Pivotal inflammatory players revealed in diabetic kidney disease

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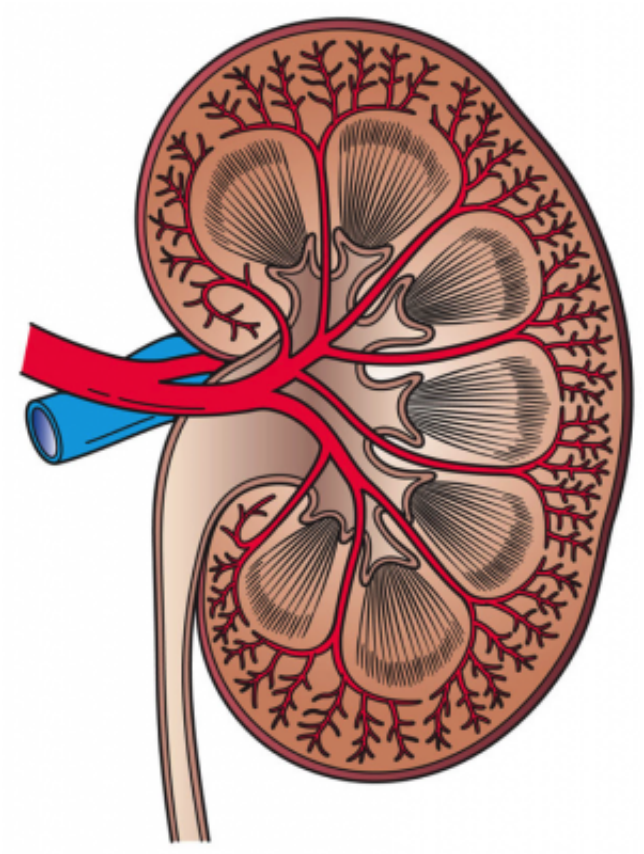

This image shows a cross section of a kidney. Credit: Holly Fischer/Wikipedia

In a new study, published in the online edition of the journal *EBioMedicine*, a multi-disciplinary team led by researchers at University of California, San Diego School of Medicine has identified key inflammatory mechanisms underlying type 1 diabetes and obesity-related

kidney dysfunction.

"We found that insulin deficiency and insulin resistance, two hallmarks of diabetes, seem to be associated with increased sphingomyelin in the kidney, which trigger damaging inflammatory mechanisms," said senior author Kumar Sharma, MD, professor of medicine and director of the UC San Diego School of Medicine Institute of Metabolomic Medicine (IMM) and Center for Renal Translational Medicine (CRTM).

In the study, the researchers analyzed the kidneys of experimental mice with type 1 diabetes and mice fed a high-fat diet. They found increased amounts of sphingomyelin, a type of fatty acid commonly found in cell membranes and nervous tissue, in both experimental groups.

Specifically, Sharma said, the sphingomyelin are believed to drive an increase in the ratio of adenosine triphosphate (ATP) and adenosine monophosphate-activated protein (AMP) in glomerular cells of the kidney in mice with diabetes, obesity or both. ATP/AMP are molecules involved in intracellular energy transfer and glomerular cells are key in the filtering and cleansing of blood, one of the primary functions of the kidney.

"ATP is involved in every cellular function. It is the energy currency of the cell," said Sharma. "But too much ATP causes inflammation. We believe that sphingomyelin fuels increases in ATP and decreases in AMP that result in inflammation which leads to cell dysfunction, fibrosis and endothelial damage underlying diabetic kidney disease."

Normally, ratios of ATP and AMP are tightly regulated, depending on energy needs of the cell. "The mechanisms triggered by diabetes and obesity, such as increased ATP, seem to disrupt that balance."

Previously, it was not known exactly how ATP was affected in this

process. "Due to difficulties in the stability of ATP, it was uncertain whether there was increased ATP or decreased ATP production with diabetes," Sharma said, adding that the investigators used mass spectrometry imaging to answer this question by identifying these difficult to measure molecules in frozen tissues.

Diabetic kidney disease is the leading cause of end-stage kidney disease, the eighth leading cause of death in the United States and a major risk factor for cardiovascular disease. An estimated 26 million American adults have chronic kidney disease, often requiring dialysis or a kidney transplant.

The study's insights could have major impact on developing new biomarkers and novel therapeutics for diabetic and obesity-related complications, such as kidney disease, said Sharma. "It may be possible to create new treatments by blocking ATP and the inflammatory pathways consequent to that or by developing ways to reduce the amount or activity of sphingomyelin in the kidney."

More information: Satoshi Miyamoto et al. Mass Spectrometry Imaging Reveals Elevated Glomerular ATP/AMP in Diabetes/obesity and Identifies Sphingomyelin as a Possible Mediator, *EBioMedicine* (2016). DOI: 10.1016/j.ebiom.2016.03.033

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