TRANSCRIPTOMICS

Whole-kidney single-cell transcriptomics identifies new cell types

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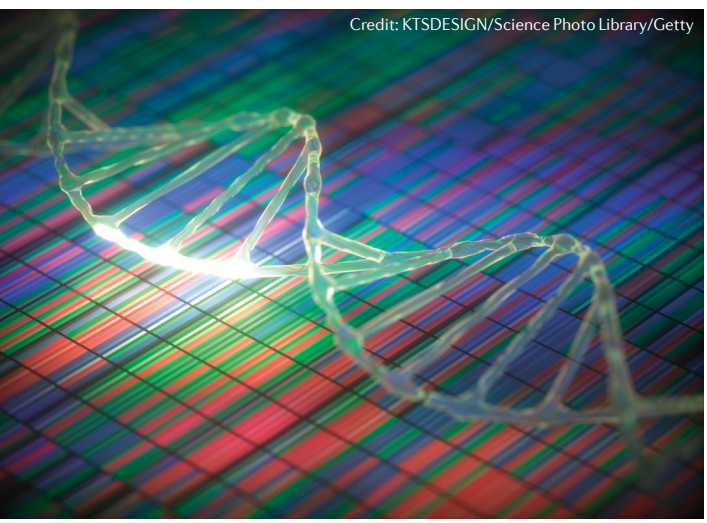
The kidney is composed of different functional segments and highly specialized cell types. Such complexity has complicated our understanding of kidney disease pathogenesis. Furthermore, kidney cell types have historically been annotated on the basis of their function, anatomical location and/or expression of a small number of markers, but these classification systems do not fully overlap. Now, Jihwan Park, Rojesh Shrestha, Katalin Susztak and colleagues catalogue mouse kidney cells using an unbiased, droplet-based, single-cell RNA sequencing approach, with the ultimate aim of enabling better understanding of kidney physiology and disease. "This method can generate global gene expression profiles in thousands of individual cells in a single experiment," says Park.

Based on the quantitative gene expression profiles of almost 58,000 cells from healthy adult mice, the researchers identified 21 distinct cell clusters that comprised 18 previously characterized kidney and immune cell types as well as three novel cell types.



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Their unbiased clustering method confirmed previously reported cell type-specific markers for many clusters, such as nephrin and podocin for podocytes, and also identified a large number of additional markers.

Next, the researchers investigated whether the expression of genes that are associated with kidney diseases is restricted to specific cell types. They demonstrate that 21 of 29 mouse homologues of genes that have been associated with monogenic proteinuria in humans are only expressed in podocytes, thereby highlighting the crucial function of these cells. Furthermore, they show that most genes that have been implicated in other monogenic disease traits are also expressed only in a single cell type, such as those that are associated with renal tubule acidosis in collecting duct cells and those that are associated with nephrolithiasis in proximal tubule cells.

The researchers also further characterized one of the newly identified cell types, which they describe as transitional cells. These cells expressed markers that are characteristic of principal cells (*Aqp2*; aquaporin 2) and intercalated cells (*Atp6v1g3*; H^+-ATPase subunit) as well as additional cell-type specific markers such as *Parm1* and *Sec23b*. They validated the existence of this cell type using co-immunofluorescence staining as well as in situ hybridization in mice. Computational cell trajectory analysis and in vivo lineage tracing experiments indicated that principal cells and intercalated cells are able to interconvert via the transitional cell type. Furthermore, low expression levels of cell cycle-regulated genes in the transitional cells suggest that they are not proliferating progenitor cells. Further analysis of gene expression patterns during the transition from intercalated cells to principal cells suggested that this process is regulated by Notch signalling. Using an inducible transgenic mouse model, the researchers show that activation of Notch signalling in differentiated adult kidney tubule cells is sufficient to drive this transition. "Together, these results indicate that cellular plasticity of epithelial cells exists not only during development but also in the adult collecting duct," says Shrestha.

Last, the findings of a computational cell deconvolution analysis of kidney samples from 91 patients with chronic kidney disease suggested that the conversion from intercalated cells to principal cells occurs in these patients and might contribute to metabolic acidosis. "Our work provides a novel approach to the development of cell-specific therapies by linking genomic discovery with cellular discovery," comments Shrestha.

The researchers now plan to characterize the other two novel cell types that they have identified and to analyse kidney samples from mouse models of disease as well as human tissue samples from healthy individuals and patients. "Single-cell transcriptomics has the potential to revolutionize how kidney diseases are categorized and could replace traditional histopathological analysis of biopsy samples," says Susztak.

"Our atlas of kidney cell types can be further utilized for comparison with molecular mechanisms that are known to cause common forms of acute and chronic kidney disease," concludes Park.

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