

Classical molecule in diabetic kidney hypertrophy is linked to defects in self-eating through fine-tuning

Diabetic kidney disease (DKD) is one of the major causes of chronic kidney disease and is an important prognosticator for diabetes patients. Glomerular sclerosis and tubulointerstitial fibrosis are well-known pathological changes in the kidneys of diabetes patients. Renal and glomerular hypertrophy are morphological changes that precede these pathological changes, and are observed early in the onset of diabetic nephropathy.

Glomerular hyperfiltration, a hemodynamic characteristic in early DKD, is often associated with renal hypertrophy. The well-known tumor suppressor protein, p53, the level of which is elevated in diabetic kidneys, has been shown to be involved in the pathogenesis of glomerular hypertrophy through its downstream effector molecule, cyclin-dependent kinase (CDK) inhibitor p21^{cip1}, and to collaborate with p27^{kip1}. p53 is also involved in renal cell apoptosis, and increases gene expression involved in renal fibrosis through the transforming growth factor- β /Smad signaling pathway.

In diabetes patients, the progression of albuminuria from normoalbuminuria to microalbuminuria or macroalbuminuria is a strong pathogenic factor in declining renal function, subsequently resulting in end-stage renal disease. Many reports have shown that a reduction in proteinuria by the renin-angiotensin-aldosterone system or sodium-glucose cotransporter 2 is relevant in the protection of the kidney, although residual risk in the progression of DKD is a

substantial burden. Many types of homeostasis defects, for example, hemodynamic alterations, inflammation, profibrotic signaling and redox stress, have been shown to be associated with renal dysfunction in diabetes patients; hence, investigating diabetes-associated cellular homeostasis defects would provide clues to fight DKD.

Autophagy is a principal catabolic process that involves the degradation of abnormal proteins and/or dysfunctional organelles, and maintains cellular homeostasis. In the developing kidney, autophagy deficiency shows no remarkable phenotypes; in disease models, autophagy deficiencies have been shown to be associated with disadvantages at diverse levels. Autophagy deficiency in the proximal tubules has been described in the diabetic kidney or models associated with metabolic defects². These novel approaches in DKD/metabolic defect models have provided advances in the understanding of the fundamental role of autophagy mainly in preclinical models; however, autophagy defects associated with classical DKD pathological features, such as kidney hypertrophy associated with p53 accumulation, have not been identified.

Focusing on this topic, in a recent publication in *Journal of Clinical Investigation*, Ma *et al.*³ reported that p53 accumulation in the proximal tubule of diabetic kidneys is linked to kidney hypertrophy and damage through microribonucleic acid (miR)-mediated autophagy defects. The authors confirmed that autophagosome formation was impaired in the proximal tubules of Akita mice, a type 1 diabetic model due to insulin gene mutation, and a streptozotocin-induced type 1 diabetic mouse

model. To test the effects of autophagy deficiency in proximal tubules on renal dysfunction, the authors analyzed Akita mice deficient in proximal tubule-specific autophagy-related gene 7 (PT-Atg7^{-/-} Akita mice), and found that renal weight, the area of tubulointerstitial fibrosis and the urine albumin-to-creatinine ratio were increased in PT-Atg7^{-/-} Akita mice compared with wild-type and littermate control Akita mice. In terms of the molecular mechanisms, the authors showed that miR-214-mediated suppression of Unc-51 like autophagy activating kinase 1 (ULK1), the central molecule for the initiation of autophagy, played a vital role in autophagy defects in diabetic kidneys. They confirmed that the miR-214 targeting sequence in the 3' untranslated region of ULK1 was well conserved in various species, and molecular biological analysis showed the suppressive effects of miR-214 on ULK1 expression. They also described the central role of p53, which accumulates in diabetic tubular epithelial cells, in the synthesis of miR-214, autophagy defects and kidney hypertrophy/damage by analyzing proximal tubular-specific p53 knockout mice in streptozotocin-induced type 1 diabetic mice or chemical inhibition of p53 *in vitro*. The authors further analyzed renal biopsy samples from diabetes patients and confirmed that p53 showed a positive or negative association with miR-214 or ULK, indicating that autophagy defects in diabetic tubular epithelial cells are induced through the p53/miR-214/ULK-1 axis.

p53 has been known to regulate autophagy in a two ways: (i) turning autophagy on; and (ii) turning autophagy off. As described, Ma *et al.*³ provided a novel pathomechanism in DKD through fusion

