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Pharmacologic pyruvate kinase M2 activation maintains mitochondrial metabolism by regulating the interaction between HIF-1α and PGC-1α in diabetic kidney disease

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Objectives: Previous findings have indicated that pyruvate kinase isoform M2 (PKM2) allosteric activation may protect kidney injury by improving mitochondrial dysfunction and anerobic glycolysis. However, the underlying molecular mechanisms are incompletely understood. Here, we aimed to clarify mechanistic link between PKM2 and HIF-1α-mediated PGC-1α suppression in animal model of diabetic kidney disease (DKD).

Methods: In an animal DKD study, *db*/*db* mice were intraperitoneally injected with TEPP-46, a PKM2 activator. *In vitro,* primary cultured renal tubular epithelial cells (RTECs) from C57BL/6 mice were treated with high glucose (HG) alone and HG+TEPP-46. The interactions between HIF-1α and PGC-1α were further investigated using HIF-1α overexpression and HIF-1α knockdown. PKM2 activity, energy metabolism, mitochondrial mass, dynamics, and morphology, and cell injury markers were examined.

Results: In the kidney of *db/db* mice, diabetes resulted in decreased PKM2 activation, aberrant glycolysis, impaired fatty acid oxidation, and decreased mitochondrial mass, integrity, and function. These changes were accompanied by increased HIF-1α levels and decreased PGC-1α levels. In addition, increased fibrosis and apoptosis markers were observed in diabetic mice. The direct PKM2 activation by TEPP-46 treatment attenuated the dysregulated energy metabolism, mitochondrial dysfunction, and cell death. Similar alterations were also observed in HG-treated RTECs, which were restored by TEPP-46. Notably, a chromatin immunoprecipitation assay revealed that HIF-1α directly binds to the regulatory region of the *Ppargc1a* promoter and that this interaction is inversely dependent on PKM2 activation. A luciferase reporter assay showed that HIF-1α regulates the transcriptional activity of PGC-1α in a PKM2-dependent manner. Moreover, *Hif1a* overexpression suppressed PGC-1α and induced aberrant energy metabolism, mitochondrial dysfunction, and apoptosis. Conversely, these changes were reversed by HIF-1α knockdown.

Conclusions: PKM2 activation improves impaired mitochondrial metabolism and function by modulating HIF-1α and PGC-1α interactions in DKD.