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The role of PCSK9 on the glomerular lipid accumulation and renal injury in the diabetic kidney disease

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Objectives: Glomerular lipid accumulation is one of the pathologic characteristic of diabetic kidney disease (DKD). Recent evidences suggested that proprotein convertase subtilisin kexin type 9 (PCSK9) has a particular effect on the cellular lipid homeostasis. We aimed to evaluate the role of PCSK9 on the lipid accumulation in glomeruli and podocyte under the diabetic conditions.

Methods: C57BL/6 and PCSK9 knockout (KO) mice were maintained with high fat diet for 12 weeks with low dose streptozocin intraperitoneal injection. Urinary albumin-to-creatinine ratio (ACR), total cholesterol and triglyceride in kidney tissues were measured. BODIPY 493/503 staining was performed for evaluating lipid accumulation in the kidney. Foot effacement in glomeruli was evaluated by standard transmission electron microscopy. In vitro study, mouse podocytes were stimulated with TNF-α and palmitic acid, and PCSK9 was up- or down-regulated by overexpressing lenti virus or siRNA. Apoptosis, mitochondrial morphology and energy metabolic key enzymes were evaluated both in vivo and vitro.

Results: Body weight, blood glucose and serum cholesterol were significantly increased, and urinary ACR and foot process effacement were increased in diabetic mice and these changes were exaggerated in the PCSK9 KO mouse with diabetes. Total cholesterol and triglyceride in the kidney tissues were higher in PCSK KO mice with diabetes than those in control and diabetic mice. Mitochondrial morphology and the expression of energy metabolic enzymes were disturbed in the kidneys of diabetic PCSK KO animal. In vitro, the intracellular lipid was accumulated and apoptosis combining with mitochondrial swelling and crista disruption were increased in podotyes with stimulations. All of these changes were ameliorated through mPCSK9 overexpression and aggravated by PCSK9 siRNA treatment.

Conclusions: These findings suggest that PCSK9 down-regulation in the podocytes is involved in lipid accumulation and consequent mitochondrial dysfunction and apoptosis in the DKD.