MedicalXpress

Study points to new biological mechanisms, treatment paradigm for kidney disease

March 3 2014

Prevention and reversal of chronic kidney disease is an urgent public health need. The disease affects 1 in 10 Americans, is debilitating and deadly, and existing drugs, at best, offer only mild delay in progression to end-stage kidney failure. New research led by Icahn School of Medicine at Mount Sinai investigators has uncovered abnormal molecular signaling pathways from disease initiation to irreversible kidney damage, kidney failure, and death. Results from their preclinical and human research are published online March 3 in the *Journal of Clinical Investigation*.

"Our group is the first to show that endothelial mitochondrial oxidative stress [damage to blood vessel lining that affects the energy-producing part of the cell caused by oxidative stress] regulates the passage of proteins from blood to urine and filtration of waste products in the kidney," said Erwin Bottinger, MD, Director of the Charles Bronfman Institute for Personalized Medicine, and the study's senior author. Specifically, the researchers found albuminuria (protein in the urine) and depletion of the cells that form the kidney's glomerular filtration barrier. "These findings were unexpected and open the door for developing new therapeutic targets," Dr. Bottinger added.

In the preclinical part of the research, investigators used a mouse model to induce scarring in the filtration part of the kidney, or glomeruli. This allowed progressive amounts of protein to pass into the urine and interfered with the clearance of waste products by the kidney. Essentially, the researchers were examining how different signaling

mechanism and cellular interactions work, and how when they are disturbed, they promote chronic kidney disease.

Initially, key cells of the glomerular filtration barrier, also called podocytes, cause alterations in endothelin-1, a vasoconstrictor, activating the endothelin receptor A. The activated endothelin receptor A triggered disturbances manifested as endothelial mitochondrial oxidative stress.

The research team was able to confirm that this worked the same way in humans. They studied kidney biopsies, comparing ten biopsies with glomerular sclerosis with six controls. Like in the animal models, the researchers confirmed activated endothelin receptor A and endothelial mitochondrial dysfunction in human glomerular sclerosis biopsies, but not in controls.

"These processes were absolutely essential in causing protein in the urine [or albuminuria], injured podocytes (tiny ball-shaped structures that constrict the blood vessels in the filtering part of the kidney), and cause scarring, all of which can ultimately lead to long-term, irreversible kidney disease. "This is called crosstalk and it is poorly understood," said Ilse S. Daehn, PhD, the study's lead researcher, and Assistant Professor of Medicine in the Division of Nephrology, at the Icahn School of Medicine at Mount Sinai. "We hope that these novel crosstalk findings lead to new therapies that help reverse or arrest chronic kidney disease, which affect millions of Americans," added Dr. Daehn.

Antioxidants that target the mitochondria and endothelin antagonists would alter the paradigm for preventing cell depletion and scarring of the filtration part of the kidney. "There is a pressing unmet medical need to prevent or reverse chronic kidney disease," Dr. Bottinger stressed. "The renin angiotensin inhibitors and angiotensin receptor blockers that are now widely used have not been proven effective in preventing end stage kidney failure. We need more effective drugs to treat the millions

of Americans suffering from chronic kidney disease with the goal to eliminate its progression to end- stage kidney failure and with it the need for chronic dialysis and kidney transplantation."

Provided by The Mount Sinai Hospital