Discovery could lead to much-needed kidney failure treatment

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The unwanted activation of an important cell-signaling pathway may play a role in two kidney problems that are major causes of end-stage renal disease, scientists at the Albert Einstein College of Medicine of Yeshiva University have found. Their research, which opens up a novel approach for treating kidney failure, is described in the March issue of *Nature Medicine*. The study was led by Dr. Katalin Susztak, an assistant professor of medicine (nephrology) at Einstein.

The kidneys filter waste products from the blood and maintain the body's fluid balance by producing urine. The filtration is carried out by numerous capillary tufts within the kidney known as glomeruli. Kidney disease occurs when glomeruli become damaged and can no longer perform their filtering function. Kidney damage may ultimately progress to end-stage renal disease, in which patients need dialysis or a kidney transplant.

The Einstein scientists focused on cells known as podocytes that line the glomeruli. Since dysfunction of podocytes cells is important in progressive kidney disease, and since a cell-signaling pathway called Notch is crucial in podocyte development, the Einstein researchers reasoned that aberrant Notch signaling might play a role in causing kidney disease.

The Notch signaling pathway plays a key role in embryonic development of humans and most other multicellular organisms. The Notch pathway tells some cells to proliferate and others to undergo programmed cell

death as it profoundly affects the way tissues are organized. Faulty Notch signaling has been found in several types of cancer and in many other diseases such as multiple sclerosis.

Collectively, the observations made in the Einstein study offer strong evidence that aberrant Notch signaling is also involved in diabetic nephropathy (DNP) and focal segmental glomerulosclerosis (FSGS)—two of the major causes of end-stage renal disease. For example:

-- When comparing biopsy samples from healthy kidneys and kidneys from people with DNP and FSGS, the researchers found evidence that the Notch pathway was active in diseased but not in healthy kidneys.

-- The researchers bred a strain of mice in which they could specifically activate the Notch pathway within podocytes. Examination revealed that the podocytes in these mice underwent programmed cell death, and the mice themselves died from end-stage renal failure.

-- After inducing glomerular disease in mice by injecting them with a toxic chemical, the researchers were able to protect the rats from developing kidney disease by injecting them with a gamma secretase inhibitor—one of a class of compounds known to “shut off” the Notch pathway.

“An exciting aspect of this new work is the therapeutic implications,” according to a *Nature Medicine* commentary on the Einstein study written by kidney experts from the University of Michigan Medical Center. The experts noted that gamma secretase inhibitors, like the one that protected the mice from kidney disease in this study, are already in phase 1 and 2 clinical trials for treating diseases including Alzheimer’s and leukemia. The Einstein findings, they wrote, “provide some hope that researchers in the field of kidney disease can reverse the grim

record of the last 20 years — during which no new therapeutic agent has been successfully implemented" for treating end-stage kidney disease.

Source: Albert Einstein College of Medicine