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Unravelling kidney fibrosis using single-nucleus transcriptomics

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Kidney fibrosis is characterized by excessive production and deposition of extracellular matrix (ECM) proteins in the tubulointerstitium of the kidney. It is a known pathological event occurred in most forms of chronic kidney diseases. Multiple hypotheses surrounding the origin of the myofibroblast have been proposed to explain the mechanism of kidney fibrosis, however, none of them have been comprehensively examined. Cell type specific profiling techniques have provided compelling data to support or refute the hypotheses in kidney fibrosis but are limited by their reliance on the equipment, mouse line, cell type specific marker, and antibody availability. Single cell RNA-seq techniques are more robust approaches to profile the kidney cell types but are hampered by the significant biases introduced in the gene expression and cell type representation due to the harsh conditions used for kidney single cell isolation. In contrast, single nucleus RNA-seq technique has many strengths in profiling the fibrotic kidney. In this lecture, I reviewed our attempts to test the prevailing hypotheses in kidney fibrosis using a cell type specific technique called Translating Ribosome Affinity Purification (TRAP) and highlighted its limitations on studying kidney fibrosis. I then present our recent data to explain why the snRNA-seq is a better approach to study kidney fibrosis. I used our published snRNA-seq data from UUO to demonstrate the feasibility of using snRNA-seq to study kidney fibrosis. Then I used our unpublished data on a mouse model of Alport Syndrome to systemically investigate the cell-cell communications and the diversity of cell states within the fibrotic kidney. The key take-home messages I delivered in my talks are included: 1) single nucleus RNA-seq is a better approach to profile the fibrotic kidney; 2) snRNA-seq revealed a proinflammatory state of PT in kidney fibrosis; 3) snRNA-seq delineated the cell-cell interactions among the cell types in the tubulointerstitium; 4) snRNA-seq uncovered the change of fibroblast states in the fibrotic kidney.