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PTEN-induced kinase 1 has association with renal aging process through cGAS-STING pathway

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Objectives: Dysfunctional mitochondria induces inflammation of the kidney, which is the major mediator of pro-aging process of chronic kidney disease. PTEN-induced kinase 1(PINK1) is a protein involved in the quality control of mitochondria and plays a role in regulating the mitochondrial dysfunction. Although it is known that the mitochondrial DNA release promoted by PINK1 deficiency stimulates cyclic GMP-AMP synthase (cGAS) - stimulator of interferon genes (STING) pathway eventually resulting in inflammatory response, the role of PINK1 and cGAS-STING pathway in renal aging has not yet been clarified. This study aimed to investigate the relationship between PINK 1 and renal aging especially through the cGAS-STING pathway.

Methods: To determine the role of PINK1 on renal aging process, renal fibrosis and tubular injury were compared in 4- and 24-month-old wild type (Pink1+/+) and PINK1 knockout (Pink1-/-) mice. To establish in vitro senescence model, H2O2 treatment on human renal proximal cells (HKC-8) was used. The changes of gene expression levels related to PINK 1 were analyzed by RNA sequencing, applying transcriptomic and metabolomic analyses.

Results: The renal fibrosis and tubular injury were significantly aggravated in 24-month-old Pink 1-/- mice compared to 24-month-old Pink 1+/+ mice. Western blot and RT-qPCR confirmed remarkably increased senescence markers and SASPs in 24-month Pink 1-/- mice and senescence induced HKC-8 cells. The RNA sequencing of mice kidneys showed that inflammation-related pathways significantly increased in 24 month Pink1-/- mice, and transcriptomic and metabolomic analyses showed that PINK1 has association with mitochondrial metabolism dysregulation. Finally, the STING pathway was significantly activated in 24-month Pink1-/- mice and senescence induced HKC-8 cells, which was inhibited by specific inhibitor of STING, H-151.

Conclusions: In conclusion, PINK1 is associated with renal aging, and the dysregulation of mitochondria caused by PINK1 deficiency might lead to aging-related inflammatory responses through the cGAS-STING pathway.