Study points to new therapeutic strategy in chronic kidney disease

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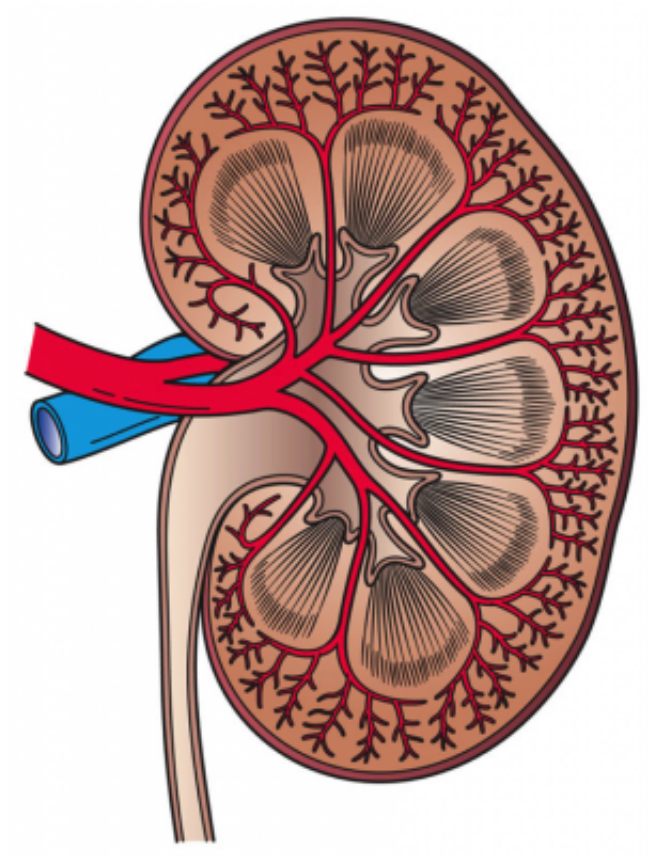

This image shows a cross section of a kidney. Credit: Holly Fischer/Wikipedia

Chronic kidney disease (CKD) affects at least one in four Americans who are older than 60 and can significantly shorten lifespan. Yet the few available drugs for CKD can only modestly delay the disease's progress towards kidney failure. Now, however, a team led by researchers at the

Perelman School of Medicine at the University of Pennsylvania, has found an aspect of CKD's development that points to a promising new therapeutic strategy.

"We found that a defect in energy production in affected kidney cells plays a key role in CKD development," says Katalin Susztak, MD, PhD, an associate professor of Medicine in the Renal Electrolyte and Hypertension Division. "Restoring the energy supply in these cells largely prevented signs of CKD in mouse models."

In the study, published online in advance of the print edition of *Nature Medicine*, Susztak and colleagues focused on a central feature of CKD: the "fibrosis" process. This is a pathological response to chronic kidney stress that includes an abnormal buildup of fibrous collagen, a loss of capillaries, a die-off of important kidney cells called tubular epithelial cells, and other changes that progressively reduce a kidney's ability to filter the blood properly.

The researchers compared the patterns of gene activity in fibrotic and normal human kidney tissue samples. They found abnormal patterns in gene networks linked to inflammation and sharp drops in activity in gene networks that support energy metabolism in the fibrotic samples.

The fact that inflammation is a factor in CKD was already well known, so Susztak and her colleagues aimed their investigation at two types of energy metabolism—glucose oxidation and fatty acid oxidation—that seemed markedly reduced in the fibrotic samples.

"What we found is that the tubular epithelial cells preferentially use fatty acid oxidation as their energy source in normal conditions," Susztak says. "Even when fatty acid metabolism drops in the context of CKD, these cells don't switch to burning glucose for energy."

Susztak's team examined several mouse models of kidney fibrosis, and again found strikingly lower activity in genes that support fatty acid metabolism. The researchers also found strong hints that the loss of cellular fuel is a driver of the fibrosis process. In mouse models, the drop in fatty acid metabolism preceded the signs of fibrosis. In human tubular epithelial cells, artificially reducing fatty acid metabolism quickly brought about fibrosis-like signs, including the buildup of fat molecules (unspent fuel) and the deaths of many affected cells.

That fat buildup in kidney cells had been hypothesized to be a significant cause of cell death in CKD fibrosis. But Susztak showed with a mouse model of fat accumulation in tubular epithelial cells that the fat accumulation on its own had minimal impact. The more important factor in fibrosis was the loss of energy in the cells as fatty acid metabolism dropped.

The researchers also found evidence that the shutdown of fatty acid metabolism in tubular epithelial cells is caused in large part by the growth factor TGFβ. This factor is known to promote fibrosis and has been linked to high blood glucose levels, high blood pressure, and inflammation—all triggers of CKD.

Encouragingly, when Susztak's team restored fatty acid metabolism in mouse models of kidney fibrosis using genetic techniques or compounds that boost the activity of fatty acid metabolism genes, the treatment prevented nearly all signs of fibrosis.

One of the compounds tested, fenofibrate, is an existing anti-cholesterol drug that activates a master switch gene, PPARA, for fatty acid metabolism. But fenofibrate could be problematic as a kidney disease drug, Susztak says, because it can distort the results of a standard test of kidney function. This side effect could impede the ability to evaluate the drug's benefit, and more generally, could make it harder for doctors to

monitor the progression of CKD in patients taking the drug.

"We hope to develop new compounds that are similar to fenofibrate, or that boost enzymes more specifically related to fatty acid metabolism," she says. "In that way we might be able to greatly slow the progress of CKD."

She and her colleagues are also trying to connect the newly revealed metabolic changes in CKD fibrosis to the epigenetic changes—alterations in the patterns of DNA markers that control gene expression in cells—that they described in a paper last year in *Genome Biology*.

More information: Defective fatty acid oxidation in renal tubular epithelial cells has a key role in kidney fibrosis development, *Nature Medicine*, DOI: 10.1038/nm.3762

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