Changing Urine Into Kidney To Combat Cystinosis

Benjamin S. Freedman, PhD
University of Washington, Seattle, WA

The kidneys are highly sensitive to the effects of cystinosis, resulting in renal Fanconi syndrome and eventually kidney failure. Unfortunately, we are born with a limited supply of kidney tissue, which we are unable to regenerate after we are born. Pluripotent stem cells are powerful cells that give rise to all of the body's cell types and organs, including the kidneys. These stem cells exist naturally only in the womb, but it is now possible to generate them after birth by 'reprogramming' other types of cells into stem cells. Using these stem cells, we have devised a plan to combat nephropathic cystinosis.

In the first step of this plan, we are creating a biobank of human pluripotent stem cells derived from patients with cystinosis. This starts from a humble urine sample, from which we purify urinary cells. We subsequently reprogram those urinary cells into pluripotent stem cells. Cystinotic stem cells are actually quite healthy under standard growth conditions, and can grow for many generations.

The second step of the plan involves gene therapy. Under certain conditions, cystinotic stem cells accumulate more than 100 times as much cystine as stem cells without cystinosis, and subsequently become sick and die. By using a gene editing technique called CRISPR, we are able to supply cystinosis stem cells with a healthy copy of the CTNS gene. This brings cystine levels in these cells back down to their normal levels.

The third step is to change these stem cells into kidney. To do this, we have coaxed cystinosis stem cells to change into kidney organoids – tiny structures that resemble kidney tissue. This process resembles the way kidneys form when we are in the womb. In our initial experiments, we have found that cystinosis stem cells can form kidney organoids. When these cells are implanted into living kidneys of a mouse, the organoids become more mature, forming filter units that integrate beautifully with the host's blood supply.

Taking this one step further, we are currently generating mice with cystinosis in which human stem cells can form grafts. This requires the use of CRISPR to create the disease in a special mouse strain that tolerates human xenografts. Growing human kidney grafts in cystinotic mice will simulate how they might grow in human cystinosis patients. We will be looking for whether the grafts get sick in the mouse, whether gene therapy helps them survive longer, and whether they have the ability to improve any symptoms observed in these animals. We will also be looking out for side effects of the grafts. These studies will establish a framework for more advanced studies in human patients.