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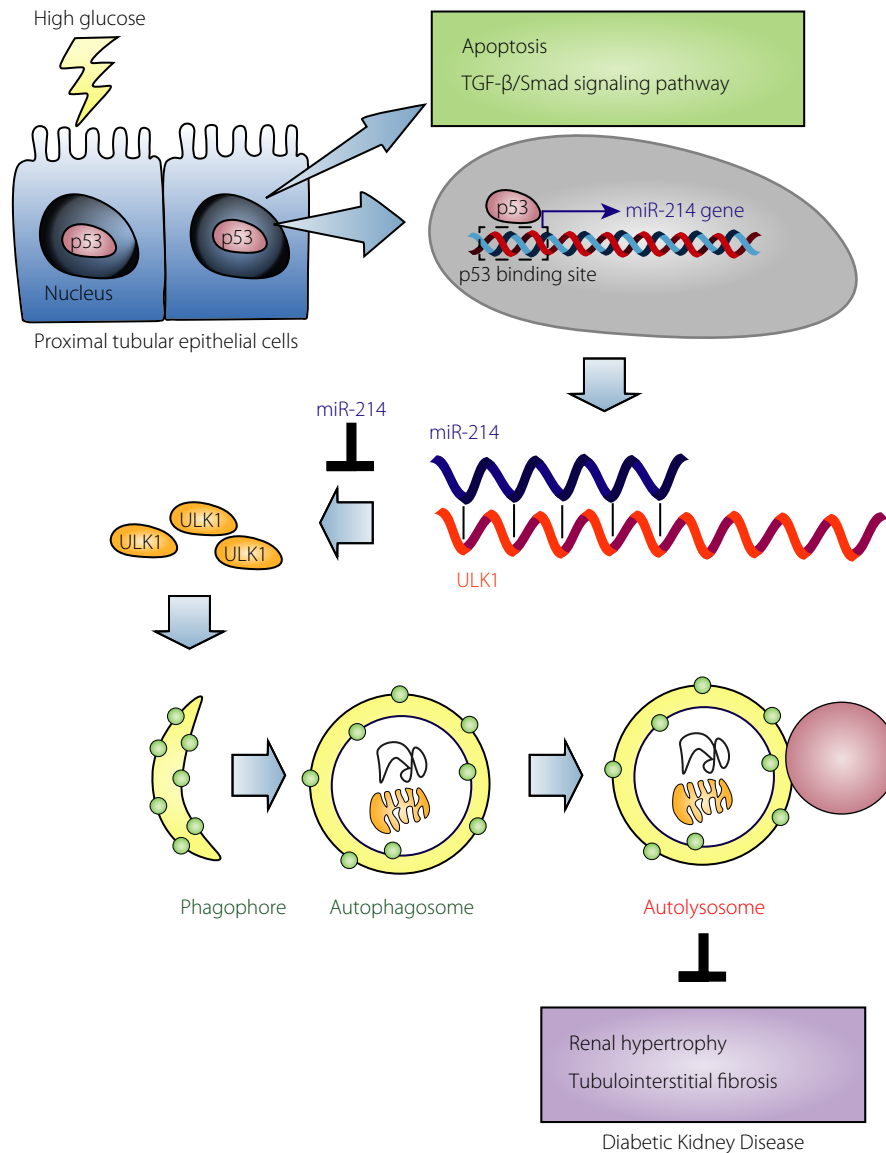


Figure 1 | p53-induced kidney hypertrophy and damage in diabetic kidney disease. Increased p53 in proximal tubular epithelial cells exposed to hyperglycemia and high glucose inhibits autophagy by suppressing Unc-51 like autophagy activating kinase 1 (ULK1) expression through transcriptional regulation of microribonucleic acid (miR)-214. The p53/miR-214/ULK1 axis might contribute to renal hypertrophy and tubulointerstitial fibrosis in the diabetic kidney. TGF- β , transforming growth factor- β .

of classical knowledge with novel molecular biology techniques, showing that p53 turns kidney tubular autophagy off and contributes to kidney damage in diabetes. However, at the same time, there are several limitations/questions in their findings.

First, the authors focused on the autophagy of renal tubular epithelial cells, but the kidney is composed of various cell types, and it is well accepted that the

interaction of diverse cell types, not only tubular cells, would be essential for the induction/progression of DKD. In regard to this, we have shown that autophagy deficiency in vascular endothelial cells induces kidney fibrosis through interleukin-6-dependent endothelial mesenchymal transition and that this profibrotic program is augmented in high-fat diet-fed mice⁴. In podocytes of

streptozotocin-induced type 1 diabetic mice and rats, a reduction in autophagy-related proteins and the accumulation of p62, an autophagy substrate, have been documented. A recent report showed that podocyte-specific autophagy-deficient high-fat diet-fed mice exhibited increased urinary albumin and glomerular endothelial cell damage⁵, suggesting that podocyte autophagy protects glomerular

endothelial cells in damaged kidneys. How tubular autophagy defects could link to autophagy defects in other kidney cell types would be interesting.

Second, even though tubular damage itself could be linked to albuminuria in part, urine albumin is essentially a strong predictor of glomerular damage or hyperfiltration. Regardless, how autophagy defects in kidney tubular cells are linked to hemodynamic-dependent or hemodynamic-independent mechanisms associated with urine albuminuria in DKD has not been analyzed.

Third, classically, renal hypertrophy is linked to p53-induced cell cycle arrest, and subsequent induction of the imbalance between protein synthesis and cell proliferation. The authors reported that, "The effect (autophagy defects in tubules) of hypertrophy was not surprising, because autophagy is a catabolic pathway whose inhibition may prevent cytoplasmic degradation and increase cell size". However, how such autophagy defects could explain the abovementioned historically described p53-dependent mechanism in renal hypertrophy is absolutely not clear. Finally, in the analysis of human kidney tissues, peritumoral tissues

were included as non-diabetic samples. p53 and autophagy, which the authors focused on in this study, could be uniquely regulated in tumor tissues.

In summary, the authors found that increased p53 in the tubular epithelium in diabetes causes renal hypertrophy by suppressing ULK1 and autophagy through miR-214 (Figure 1). Although some points require further investigation, the report by Ma *et al.*³ indicates that the p53/miR-214/ULK1 axis in the tubular epithelium sheds new light on the molecular mechanisms of DKD and provides a therapeutic target for diabetic nephropathy.

DISCLOSURE

The authors declare no conflict of interest.

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