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Researchers prevent, reverse renal injury by inhibiting immune-regulating molecule

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Special cells called podocytes aid the kidneys as they clean the blood and balance the body's fluid levels. Podocytes filter blood as it passes through the cells' foot-like projections they are named for, interwoven like the fingers of clasped hands. Podocyte damage—indicated by proteinuria or abnormal proteins in the urine—is a common symptom of diseases including the autoimmune disorder lupus and non-immune diseases and can result in kidney failure requiring dialysis or organ transplant.

In a research article published in the *Journal of Clinical Investigation* on July 9, a team of scientists led by George C. Tsokos, MD, Chief of the Division of Rheumatology at Beth Israel Deaconess Medical Center (BIDMC), describes how overexpression of an immune regulating molecule called CaMK4 can destroy podocytes' structure and function. What's more, the researchers demonstrated that inhibiting CaMK4 can prevent and even reverse podocyte damage in lupus-prone mice.

"When we looked at human tissue samples from kidney biopsies, we observed that people with lupus and non-autoimmune kidney disease showed increased levels of CaMK4," said Tsokos, who is also a Professor of Medicine at Harvard Medical School. "We wondered what would happen if we inhibited CaMK4 specifically?"

Working in mice which develop lupus spontaneously, Tsokos and colleagues—including bioengineers at Yale University and Yale Medical School—blocked CaMK4's deleterious effects on podocytes by

delivering an inhibitor directly to the special cells. The podocytes maintained their structure and function in the lupus-prone mice. In fact, the inhibitor prevented podocyte damage in mice with autoimmune disease and reversed podocyte damage in mice injected with Adriamycin, a drug known to cause kidney damage—a finding Tsokos says opens the door to potential new therapies not just for people with lupus, but also other autoimmune and non-autoimmune diseases that impact the kidney.

"The finding that preserving the structure and function of podocytes through inhibition of CaMK4 inhibits inflammatory immune complexes and thus prevents damage reverses the classical dogma—widely accepted for the last 60 years—that inflammation instigates damage to the kidney ," said Tsokos. "Only if podocytes are damaged can the immune complexes be deposited."

Next, Tsokos and colleagues would like to learn more about how podocyte damage occurs, how late in the process inhibiting CaMK4 can reverse podocyte damage and how these findings apply to other renal diseases, including diabetes. They also hope to initiate a clinical trial.

Provided by Beth Israel Deaconess Medical Center