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

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Objectives: Adequate angiogenic stimuli are required for maintaining metabolic homeostasis and for coping with stress and stimuli in the kidney in diabetic nephropathy. Among the vascular endothelial growth factor (VEGF) family, placental growth factor (PlGF) promotes angiogenesis through VEGF receptor (VEGF-R) and AMP-activated protein kinase (AMPK) in hypoxic tissues of pathologic condition.

Methods: Diabetes was induced by a low-dose streptozotocin in 9-week-old male C57BL/6J PlGF-KO and wild-type mice, and biochemical and morphological parameters were examined at 12 weeks later.

Results: Streptozotocin-induced PlGF-KO diabetic mice showed much aggravation of albuminuria and pathologic diabetic renal phenotypes due to decreases in VEGF-receptor2 (VEGF-R2) and CaMKK/phosphorylation of LKB1 and AMPK and their downstream signals including PI3K/phospho-Akt/FoxO3a/phospho-eNOS and PPARa/PGC-1a/ERRa/ChREBP/SREBP-1c, which caused endothelial dysfunction and lipotoxicity-induced renal inflammation (M1 polarization), oxidative stress, and apoptosis, respectively, in the kidney. Furthermore, we demonstrated that PlGF expression was detected in glomerular endothelial cells (GECs) and PDGFR-b-positive-mesangial cells, which were significantly decreased in diabetic PlGF-KO compared to non-diabetic PlGF-KO mice related to vascular rarefaction, expressed as reduced PECAM-1 expression. In cultured human GECs and human renal mesangial cells in high-glucose condition, we uncovered that PlGF-deficient induced by si*PlGF* decreased the expression of VEGF-R2 and AMPK-PI3K-Akt phosphorylation/eNOS and suppressed PGC-1a/PPARa, which ultimately led to oxidative stress and apoptosis.

Conclusions: This study provides a new insight into the role of PlGF in renal damage and PlGF activation may be a promising therapeutic target for diabetic nephropathy.