# Single-cell atlas of the human kidney provides new resources to study kidney disease

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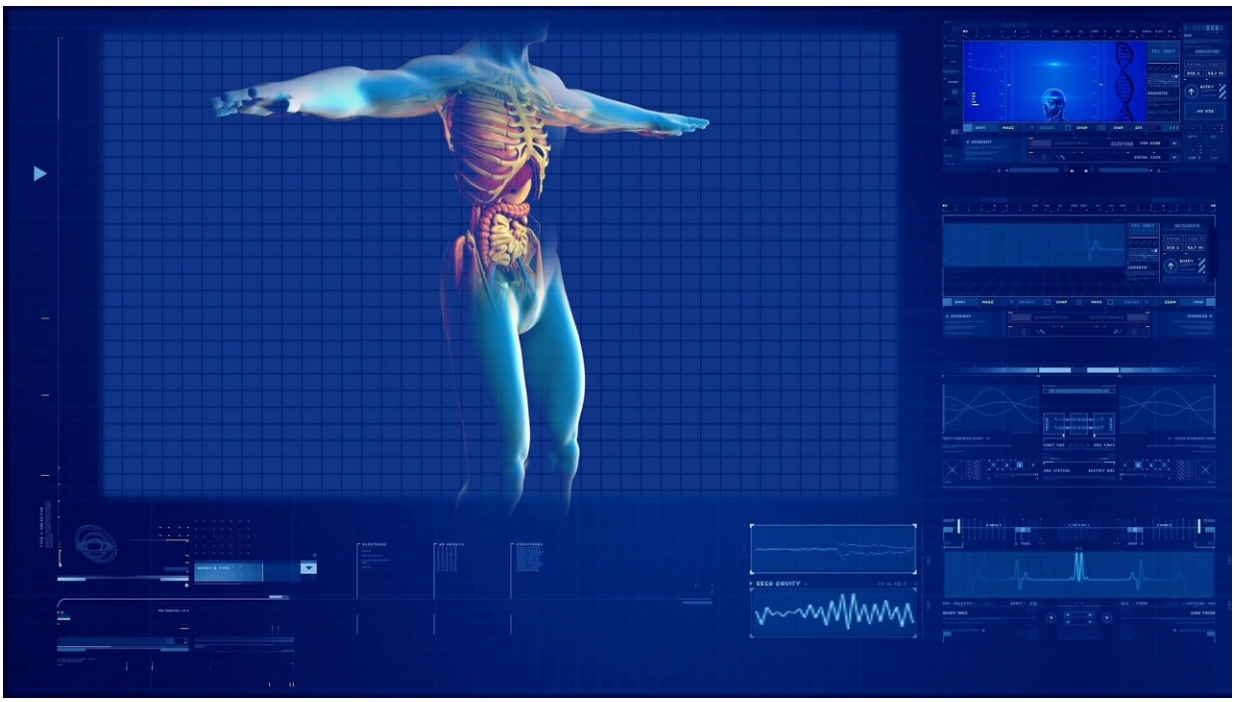

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What causes certain individuals who experience a sudden decline in kidney function to develop kidney disease while others recover? A new study co-led by bioengineers at the University of California San Diego could provide detailed insight—at the level of individual cells—into the

underlying factors contributing to these divergent outcomes.

The researchers constructed the largest single-cell atlas of the human kidney to date that maps healthy and diseased cell states across over 90 patients. The atlas is intended to serve as a foundation to better understand the progression of kidney disease after acute kidney injury, a condition in which the kidneys suddenly lose their ability to filter waste from blood.

"We want to understand that progression at the single-cell level," said study co-first author Blue Lake, who conducted this research as a project scientist in the Department of Bioengineering at UC San Diego. "By building an atlas of the different types of cells that make up a healthy kidney, as well as injured and diseased kidneys, we can start to figure out which cell types may be contributing to disease progression. We can get an idea of what changes are happening that cause some injured cell types to repair, and in some cases, transition into a state that can no longer be repaired."

The work, titled "An atlas of healthy and injured cell states and niches in the human kidney" and published July 19 in the journal *Nature*, was jointly led by the lab of former UC San Diego bioengineering professor Kun Zhang, who is now at San Diego Institute of Science, Altos Labs, and researchers at Washington University, Indiana University, and University of Michigan.

To construct their atlas, the researchers analyzed more than 400,000 cells and nuclei from a broad range of kidney samples from individuals with healthy kidneys, acute kidney injury, and chronic kidney disease.

Single-cell and single-nucleus sequencing technologies were used to generate RNA expression and gene expression profiles of the cells. These profiles enabled the researchers to identify 51 different

populations of cell types. Using spatial imaging technologies, the researchers were able to map where the different cell types are arranged in the kidney.

"This is the most comprehensive atlas so far of cell types in the human kidney," said Lake.

The researchers also discovered that 28 of these cell types are altered in acute kidney injury.

What normally happens when kidney cells get injured is that they enter a repair state in which they make new copies of themselves, as well as release signals that recruit immune cells and fibroblasts, to heal the injured area. Afterwards, they return to their normal cell state.

But with the altered cell types, a return to the normal state does not happen, the researchers found. Instead, they get stuck in the repair state. As a result, they continue to recruit more immune cells and fibroblasts. This drives inflammation and fibrosis, which in turn leads to progression of disease and irreversible reduction of kidney functions.

"These repair states are normally important for healing but can become maladaptive," said Lake. "If they persist or are constantly being stimulated, that will cause the kidney to continue into a diseased state."

The researchers found that these altered cell types, with the so-called "maladaptive repair state," live in two areas of the nephrons, which are the major filtering units of the kidney. The first area is called the proximal tubule, which has been known from previous studies in mice. This new study reveals that a second area in the nephrons, called the thick ascending limb, also houses these altered cell types.

"We were surprised to see this maladaptive repair state show up in

human cells in this other area," said Lake. "We have now identified another area in the kidney that can be associated with disease progression. Hopefully, these insights will lead the way to further developments in the field."

The researchers are constructing the next version of their kidney atlas. Their goal is to include data from a more diverse population of patients.

**More information:** An atlas of healthy and injured cell states and niches in the human kidney, *Nature* (2023). DOI: 10.1038/s41586-023-05769-3

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