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The effect of interplay between PGC-1 and HIF-1 on PKM2 activity to preserve mitochondrial metabolism in diabetic kidney disease

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Objectives : Hypoxia-inducible factor-1α (HIF-1α) plays a multifaceted role in energy metabolism including enhancing glycolytic flux and suppressing pyruvate kinase M2 (PKM2) activity. However, the interactions between peroxisome-proliferator-activated receptor gamma coactivator-1α (PGC-1α), and HIF-1α remain unknown. This study aimed to investigate the mechanisms through which PGC-1α influences HIF-1α to regulate PKM2 in renal tubular epithelial cells (RTECs) under diabetic conditions.
Methods : Primary cultured RTECs from the C57BL/6 mice were exposed to high glucose (HG) with or without Ppargc1a plasmid (pPGC1α) or Ppargc1a small interfering RNA (siPGC1α) plasmid. Primary cultured RTECs were also exposed to succinate with or without pPGC1α or siPGC1α. Chromatin immunoprecipitation (ChIP) assay and luciferase reporter activity assay was performed to assess the direct regulatory action of PGC-1α on HIF-1α. In vivo, db/db mice were treated with metformin, or resveratrol for 12 weeks. We examined PGC-1α, HIF-1α, PKM2, glycolysis, fatty acid oxidation (FAO), and mitochondrial function.
Results : HG-treated RTECs exhibited decreased Ppargc1a and Pkm2 expression, increased Hif1a expression, and shift toward aberrant glycolysis and impaired FAO. The defective metabolic alterations led to the accumulation of succinate, a TCA cycle intermediate. Ppargc1a overexpression reversed these changes, while silencing Ppargc1a exacerbated them. Succinate treatment in RTECs increased Hif1a expression but decreased Pkm2 expression along with induced aberrant glycolysis. These changes were mitigated by silencing Hif1a. ChIP assay revealed that PGC-1α directly bound to the regulatory region of the Hif1a promoter. The regulatory action of Ppargc1a on Hif1a was inhibited under succinate exposure and potentiated by Ppargc1a overexpression. In an animal diabetic kidney disease study, Ppargc1a activation with metformin and resveratrol partially recapitulated the in vitro findings.
Conclusions : PGC-1α deficiency under diabetic conditions led to the accumulation of TCA cycle intermediates, which subsequently enhanced HIF-1α activity while reducing PKM2 activity. Additionally, PGC-1α directly suppressed HIF-1α activity, elucidating its regulatory role in mitochondrial energy metabolism.

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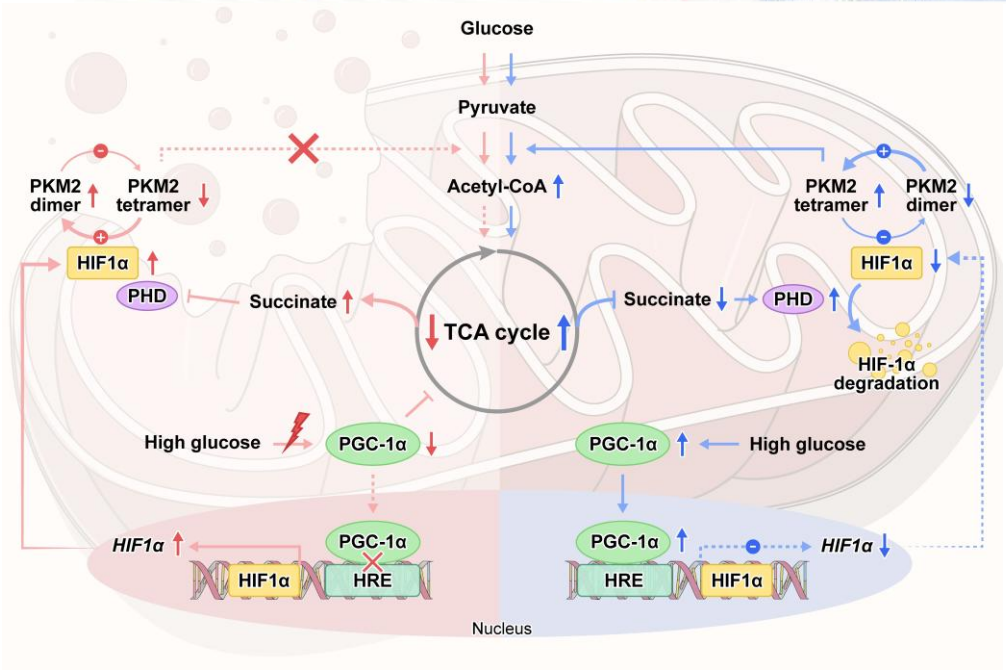
Glucose
Pyruvate
Acetyl-CoA
PKM2 dimer
PKM2 tetramer
HIF1α
PHD
Succinate
TCA cycle
High glucose
PGC-1α
HIF1α
HRE
Nucleus
PKM2 tetramer
PKM2 dimer
HIF1α
PHD
Succinate
HIF-1α degradation
PGC-1α
High glucose
PGC-1α
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