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The Role of RIPK3 in Mitochondrial Dysfunction of Diabetic Podocytes

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Objectives : Receptor-interacting protein kinase (RIPK)3 is an essential molecule for necroptosis and its role in kidney fibrosis has been investigated using various kidney injury models. However, the relevance and the underlying mechanisms of RIPK3 in diabetic kidney disease (DKD) are poorly understood. In this study, we explored the role of RIPK3 in glomerular injury of DKD.
Methods : RIPK3 expression was examined in the kidneys from diabetic patients and animals. To investigate the role and underlying mechanism of RIPK3 in diabetic kidney injury, immortalized podocytes were stimulated with 30mM high glucose (HG) to induce diabetic mimic conditions with or without GSK872, a RIPK3 inhibitor. Podocytes depleted or overexpressed RIPK3 were analyzed by Western blot, quantitative real time-PCR, or immunofluorescence staining to evaluate the effects of RIPK3 on podocyte injury. For mitochondrial analysis, oxygen consumption rate (OCR), MitoTracker green, MitoTracker red, TMRM, MitoSOX red, and DHE label were performed.
Results : RIPK3 expression was increased in podocytes from diabetic human and mouse glomeruli with increased albuminuria and decreased podocyte numbers. RIPK3 overexpressed-podocytes showed decreased OCR than control cells. HG-mediated elevation in mitochondrial fragmentation, mitochondrial or cytosolic ROS, and mitochondrial fission-related proteins such as phosphoglycerate mutase family member 5 (PGAM5) and dynamin-related protein 1 (Drp1) were decreased in RIPK3 depleted-podocytes. In addition, RIPK3 inhibition restored mitochondrial fission and morphology by reducing mitochondrial translocation of Drp1 and phosphorylation of Drp1 at Ser616.
Conclusions : RIPK3 induces diabetic podocytopathy by regulating mitochondrial fission via PGAM5-Drp1 signaling. These results suggest that inhibition of RIPK3 might be a promising therapeutic option for treating DKD.