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Elucidation of Podocyte Apoptosis Mechanisms in Diabetic Nephropathy Using Multi-omics Approaches

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Glomerulus is the epicenter of diabetic kidney disease (DKD) but our understanding on this structure remains incompletely understood. To advance our understanding of glomerular cells in normal and diabetic kidneys, we created an integrated 54,034 cell census from db/+ and db/db mouse kidneys by single-cell RNA sequencing after isolation of glomerular cells using magnetic beads. Based on gene expression patterns, we identified the potential function of parietal epithelial cells (PECs) with their heterogeneous cell states and subclustered podocytes into healthy, stressed, and de-differentiated podocytes. Trajectory analyses revealed their hierarchical transition that podocytes were replenished through two intermediate states, transitional cell and podocyte-committed progenitor, which predominantly observed in normal kidneys, and injured via biphasic states of adaptive/maladaptive changes and then de-differentiation in DKD. Following reconstructed cell-state transition, we delineated dynamic transcriptional reprogramming under a set of gene regulatory network. Our study constructed single-cell transcriptional architecture presenting a blueprint for podocyte trans-differentiation and injury that can be manipulated for therapy.

Keywords: single cell RNA sequencing, diabetic kidney disease