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Pink1 Deficiency impairs mitochondrial homeostasis and aggravate diabetic tubulopathy

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Objectives: Mitochondrial dysfunction is involved in diabetic kidney disease (DKD) and recent evidence proposed that abnormal mitochondrial dynamics are pathological mediators of DKD. Mitochondrial serine/threonine-protein kinase, PINK1 senses damaged mitochondria and remove them through mitophagy in order to protect cells from stress-induced mitochondrial dysfunction. We designed this study to explore the roles of PINK1 in the pathogenesis of diabetic tubulopathy.

Methods: Human renal proximal tubular epithelial cells (hRPTCs, HKC8) were subjected to low or high-glucose conditions (5mM, or 30mM D-glucose). Transient transfection of siRNA PINK1 was performed in HKC8 cells. Diabetes was induced with streptozotocin (STZ, 50mg/kg i.p. for 5 days) in male PINK1+/+ and PINK-/- mice.

Results: We found that downregulation of PINK1 was associated with low mitochondrial mass, increased mitochondrial fragmentation, and suppressed mitophagic removal of damaged mitochondria in hRPECs when exposed to low or high glucose conditions. Subsequently, low expression of PINK1 amplified mitochondrial ROS production, and exacerbated expressions of profibrotic, imflammatory and apoptotic markers in hRPECs. Moreover, PINK1-/- mice developed severer diabetic tubulopathy accompanied with much more albuminuria than PINK+/+ mice after induction of diabetes using STZ injection. Dysmorphic and fissional mitochondria increased in the kidneys of diabetic PINK-/- mice and they were vulnerable to apoptosis and production of inflammatory and profibrotic cytokines, eventually culminating in aggravated interstitial fibrosis.

Conclusions: Our data indicate that PINK1 deficiency results in fragmented, dysfunctional mitochondria and defective mitophagy, and promotes tubular injury in the diabetic kidneys.