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Placental Growth Factor Deficiency Aggravates Diabetic Kidney Disease through AMP-Activated Protein Kinase-dependent Pathway

Yaeni Kim, Ji Hee Lim, Tae Woo Kim, Eun Nim Kim, Cheol Whee Park
Department of Internal Medicine-Nephrology, The Catholic University of Korea Seoul St. Mary's Hospital , Korea, Republic of

Objectives : Placental growth factor (PlGF) plays a crucial role in promoting angiogenesis via vascular endothelial growth factor receptors (VEGF-Rs) and AMP-activated protein kinase (AMPK) in hypoxic tissues. Reduced angiogenesis has been implicated in the progression of diabetic kidney disease (DKD). This study aimed to investigate the role of PlGF in DKD pathogenesis and explore its potential as a therapeutic target.
Methods : Diabetes was induced using streptozotocin in male C57BL/6J PlGF-knockout (KO) and wild-type mice. Biochemical and morphological parameters were assessed 12 weeks post-induction to evaluate the impact of PlGF deficiency on DKD progression.
Results : In diabetic PlGF-KO mice, PlGF expression in PECAM-1-positive glomerular endothelial cells (GECs) and PDGFR-β-positive mesangial cells was significantly reduced compared to non-diabetic PlGF-KO mice, accompanied by vascular rarefaction. Diabetic PlGF-KO mice exhibited worsened albuminuria and pathological DKD phenotypes due to reduced VEGF-R2 expression and impaired CaMKKβ/phospho-LKB1/phospho-AMPK signaling. Downstream pathways, including PI3K/phospho-Akt/FoxO3a/phospho-eNOS and PPARα/PGC-1α/ERRα/ChREBP/SREBP-1c, were suppressed, leading to endothelial dysfunction, lipotoxicity-induced inflammation, oxidative stress, apoptosis, and autophagy in the kidney. In vitro studies using cultured human GECs and mesangial cells exposed to high glucose conditions further supported these findings. PlGF deficiency induced by siPlGF decreased VEGF-R2 expression and AMPK-PI3K-Akt phosphorylation/eNOS activity while suppressing PPARα/PGC-1α, resulting in increased oxidative stress, inflammation, and apoptosis.
Conclusions : This study provides new insights into the role of PlGF in renal damage and its potential as a therapeutic target for DKD. PlGF deficiency exacerbates DKD through AMPK-dependent signaling pathways, contributing to endothelial dysfunction and renal damage. These findings highlight the importance of PlGF in maintaining renal health and suggest its potential for therapeutic intervention in DKD management.