Autophagy is an evolutionarily conserved cellular catabolic process in which cytoplasmic components are isolated from the rest of the cell within double-membrane structures (autophagosomes) and degraded through lysosomal degradation. Autophagy is activated under conditions of metabolic stress in which there is a shortage of energy for cells to maintain cellular homeostasis.1 A number of recent studies demonstrated that the induction of autophagy serves a crucial role in protecting renal proximal tubular cells from many stresses, including ischemia/reperfusion and nephrotoxic agents.2-4 However, few studies have examined the role of proteinuria in the regulation of autophagy and the conditions that impair the activity of autophagy in the course of renal dysfunction.

By characterizing an albumin-overload mice model and tissues from obese patients with proteinuria, Yamahara and coworkers, as described in this issue of JASN,5 present evidence that autophagy plays an important role in protecting renal proximal tubular cells from harmful proteinuria. They demonstrated that proteinuria is a strong cue for autophagy induction in the proximal tubular cells of mice with albumin overload. Furthermore, high-fat diet and obesity blunt proteinuria-induced autophagy induction in the proximal tubules and thereby exacerbate tubular cell damage by proteinuria.

The term “autophagy” is derived from the Greek words “phagy,” meaning eat, and “auto,” meaning self. Interestingly, this “self-eating” behavior was first discovered in renal proximal tubular cells of newborn mice in 1957.6 Dr. Clark described the observations of autophagy in his paper:

The large round bodies in the proximal tubules consist of an amorphous material and contain concentrically lamellar structures and mitochondria. They resemble the cytoplasmic droplets produced in the proximal tubules of adult rats and mice by the administration of proteins. The large round bodies disappear from the proximal tubules of infant mice during the first week after birth, but the concentric lamellar structure may be found in adult mice.

From these observations, Clark hypothesized that the formation of the large round bodies (autophagosome) in the proximal tubules was likely due to the absorption of proteins that passed through immature newborn glomeruli. Now, Yamahara and coworkers have re-evaluated the process of renal tubular autophagy first described more than a half-century ago using their modern technologies under clinically relevant conditions.

Compared with control mice, mice lacking autophagy activity in the renal proximal tubular cells displayed more severe damage of their tubular cells in response to free fatty acid (FFA)-albumin–induced proteinuria. Furthermore, the renoprotective activity of proteinuria-induced autophagy in proximal tubular cells was suppressed in obese mice and humans. Yamahara and coworkers found that the activation of 5′AMP-activating protein kinase (AMPK) but not the enhanced endoplasmic reticulum stress played a critical role in the induction of autophagy by proteinuria. Moreover, the activation of mammalian target of rapamycin complex 1 (mTORC1) in the proximal tubules of obese mice or patients was responsible for...
the insufficient autophagy induction that was necessary for protecting the cells from harmful proteinuria.

mTORC1 is a protein kinase complex that stimulates cellular anabolic processes, such as protein and lipid synthesis, while inhibiting autophagy.7 mTORC1 is activated by multiple cellular cues, including growth factors and nutrients, such as amino acids, glucose, and cellular ATP, to promote cell growth and proliferation. In contrast, AMPK inhibits anabolic processes but stimulates catabolic reactions, including autophagy, in order to maintain sufficient cellular energy levels for survival under adverse environment conditions.8 In general, these two protein kinases exert opposite biologic outputs and antagonize one another in the regulation of autophagy. The molecular crosstalk among AMPK, mTORC1, and autophagy induction has recently been extensively studied. For example, AMPK inhibits mTORC1 activation under nutrient insufficient conditions.7 In addition, AMPK directly phosphorylates and activates ULK1, a mammalian ortholog of yeast Atg1, to induce autophagy.9,10 In contrast, mTORC1 also directly phosphorylates ULK1 and inhibits AMPK association with ULK1, thereby inhibiting ULK1-dependent autophagy induction.9

Although Yamahara et al.5 have proposed a simple model in which excess calorie intake–induced mTORC1 activation alleviates AMPK-dependent autophagy induced by proteinuria, several questions regarding the molecular mechanisms remain unanswered. First, it remains unclear how FFA-albumin activates AMPK and autophagy induction in proximal tubules. Intriguingly, FFA-albumin but not FFA-free albumin was able to stimulate autophagy, suggesting that it is the FFA that triggers autophagy induction in the proximal tubular cells, although albumin should play a role in transporting FFA into the cells. These observations are consistent with a previous report demonstrating that FFA-bound albumin but not FFA-free albumin causes severe tubulointerstitial damage.11

