Obesity and Kidney Damage: Key Cell Process Likely Involved

It is well known that obesity is an important risk factor for kidney dysfunction in patients with diseases such as diabetic nephropathy, but the mechanism underlying this connection has remained unclear. Now researchers have found that suppression of a critical cellular process called autophagy, which is important for preventing kidney damage, may be involved. The findings are published in a recent Journal of the American Society of Nephrology article.

“This study is the first to clarify one of the mechanisms by which obesity induces kidney dysfunction,” said first author Kosuke Yamahara, of the Department of Medicine at Shiga University of Medical Science, in Japan.

Mechanism found in mice

Yamahara, along with senior author Takashi Uzu, MD, PhD, and others, looked at the potential role of autophagy in obesity’s effects on kidney function because autophagy insufficiency is common in obese individuals and is involved in the pathogenesis of obesity-related metabolic diseases. Autophagy is a degradation system within cells that removes damaged proteins and other defective cellular components to maintain intracellular homeostasis during stress conditions, including starvation, hypoxia, and endoplasmic reticulum stress.

In the kidneys, autophagy appears to play a protective role against normal aging and acute kidney injury. Previous work by Uzu and colleagues revealed that calorie restriction in mice promotes increased expression of a protein called NAD-dependent deacetylase sirtuin 1 (Sirt1) in aged kidneys and attenuates kidney damage by restoring autophagy activity (Kume S, et al. J Clin Invest 2010; 120:1043–1055).

In their latest work, when the investigators conducted a variety of additional experiments in mice, they found that in normal-weight animals with proteinuria, autophagy was active in kidney cells. However, in obese mice with proteinuria, autophagy was suppressed and kidney cells—specifically, proximal tubular epithelial cells—became damaged. In addition, when normal-weight mice with proteinuria were genetically altered so that autophagy was defective (by deletion of the Atg5 gene), the animals also experienced damage to proximal tubular epithelial cells.

During the course of evolution, the researchers noted, organisms have developed... Continued on page 2
mechanisms by which autophagy can be induced by calorie restriction and various intracellular stresses to overcome stress conditions during prolonged starvation. It makes sense that a “hypernutrient” state would suppress fasting-induced autophagy in the tissues of obese mice.

Relevance to humans
With more thorough experiments, the researchers discovered that a potent suppressor of autophagy (called mTOR) was hyperactivated in the kidneys of obese mice. Treatment with an mTOR inhibitor ameliorated autophagy insufficiency.

Next, the investigators conducted experiments to assess the potential application of their findings in humans. By examining human renal biopsy specimens from two nonobese patients with IgA nephropathy, an obese patient with IgA nephropathy, and an obese patient with type 2 diabetes with overt proteinuria, the scientists found that both mTOR hyperactivation and autophagy suppression were present in specimens from obese, but not nonobese, patients with kidney disease.

“Obesity suppresses autophagy via an abnormal activation of nutrition sensing signals in the kidney,” said Yamahara. “Our results suggest that restoring the kidney-protective action of autophagy may improve the kidney health of obese patients.”

While the results are preliminary, they offer new avenues of research for protecting the kidney health of obese individuals.

According to Ken Inoki, PhD, of the University of Michigan in Ann Arbor, the study indicates that induction or restoration of the “self-eating” process in the proximal tubules plays an important renoprotective role in acute kidney injury as well as in chronic glomerulopathy with proteinuria. In an accompanying editorial (Proximal Tubules Forget “Self-Eating” When They Meet Western Meal), he stated that in order to study the molecular mechanisms involved, it may be important to examine the activity of mTOR in the proximal tubules of newborn mice whose tubular cells are exposed to physiologic proteinuria, and to determine whether reversible alteration or damage of proximal tubules occurs in autophagy-deficient newborn mice.

Yamahara and his team also note that because obesity-related exacerbation of proteinuria-induced kidney damage may involve molecular mechanisms besides impaired autophagy, efforts to identify these mechanisms may lead to better renal outcomes and increased healthy life expectancy in obese patients with proteinuria.

The findings may also have relevance to wider health topics because autophagy is currently the focus of research in various fields, including aging, metabolic diseases, and immune diseases. The results from this study and the researchers’ earlier work should help in the design of future studies aiming to further explore autophagy-related diseases. The findings and methods used might also help in the development of new therapies to delay the progression of tissue damage that occurs when autophagy is suppressed.

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