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RIPK3 Promotes Mitochondrial Fission and Dysfunction in Diabetic Podocyte Injury

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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 of podocyte injury in DKD are poorly understood.

Methods: Diabetic animal model was induced by a high fat diet in *Ripk3* knockout (KO) mice. For *in vitro* research, we exposed mouse or human podocytes to high glucose (30 mM), with or without GSK872, a RIPK3 inhibitor. The role and the underlying mechanism of RIPK3 in diabetic podocyte injury were analyzed *in vivo*, *in vitro*, and human DKD specimens.

Results: We used single-cell RNA sequencing on kidney cortex to characterize cell-type-specific gene expression. Cell trajectory analysis identified that *Ripk3* had a function associated with the mitochondrial pathway. RIPK3 deficiency in DKD mice improved albuminuria, podocyte numbers, and renal histopathological features including foot process effacement and glomerular basement membrane (GBM) thickening. Increased mitochondrial fragmentation, upregulated mitochondrial fission-related proteins such as phosphoglycerate mutase family member 5 (PGAM5) and dynamin-related protein 1 (Drp1), and mitochondria dysfunction were decreased in RIPK3-depleted diabetic podocytes both *in vitro* and *in vivo*. Finally, elevated expression of RIPK3 was confirmed in human diabetic podocytes and plasma, which was associated with renal outcome.

Conclusions: Our data showed that expression of RIPK3 in diabetic podocytes was upregulated and that such upregulation mediated the development of diabetic podocytopathy, likely by regulating mitochondrial fission via PGAM5-Drp1 signaling thorough MLKL. These results suggest that RIPK3 might be a promising therapeutic target for treating DKD.

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