Medicine / Healthcare, Drug development

Developing strategies to treat diabetic kidney disease by targeting autophagic activity

Department of Nephrology, Graduate School of Medicine
Professor Yoshitaka Isaka Researchmap https://researchmap.jp/isaka-handai3857
Clinical Fellow Takeshi Yamamoto Researchmap https://researchmap.jp/tyamamoto-handai3857

Abstract

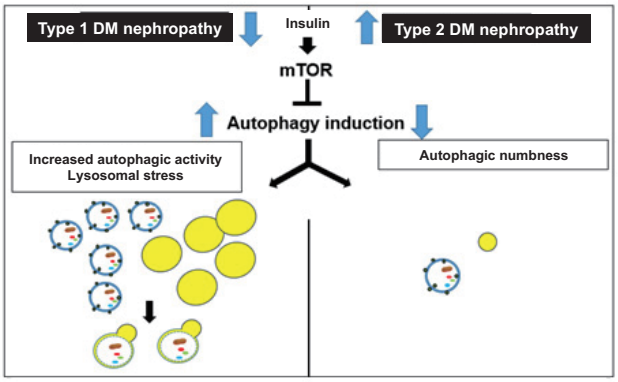
Studies suggest that autophagy may be protective in kidney diseases, but understanding how the autophagic process is specifically altered in each disorder is important for applying it therapeutically. On the basis of the observation that autophagy in proximal tubule epithelial cells (PTECs) is mainly regulated by insulin, we used diabetic mouse models to investigate whether types 1 and 2 diabetic nephropathy differ in autophagic status. We found distinct patterns of autophagic dysregulation involved in the pathophysiology of types 1 and 2 diabetic nephropathy, with autophagy induction suppressed in the type 2 diabetic kidney (even under starvation) and basal autophagic activity enhanced in the type 1 diabetic kidney (even under fed conditions). We also provide evidence that activated autophagy protects the type 1 diabetic kidney, whereas autophagic suppression jeopardizes the kidney in type 2 diabetes. Consequently, autophagic activity differs in types 1 and 2 diabetic nephropathy, which should be considered when developing strategies to treat diabetic nephropathy by modulating autophagy.

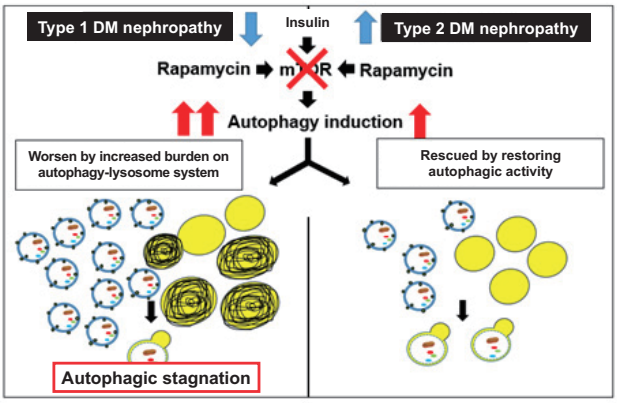
Background & Results

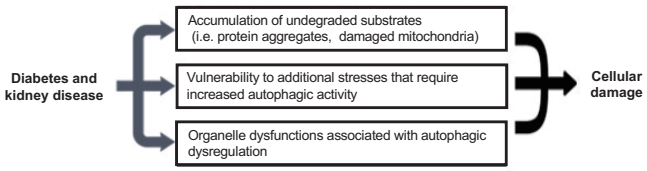
Background The prevalence of obesity and obesity-related diseases, including type 2 diabetes, dyslipidemia, and hypertension, is increasing, with the number of patients who develop diabetic kidney disease (DKD), and end stage renal disease increasing worldwide. Evidence of a protective role of autophagy in kidney diseases has sparked interest in autophagy as a potential therapeutic strategy. However, understanding how the autophagic process is altered in each disorder is critically important in working toward therapeutic applications. **Results** Using cultured PTECs and diabetic mouse models, we investigated how autophagic activity differs in type 1 versus type 2 diabetic nephropathy. We explored nutrient signals regulating starvation-induced autophagy in PTECs and used autophagy-monitoring mice and PTEC-specific autophagy-deficient knockout mice to examine differences in autophagy status and autophagy's role in PTECs in streptozotocin (STZ)-treated type 1 and db/db type 2 diabetic nephropathy. Administering insulin or amino acids, but not glucose, suppressed autophagy by activating mTOR signaling. In db/db mice, autophagy induction was suppressed even under starvation; in STZ-treated mice, autophagy was enhanced even under fed conditions but stagnated under starvation due to lysosomal stress. We found that, in STZ-treated mice, activated autophagy counteracts mitochondrial damage and fibrosis in the kidneys, whereas in db/db mice, autophagic suppression jeopardizes kidney even in the autophagy-competent state. We also examined the effects of rapamycin (an inhibitor of mTOR) on vulnerability to ischemia-reperfusion injury. Rapamycin-induced pharmacologic autophagy produced opposite effects on ischemia-reperfusion injury in STZ-treated and db/db mice.

Significance of the research and Future perspective

Building on the above findings, we proposed two major types of autophagic dysregulation; autophagic stagnation and autophagic numbness. Our studies will ultimately lead to fundamental insights in understanding, diagnosing, and preventing DKD by modulating autophagy. Our final goal is to develop and apply a new drug to DKD patients, which will reduce the number of dialysis patients in the future.







Patent	patent pending
Treatise	Sakai, Shinsuke; Yamamoto, Takeshi; Isaka, Yoshitaka et al. Proximal Tubule Autophagy Differs in Type 1 and 2 Diabetes. J Am Soc Nephrol. 2019; 30(6): 929-945. doi: 10.1681/ASN.2018100983
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