

Abstract Submission No.: A-0937**The effect of PGC-1 on the interaction between HIF-1 and PKM2 to preserve mitochondrial metabolism in diabetic kidney disease**

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Objectives : Peroxisome proliferator-activated receptor (PPAR) gamma coactivator-1 α (PGC-1 α) is pivotal in mitochondrial biogenesis regulation, and its deficiency play a key role in kidney injury. Pyruvate kinase M2 (PKM2), acting as a glycolytic sensor, is implicated in mitochondrial dysfunction when defective. However, the potential interaction between PGC-1 α and PKM2 remains unexplored. This study aimed to investigate the regulatory action of PGC-1 α on PKM2 in renal tubular epithelial cells (RTECs) using mouse diabetic kidney disease (DKD) models.

Methods : In an in vitro study, primary cultured RTECs from the C57BL/6 mice were exposed to high glucose (HG) with or without Ppargc1 α plasmid or Ppargc1 α small interfering RNA (siRNA). In an animal DKD study, db/db mice were treated with saline, metformin, or resveratrol daily via oral gavage for 12 weeks. We examined TCA cycle intermediates, hypoxia-inducible factor 1 α (HIF-1 α), PKM2 activity, and mitochondrial function and morphology.

Results : HG-treated RTECs exhibited decreased PGC-1 α expression, aberrant glycolysis, impaired fatty acid oxidation (FAO), and decreased mitochondrial function. We observed accumulation of succinate and fumarate, increased HIF-1 α levels, and decreased PKM2 activity in these cells. These changes were restored by Ppargc1 α overexpression, while exacerbated by silencing Ppargc1 α . Notably, treatment with succinate in RTECs increased HIF-1 α levels and decreased PKM2 activity, resulting in mitochondrial dysfunction. Moreover, chromatin immunoprecipitation assay revealed that PGC-1 α directly bound to the regulatory region of the Hif1 α promoter. The regulatory action of PGC-1 α on HIF-1 α was inhibited under HG exposure and potentiated by Ppargc1 α overexpression and pharmacologic PGC-1 α activation. In an animal DKD study, PGC-1 α activation with metformin and resveratrol resulted in reduced accumulation of TCA intermediates, decreased HIF-1 α levels, and improved PKM2 activity.

Conclusions : This study demonstrates that PGC-1 α enhances PKM2 activity via decreasing TCA cycle intermediate accumulation and suppressing HIF-1 α activity. This dynamic interplay elucidates the mechanism underlying the observed improvement in mitochondrial function in DKD model.