Mouse study shows potential for gene therapy in Alport syndrome, an inherited kidney disease

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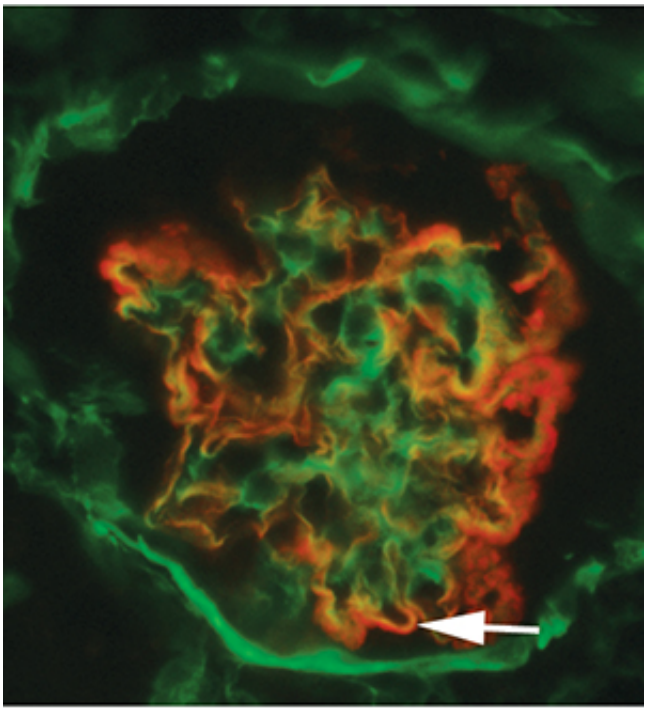

Due to an inherited genetic defect in the kidneys, people with Alport syndrome can't adequately filter waste from the blood into urine. This dysfunction has been traced to disruptions in the collagen network within the kidney's filters, which are called glomeruli. Working in mice, researchers have shown they can at least partially restore the missing collagen network, shown in red, thereby slowing progression of kidney disease and extending life span.

(Medical Xpress)—A new study in mice suggests that gene therapy one day may be a viable treatment for Alport syndrome, an inherited disease that leads to kidney failure. The research, by scientists at Washington University School of Medicine in St. Louis, is available online in the *Journal of the American Society of Nephrology*.

Alport syndrome affects one in 5,000 people and is more severe in men than in women. The disease is caused by mutations in any one of three genes that collectively produce a special type of collagen. This collagen is a critical component of a membrane in the kidney's glomeruli, where waste is filtered from the blood into urine. Disrupting any of these genes alters the collagen network, leaving the so-called basement membrane in the glomeruli with defects that make it unable to adequately filter waste.

Early treatment with certain blood pressure medications can slow progression of the syndrome, but many patients develop end-stage kidney disease by the time they reach young adulthood. At that point, the standard treatment is either a kidney transplant or dialysis, with the goal of an eventual kidney transplant.

Senior author Jeffrey Miner, PhD, and his colleagues asked whether it is possible in mice with Alport syndrome to repair a defective basement membrane once it is formed and functioning abnormally. Their work indicates that the therapy can restore, at least partially, the missing collagen network, thereby slowing progression of kidney disease and extending life span.

As part of the research, Miner and his colleagues demonstrated they could induce expression of a missing collagen gene 21 days after the mice were born.

"This time point is important because it is equivalent in age to preadolescence in humans," explained Miner, a professor of medicine

and of cell biology and physiology. "Most people with Alport syndrome have little or no scarring of the kidneys at that time, so correcting the basement membrane defect could prevent loss of kidney function."

When activated, the gene produced enough collagen to repair the basement membrane, although some irregularities persisted.

Without the therapy, Alport mice survived no longer than 32 weeks, compared with treated mice, which typically lived twice as long. Several survived for well over a year, clearly benefiting from the therapy.

"Even with treatment, there were some abnormalities in the basement membrane and in kidney function," Miner said. "But the damage was not significant enough to cause end-stage kidney disease. If the same treatment were successfully translated to patients, it could postpone the need for dialysis and buy patients more time to find the right kidney donor, and that could make a huge difference."

Much more research remains, he cautioned, but the new study suggests that some form of gene therapy eventually could be used as a treatment for patients with Alport syndrome.

More information: Lin X, Suh J, Go G, Miner J. Feasibility of repairing glomerular basement membrane defects in Alport syndrome. *Journal of the American Society of Nephrology*. Nov. 21, 2013.

Provided by Washington University School of Medicine in St. Louis