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Placental Growth Factor Deficiency Aggravates Diabetic Nephropathy Related to Glomerular Endothelial Cells and Pericytes Dysfunction

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Objectives: Placental growth factor (PlGF) is an angiogenic growth factor operating under pathologic conditions, promoting angiogeneis in hypoxic tissues through AMPK activation. AMPK is also known as a metabolic master switch that regulated downstream signals. Therefore, we investigated the role of PlGF on the development of diabetic nephropathy by using PlGF-knockout mice.

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: In the kidney, PlGF was expressed in glomerular endothelial cells (GECs) and PDGFR-β-positive pericytes (PDGFR-β-pericytes). In diabetic PlGF-KO mice, systolic blood pressure level was increased compared with those of diabetic wide-type mice. More glomerular sclerosis and mesangial area expansion were accompanied by increasing 24-hr urinary albuminuria and NOx, as well as lipid accumulation in the kidney. Diabetic PlGF-KO mice exhibited increased expressions of Col IV, TGF-β, and TUNEL-positive cells, whereas, nephrin, PECAM-1 and WT-1-positive cells and VEGF-R1,-R2,-R3 expressions were decreased compared with wide-type diabetic mice. Furthermore, intrarenal F4/80-positive cell and 8-OH-dG expressions were markedly increased associated with increasing urinary isoprotane and 8-OH-dG levels. In diabetic PlGF-KO mice, increased intrarenal expressions of CD68, arginase-II, Bax/Bcl2 and decreased SOD1, SOD2 expression were noted. At the molecular levels, intrarenal expression of pLKB1/pAMPK/PPARα/PGC-1α/ERRα, and p-eNOS, indicating glomerular endothelial dysfunction in diabetic PlGF-KO mice related to the intrarenal FFA, TG, and cholesterol accumulation. In cultured human GEC and PDGFR-β-pericytes in high-glucose media, increased apoptosis and oxidative stress were more prominant in both *siPlGF* human GEC and PDGFR-β-pericytes compared to those of control *siPlGF* human GECs and PDGFR-β-pericytes, which were related to decreases in pAMPK and its downstream signals.

Conclusions: PlGF-deficienct-induced cellular dysfunctions of GECs and PDGFR-β-pericytes were implicated in the deterioration of renal functional and phenotypic parameters in STZ-induced diabetic PlGF-KO mice, which promotes inflammation, oxidative stress, and apoptosis.