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Single cell transcriptome of proximal tubular cells showed dynamic aging trajectory in human and mouse

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Objectives: Proximal tubular cell (PTC) is a high energy-requiring cell type in the kidneys. But how this cell type ages remains incompletely understood through life course.

Methods: We explored transcriptional profiles through life time using the two public dataset, Tabula Muris Senis for mouse and Kidney Precision Medicine Project for human. And we performed electron microscopy and immunocytochemistry on mouse kidneys.

Results: We reclustered human PTCs through 10s to 70s and reannotated as healthy, adaptive/maladaptive, degenerative, and proliferating cells with minor modification. The two populations of healthy PTCs were divided into the two distinct subpopulations, one of which was mostly derived from the people aged from 30s to 50s and represented more active cell state as exemplified by higher level of fatty acid oxdiation and gluconeogenesis. Through age groups, these metabolic activities showed inverted U-shaped pattern with peaks at 30s to 40s. On the view of autophagy, autophagy induction had U-shaped with nadir at 30s to 40s, whereas lysosome had inverted U-shaped with peaks at 30s to 40s. Decreased expression of the genes related to lysosome and gluconeogensis was similarly observed in far aged mouse PTCs, which harbored huge lipid-laen conglomerated autophagosome. On this view, defective lysosomal activity despite increasing autophagic induction is hallmark of aging PTCs, promoting accumulation of undigested huge autophagosome.

Conclusions: PTCs undergo dynamic changes through the course of lifetime with the highest active state in 30s to 40s, fading away its activity thereafter, and finally reaching maladptive state.