Stem cell study reveals how infantile cystinosis causes kidney failure, and how to cure it

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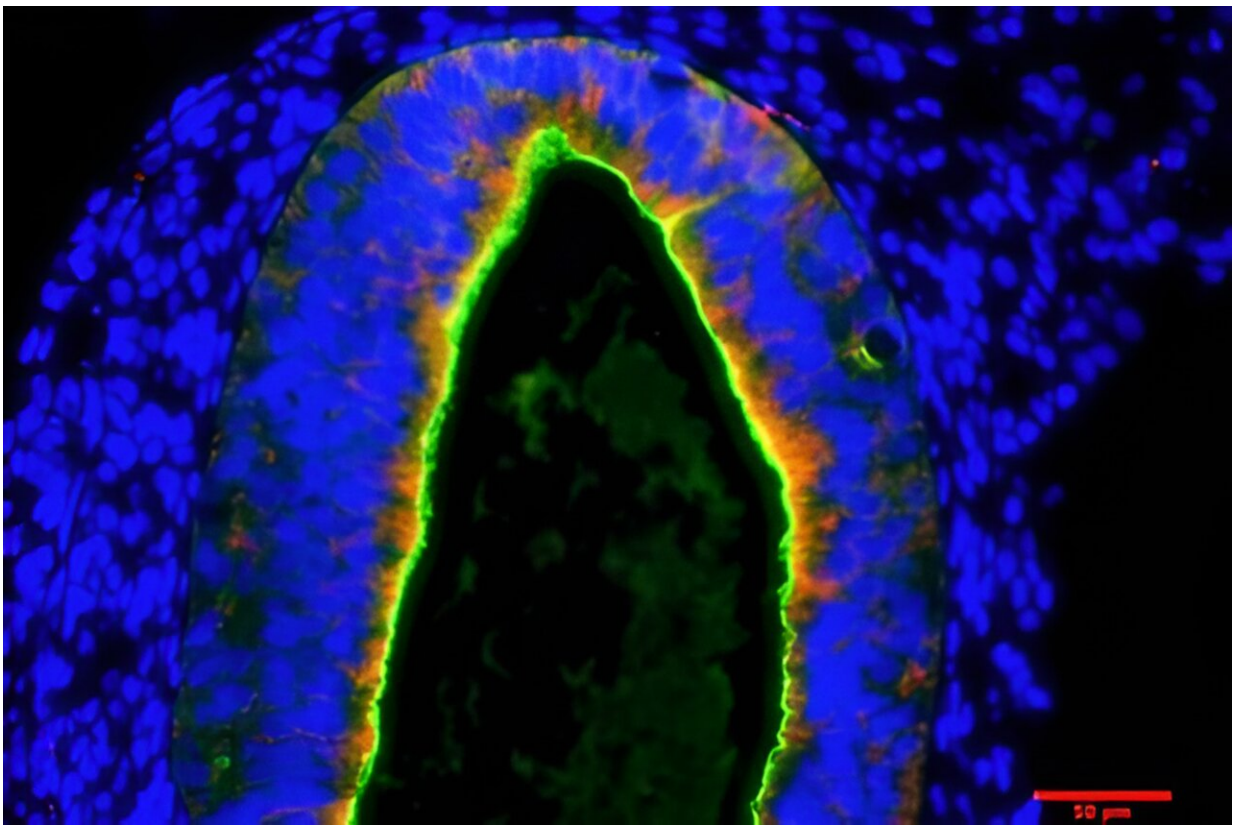

This image, produced by a fluorescence microscope, shows a normal renal proximal tubule, the specific nephron segment in the kidney that is impaired in the rare disease infantile cystinosis. The red, green and yellow regions indicate the presence of different proteins in the tubule and the blue indicates the presence of nuclei. The UB researchers generated the tubule in the image from stem cells derived from an individual who does not have the disease. Credit:

Alexandra Kojac

University at Buffalo research has identified how a misstep in the genesis of a key component of the kidney causes infantile cystinosis, a rare disease that significantly shortens the lifespan of patients.

