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Single-cell transcriptome analysis of kidney diseases

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Lack of proper molecular definition of cell types responsible for specific homeostatic functions has been a key limitation in understanding kidney disease. To fill this gap, we characterized 57,979 cells from healthy mouse kidneys using unbiased single-cell RNA sequencing. We showed that genetic mutations with similar phenotypes were mostly expressed by well known, single unique differentiated cell types. On the other hand, unexpected plasticity of epithelia in the terminal segment of the kidney (collecting duct) responsible for final composition of the urine generated cell types that explain a wide range of kidney diseases. Computational cell trajectory analysis and in vivo lineage tracing, showed that intercalated cells (that secrete protons or bicarbonate) and principal cells (that maintain salt, water and potassium balance) undergo a Notch mediated interconversions via a newly identified transitional cell type. In disease states, this transition is shifted towards the principal cell fate, which likely contributes to metabolic acidosis observed in kidney disease. In summary, single cell analysis advanced a mechanistic description of kidney diseases by identifying defective homeostatic cell lineages.