Second, the study demonstrated that FFA-albumin largely induced AMPK activity in the proximal tubules even under high-fat diet (HFD) conditions. The question that arises from these observations is why HFD- or obesity-induced mTORC1 activity is able to maintain the inhibition of autophagy under conditions in which cellular AMPK is highly activated by FFA-albumin. One of the possible mechanisms underlying FFA-albumin–induced AMPK activation may involve reactive oxygen species (ROS).12 It has been demonstrated that the oleic acid–bound albumin enhances the production of superoxide through the activation of NADPH oxidase in renal proximal tubular cells.13 Oleic acid–bound albumin is a major component of FFA-albumin in the serum and urine of patients with CKD.14 Importantly, ROS such as H2O2 and ONOO− are independent activators of AMPK.12 Moreover, oxidants enhance mTORC1 activity by inhibiting the tuberous sclerosis complex gene products (TSC complex), an essential negative regulator of mTORC1.15,16 Under suppression of the TSC complex by oxidation, mTORC1 is constitutively activated if the cells are able to access to nutrients, such as amino acids. Therefore, under these conditions, AMPK activated by FFA-albumin may have limited ability to suppress mTORC1. Further experiments characterizing the level of ROS and the status of ULK1 phosphorylation may improve understanding of the precise molecular mechanism by which HFD or obesity-related mTORC1 activation inhibits proteinuria-induced autophagy induction.

Obesity is an independent risk factor for renal dysfunction in patients with CKD. The results of this study provide an important pathomechanism underlying obesity-associated renal proximal tubular cell damage. The study indicates that induction or restoration of the “self-eating” process in the proximal tubules plays a crucial renoprotective role in not only AKI but also in chronic glomerulopathy with proteinuria. To study the molecular mechanisms underlying proteinuria-induced autophagy under more physiologic settings, it may be important to examine the activity of AMPK and mTORC1 in the proximal tubules of newborn mice whose tubular cells are exposed to physiologic proteinuria.6 Furthermore, it is also intriguing to determine whether reversible histologic alteration or damage of proximal tubules occurs in autophagy-deficient newborn mice. Nevertheless, growing evidence including the results in this work support the idea that dietary restriction in combination with treatment with autophagy-promoting agents may be a promising therapeutic approach for CKD with proteinuria.

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DISCLOSURES

None.

REFERENCES

Should Glucose-Sparing Prescriptions Be Expected to Reduce the Cardiovascular Risk of Peritoneal Dialysis Patients?

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The median life expectancy of patients with ESRD starting maintenance dialysis ranges from only 3 to 5 years.\(^1\) This high risk for death for patients undergoing maintenance dialysis represents the summative influence of the complications of frequently occurring coexisting illnesses (viz., diabetes mellitus, hypertension, or cardiovascular comorbidity), consequences of uremia, and potential adverse effects of the dialysis procedure. Although laboratory investigations and/or epidemiologic studies have identified a large number of risk factors in each of these three categories, most clinical trials testing the efficacy of various interventions have been unable to demonstrate any significant reduction in mortality for individuals undergoing maintenance dialysis.\(^2\)–\(^8\) This highlights the need to exercise caution in projecting potential benefits on patient-centered outcomes for individuals undergoing maintenance dialysis from studies with surrogate outcome measures.

In patients undergoing peritoneal dialysis (PD), the obligatory systemic absorption of carbohydrates is a potential adverse effect of the dialysis procedure. Patients treated exclusively with conventional dextrose-based PD solutions are estimated to absorb approximately 50–150 g of glucose daily.\(^9\) It has been posited that the systemic glucose absorption is atherogenic and hence has the potential to amplify the cardiovascular risk of patients undergoing PD. However, the mechanistic pathways underlying the increase in risk, if any, remain uncertain. There is a demonstrable association between the concentration of dextrose in the PD dialysate and daily mean blood glucose concentration on Continuous Glucose Monitoring (CGM).\(^10\) This suggests that conventional PD prescriptions could contribute to worsening of glycemic control, and observational studies have indicated that patients undergoing PD with poor glycemic control have a higher risk for death.\(^11\) Increased peritoneal glucose absorption could also lead to adverse outcomes through weight gain and worsening of lipid abnormalities; however, evidence evaluating these potential mechanisms is inconsistent.\(^12\)–\(^14\) Moreover, the only study to examine the relationship between the magnitude of glucose absorption and patient outcomes was unable to demonstrate any association with either risk for death or a need for transfer to hemodialysis.\(^15\)

It also remains uncertain whether the higher risk for death or transfer to hemodialysis in individuals with a higher prescribed PD glucose concentration is a consequence of systemic glucose absorption or a reflection of low residual renal function or inadequate ultrafiltration capacity.\(^16\),\(^17\)

In addition to concerns about the adverse effects of systemic glucose absorption, a large body of laboratory data suggests that the continued exposure to high concentrations of glucose and glucose degradation products in conventional PD solutions may lead to structural and functional changes in the peritoneal membrane that may eventually lead to peritoneal sclerosis and ultrafiltration failure.\(^18\) Glucose-sparing PD regimens have been developed with the hope of minimizing these potential systemic and local adverse effects of glucose. The use of one bag of icodextrin in lieu of glucose is a central component of such glucose-sparing regimens; although icodextrin is absorbed and contributes to the systemic carbohydrate load, it generates a higher volume of ultrafiltration for each gram of carbohydrate...