Published Nov. 30 in the *International Journal of Molecular Sciences*, the work reveals that the mechanisms that cause the disease could be addressed and potentially cured through the genome-editing technique CRISPR. That could make kidney transplants, the most effective treatment currently available for these patients, unnecessary.

Infantile cystinosis, the most common and most severe type of cystinosis, occurs as the result of an accumulation in the body's cells of cystine, an amino acid. The buildup damages cells throughout the body, especially the kidneys and the eyes. Treatment consists of medications that work to lower the level of cystine in the body, as well as therapies that address the impaired growth of these children due to the inability to properly absorb nutrients. Some children require feeding tubes. Eventually, patients with infantile cystinosis, also called nephropathic cystinosis, will require dialysis and a kidney transplant.

Promise of stem cells

Human-induced pluripotent stem cells (hiPSCs) are stem cells that can differentiate into many different cell types. They hold tremendous potential for studying genetic diseases; the drawback has been that differentiation into certain cell types has been problematic. Such is the case with many cell types found in the kidney.

But a new protocol developed by this research team was successful.

"When our normal human-induced pluripotent stem cells were subjected to the differentiation protocol we developed, we were able to demonstrate extensive expression of physiologically important markers of the renal proximal tubule, the specific nephron segment that is altered in this disease," says Mary L. Taub, Ph.D., senior author on the paper and professor of biochemistry in the Jacobs School of Medicine and Biomedical Sciences at UB.

Ramkumar Thiyagarajan, Ph.D., assistant professor of geriatric studies at the University of Kansas and formerly a postdoctoral fellow at UB, is first author on the paper.

The protocol involved extracting stem cells from a healthy individual and an individual with infantile cystinosis. The researchers developed a culture medium to grow stem cells that included a small number of defined components present in blood, including insulin, specific proteins, growth factors and others. "Conducting the differentiation protocol under these conditions occurred in a timely manner," says Taub, "we didn't have to wait for weeks on end, and it occurred in a reproducible manner."

The researchers were able to efficiently differentiate the hiPSCs into the kidney proximal tubule, the type of nephron in the kidney that is impaired in infantile cystinosis, as well as in other kidney diseases.

"Unlike in other studies, we were able to retain a number of markers in the tubule that are physiologically important in the kidney's reabsorptive functions," says Taub. "Although these markers were expressed in both the normal and the cystinosis-derived hiPSCs, the genesis of the tubule was impaired in the cystinosis-derived cells, mimicking what happens in infantile cystinosis."

A potential cure

That finding means that the CRISPR genome-editing technique could be used to repair the defective genome and potentially cure the disease. "The normal gene can be introduced in the genome of cystinotic hiPSCs, which can then be injected in the kidney to replace the defective proximal tubules of individuals with infantile cystinosis," Taub says.

"In cystinotic individuals, it is the renal proximal tubule that degenerates, presumably due to programmed cell death," explains Taub, "so the entire kidney would not need to be replaced. The defective renal proximal tubules of individuals with this disease can be replaced with normal tubules following the introduction of the normal gene into cystinotic hiPSCs obtained from the patient. And because these tubules are from cells derived from the patient, there should be no problem with tissue rejection."

The findings are applicable to other kidney diseases where the renal proximal tubule is damaged, including acute kidney injury that can lead to chronic kidney disease and renal failure, and can be fatal.

Initial studies will need to be conducted with animal models as well as with in vitro tissue culture cells.

More information: Ramkumar Thiyagarajan et al, Studies with Human-Induced Pluripotent Stem Cells Reveal That CTNS Mutations Can Alter Renal Proximal Tubule Differentiation, *International Journal of Molecular Sciences* (2023). DOI: 10.3390/ijms242317004

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