The world's first successful identification and characterization of in vivo senescent cells

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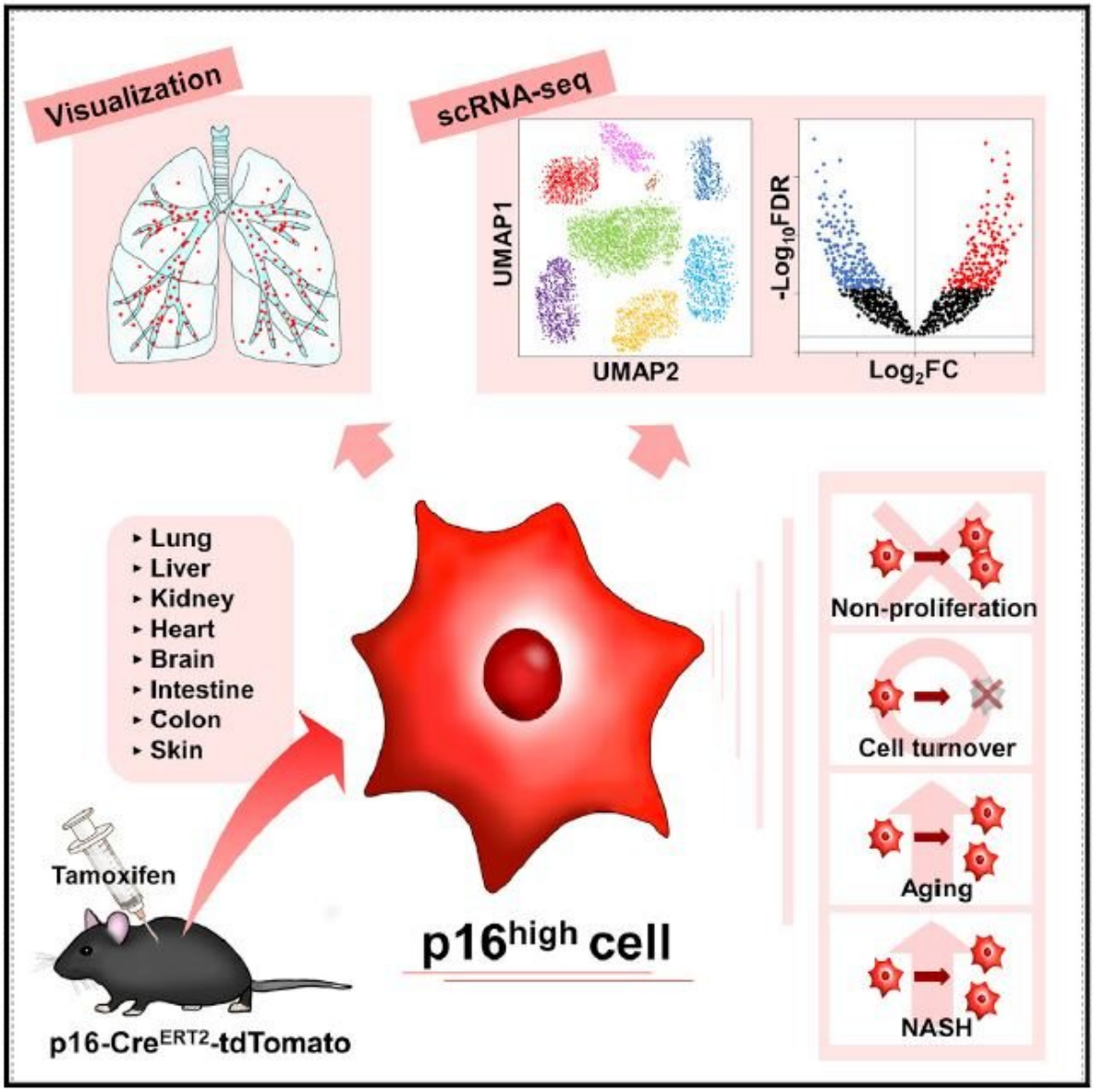

The research team generate a p16-Cre ERT2 - tdTomato mouse model to uncover the in vivo dynamics and properties of p16high cells. Single-cell RNA-seq analyses of various tissues from early middle-aged p16-CreERT2-tdTomato mice reveal that p16high cells exhibit heterogenous senescence-associated phenotypes, while elimination of p16high cells ameliorates steatosis and inflammation in a NASH model. Credit: The Institute of Medical Science, The University of Tokyo

Cell senescence is a state of permanent cell cycle arrest that was initially defined for cells grown in cell culture. It plays a key role in age-associated organ dysfunction and age-related diseases such as cancer, but the in vivo pathogenesis is largely unclear.

A research team led by Professor Makoto Nakanishi of the Institute of Medical Science, the University of Tokyo, generated a p16-Cre ERT2 -tdTomato mouse model to characterize in vivo p16 high cells at the single-cell level.

They found tdTomato-positive p16 high cells detectable in all organs, which were enriched with age. They also found that these cells failed to proliferate and had half-lives ranging from 2.6 to 4.2 months, depending on the tissue examined.

Single-cell transcriptomics in the liver and kidneys revealed that p16 high cells were present in various cell types, though most dominant in hepatic endothelium and in renal proximal and distal tubule epithelia, and that these cells exhibited heterogeneous senescence-associated phenotypes.

Further, elimination of p16 high cells ameliorated nonalcoholic steatohepatitis-related hepatic lipidosis and immune cell infiltration.

These results were published in *Cell Metabolism* on September 18, 2020.

There were a variety of senescent cells in the kidney, lung, liver, heart, brain

According to the research team, tamoxifen (TAM) was administered to middle-aged mice to investigate the location of senescent cells. What they found was that they could detect these cells in all organs they investigated such as kidney, lung, liver, heart, brain, etc.

In addition, they investigated how senescent cell presence changed with age, and found that individual senescent cells did not proliferate, but the number of senescent cells in all organs increased significantly with aging.

It was also shown that non-alcoholic steatohepatitis (NASH) was significantly improved when senescent cells were removed from the liver and kidneys. This is an interesting result from the perspective of NASH prevention and treatment.

For details of the research, please see the paper.

Contribution to the further elucidation of the causes of human aging and the development of anti-aging therapies

These results have shown that senescent cells in vivo are diverse depending on the type of progenitor cell and the stimulus.

And their new mouse model and single-cell analysis provide a powerful resource to enable the discovery of previously unidentified senescence functions in vivo.

Lead Scientist Professor Nakanishi said " These are the first results in the world showing the comprehensive transcriptome profiles of individual senescent cells in vivo, and we hope that it will contribute to the further elucidation of the causes of human aging and the development of anti-aging therapies".

More information: Satotaka Omori et al. Generation of a p16 Reporter Mouse and Its Use to Characterize and Target p16high Cells In Vivo, *Cell Metabolism* (2020). DOI: 10.1016/j.cmet.2020.09.006

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