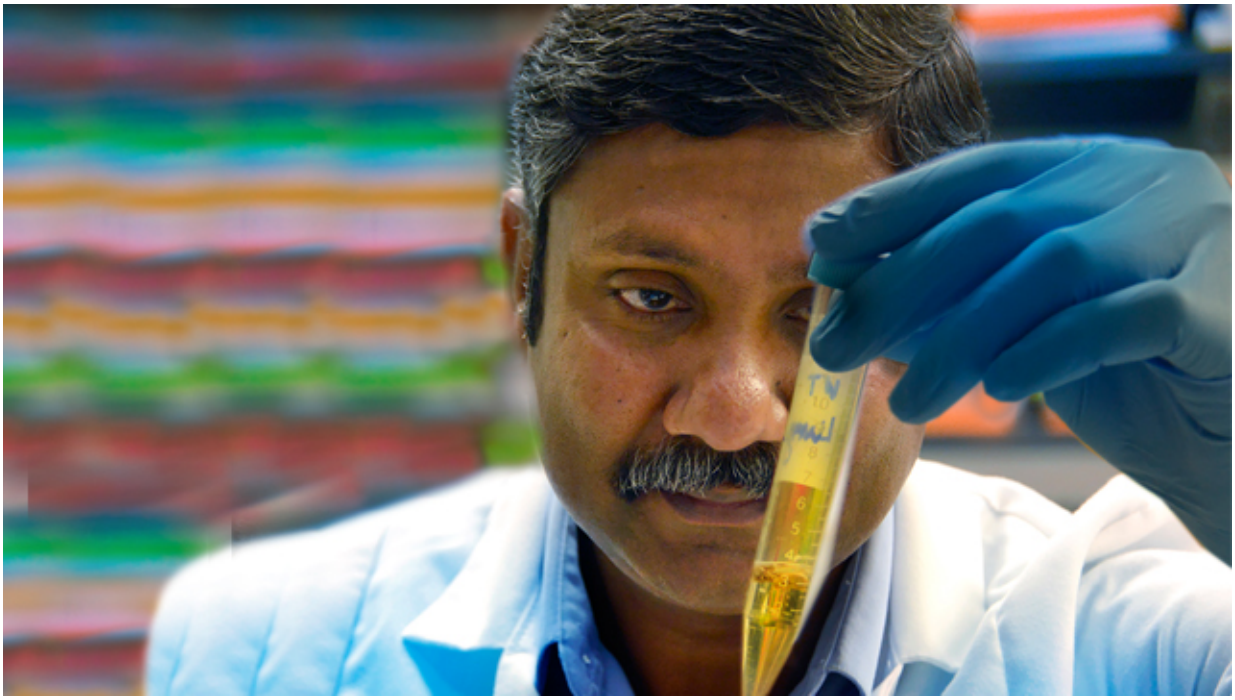
MedicalXpress

Scientists prevent, reverse diabetes-related kidney destruction in animal model

December 28 2015



Dr. Ganesan Ramesh, Medical College of Georgia at Georgia Regents University. Credit: Augusta University Senior Photographer Phil Jones

Diabetes is the leading cause of kidney failure, and scientists have found that infusing just a small dose of a cytokine, thought to help cause that failure, can instead prevent or reverse it.

The cytokine IL-17A has long been considered a classic promoter of

inflammation, which plays a major role in progression of diabetes-related kidney disease, or diabetic nephropathy, said Dr. Ganesan Ramesh, kidney pathologist at the Vascular Biology Center at the Medical College of Georgia at Augusta University.

His lab was pursuing its role in kidney damage but found that when they deleted the IL-17 gene in mice, then induced diabetes, it resulted in increased kidney injury, Ramesh said. They looked next at patients with severe diabetic nephropathy, and found levels of IL-17A reduced in their blood and urine.

In follow-up studies in animal models of both type 1 and type 2 diabetes, IL-17A's surprising role grew: When researchers infused a small amount of IL-17A every 48 hours for several weeks, it prevented or reversed diabetic nephropathy in their diabetes models. In fact, the therapy worked best in late-stage diabetic nephropathy, Ramesh said. IL-17A therapy also reduced high levels of fat in the blood, a hallmark of type 2 diabetes that is believed to contribute to related kidney and cardiovascular problems.

"It clearly indicates that IL-17A is protective," Ramesh said. "It does well for the kidney in suppressing damage in response to diabetes." Ramesh is corresponding author of the study, published in the *Journal of the American Society of Nephrology*, which is the first to look at IL-17's role in chronic kidney disease.

IL-17A seems to protect kidney cells multiple ways, including inducing the anti-inflammatory molecule AMWAP, or activated microglia/macrophage WAP domain protein. The cytokine also appeared to aid survival and regeneration of key kidney cells, including podocytes and epithelial cells in the tubules. Podocytes help the kidney retain important large molecules such as protein, and epithelial cells line tubules where these essentials are reabsorbed.

To date, the MCG research team has seen no ill effects from overexpressing IL-17A in mice kidneys and to some extent in their circulation. Currently, there are no drugs available to increase patients' IL-17A levels, but there are inhibitors for the cytokine that is considered causative in autoimmune diseases such as Crohn's. Emerging laboratory and clinical trial data indicate there may need to be drugs that do both.

As examples, in a clinical trial of an antibody for IL-17A in patients with Crohn's, the drug did not seem to help patients, and, in fact, some patients reported worsening symptoms. However, the National Psoriasis Foundation reports good experience with the use of biologics that block 1L-17 for the skin disorder. Meanwhile, French researchers have shown that giving IL-17A to mice suppressed the development of atherosclerosis, while a deficiency in the cytokine gene accelerated development of the arterial disease associated with inflammation.

The MCG researchers note that whether IL-17 promotes or suppresses inflammation may be related to the level and length of time it's stimulated. Response may also depend on which of the six different forms of IL-17 is activated, the receptors activated and resulting downstream signaling. In their studies, for example, increasing IL-17C and IL-17E levels did not have the same positive effect on diabetic nephropathy as IL-17A as well as IL-17F.

In follow up to the therapy's particular success with advanced disease, next steps include examining its impact on essentially destroyed kidneys. "If you can recover function from the dead kidney, you could save millions of people from a lifetime of dialysis," Ramesh said.

A primary way physicians check kidney function is looking for signs of patients excreting the protein albumin in their urine. Albumin, which is made by the liver, is a major protein in the blood that helps keep blood from leaking out of blood vessels and helps keep other vital substances

such as nutrients and hormones in the blood. Well-functioning kidneys retain albumin, and, even on dialysis, patients with diabetic nephropathy secrete a lot of protein in their urine.

The annual cost of diabetic nephropathy in the United States is estimated at more than $20 billion.

Provided by Medical College of Georgia