



## Oral Communication Abstract

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### **PTEN-induced kinase 1 exerts a protective effect in diabetic tubulopathy by attenuating necroptosis.**

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**Objectives:** Mitochondria are cell generators that are critical to cell metabolism, survival, and homeostasis. Necroptosis, a programmed form of cell death mimicking features of apoptosis and necrosis, has emerging significance in various human disease. PTEN-induced serin/threonine kinase 1 (PINK1) is one of the core organizer of mitochondria quality control and contributes to mitochondrial homeostasis. We designed this study to explore the relationship of PINK1 and tubular cell necroptosis under high glucose conditions and investigate its effects on the progression of diabetic kidney disease.

**Methods:** Diabetes was induced with streptozotocin (STZ, 50mg/kg i.p. for 5 days) in male PINK1<sup>+/+</sup> and PINK1<sup>-/-</sup> mice. Human renal proximal tubular epithelial cells (hRPTCs, HKC8) were subjected to low or high-glucose conditions (5mM, or 30mM D-glucose). PINK1-overexpressed (OE) HKC8 and primary renal tubular epithelial cells from kidneys of PINK1<sup>+/+</sup> and PINK1<sup>-/-</sup> mice were used.

**Results:** PINK1<sup>-/-</sup> mice developed severer diabetic tubulopathy accompanied with much more albuminuria than PINK1<sup>+/+</sup> mice after induction of diabetes using STZ injection. More inflammatory and profibrotic cytokines were produced in the kidneys of diabetic PINK1<sup>-/-</sup> mice, eventually culminating in aggravated interstitial fibrosis. Dysmorphic and fissional mitochondria increased in the renal tubular cells of diabetic PINK1<sup>-/-</sup> mice and lower levels of mitochondrial ROS and increased mitophagy were observed in PINK1 OE HKC8. We found that upregulation of PINK1 reduced necroptosis of renal tubular cells under high glucose conditions and mitigated the expressions of profibrotic markers. However, PINK1 deficiency was associated with amplified mitochondrial ROS production, exacerbated expressions of necroptosis regulator proteins, and profibrotic markers in hRPECs. Inhibitor of necroptosis and antioxidant attenuated the expressions of profibrotic and inflammatory proteins in HKC8 during treatment with high glucose media.

**Conclusions:** Our data suggest that PINK1 has roles in suppression of tubular cell necroptosis under high glucose conditions and exerts a protective effect in diabetic tubulopathy.