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The roles of mitochondrial dynamics in the pathogenesis of diabetic nephropathy

So-young LEE[1], Jun mo KANG[1], Dong-jin KIM[2], Seon hwa PARK[2], Hye yun JEONG[1], Yu ho LEE[2], Yang gyun KIM[2], Dong ho YANG[1], *Sang ho LEE[2]

[1] 신장내과, 차의과학 대학교 분당차병원, Korea,South, [2] 신장내과, 경희대학교 강동경희대 병원, Korea,South

Objectives : In this study, we investigated the effect of PGC1α activators on mitochondrial fusion, fission and autophagic quality control in renal tubular cells in a diabetic environment in vivo and in vitro. We also examined whether the up-regulation of PGC1α attenuates diabetic tubulopathy by normalizing mitochondrial homeostasis.

Methods : HKC8 cells were subjected to high-glucose conditions (30 mM D-glucose). Diabetes was induced with streptozotocin (STZ, 50 mg/kg i.p. for 5 days) in male C57/BL6J mice. AICAR or metformin was used as a PGC1α activator.

Results : Treatment with the PGC1α activators AICAR and metformin improved functional mitochondrial mass in HKC8 cells in high-glucose conditions. Moreover, in renal proximal tubular cells, increased PGC1α activity correlated with the reversal of changes in Drp1, Mfn1, and LC3II protein expression in a high-glucose environment. Normalized mitochondrial life cycles resulted in low ROS production and reduced apoptosis. AICAR and metformin treatment effectively mitigated albuminuria and renal histopathology and decreased the expression of TGFβ1 and αSMA in the kidneys of diabetic mice.

Conclusions : Our results demonstrate that increases in PGC1α activity improve diabetic tubulopathy by modulating mitochondrial dynamics and autophagy.

Keywords : diabetic kidney disease, mitochondria, PGC1α, tubule