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PGC-1 α inhibits the NLRP3 inflammasome via preserving mitochondrial viability to protect kidney fibrosis

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Objectives: NOD-like receptor, pyrin domain containing-3 (NLRP3) contributes to inflammation, cell death, and fibrosis in animal models of kidney disease. The NLRP3 inflammasome is activated by mitochondrial damage. However, it is unknown whether PPAR γ -coactivator 1 α (PGC-1 α), a key mitochondrial biogenesis regulator, can modulate NLRP3 pathway. Here, we demonstrated that PGC-1 α inhibits activation of NLRP3 inflammasome via preserving mitochondrial viability.

Methods: We isolated primary tubular epithelial cells (TECs) from C57BL/6 mice. The NLRP3 inflammasome pathway, mitochondrial dynamic proteins and morphology, oxidative stress marker, and profibrotic markers were examined after the TECs were treated with TGF- β 1 (5 ng/ml) alone, TGF- β 1+PGC-1 α plasmid DNA (1 μ g), TGF- β 1+siPGC-1 α (50 nM), and TGF- β 1+PGC-1 α activators (Metformin, AICAR, and Resveratrol). For animal study, C57BL/6 mice underwent unilateral ureteral obstruction (UUO) and were treated with PGC-1 α activators.

Results: *In vitro*, TGF- β 1 treatment suppressed PGC-1 α , dysregulated mitochondrial dynamics, and impaired mitochondrial morphology. In addition, the NLRP3 inflammasome pathway was activated and the expression levels of profibrotic markers and oxidative stress marker were increased in TGF- β 1-treated TECs. These changes were further accentuated by PGC-1 α knock-down. In contrast, restoration of PGC-1 α with the activators and the plasmid improved mitochondrial dynamics and morphology and attenuated the NLRP3 inflammasome activation and profibrotic marker expression. The release of mtDNA in the cytosol, the expression of TNFAIP3 and the increased degree of oxidative stress, which are inducers of the NLRP3 inflammasome after mitochondrial damage, were increased by TGF- β 1 and PGC-1 α knock-down. Restoration of PGC-1 α significantly reversed these alterations. *In vivo*, UUO resulted in the decreased expression of PGC-1 α and mitochondrial defects, while the NLRP3 inflammasome was activated and fibrosis was increased by UUO. These changes were significantly improved by PGC-1 α activators.

Conclusions: This study demonstrates that kidney injury is ameliorated by PGC-1 α -induced inactivation of the NLRP3 inflammasome.