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Commentary

Charting human cellular senescence in aging and disease

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Cellular senescence comprises diverse cell states emerging across human tissues during aging and disease. Integrating single-cell and spatial multi-omics with AI-driven analyses enables systematic mapping of senescent cell heterogeneity (“senotypes”), revealing tissue-specific programs and microenvironmental interactions. These advances provide frameworks for biomarker discovery and development of targeted senotherapeutic strategies.

Cellular senescence was first recognized in long-term *in vitro* cultures, where cells eventually ceased dividing yet remained metabolically active. Later studies revealed that senescence also occurs *in vivo* as a distinct cellular state induced by stress, damage, or other stimuli, resulting in permanent cell-cycle arrest alongside widespread alterations in intracellular and extracellular signaling, including the senescence-associated secretory phenotype (SASP).[1] Over the past decades, model systems have helped identify candidate biomarkers and provided insights into genetic drivers (i.e., p16, p21) and potential functions of senescent cells. However, in the human body, we still know surprisingly little about which cell types undergo senescence, their abundance, their spatial distribution, and the impact on the microenvironment across different organs and tissues. Without such a comprehensive “blueprint” of senescent cells in human tissues and organs, it is nearly impossible to address fundamental questions about their roles in maintaining tissue homeostasis, driving age-related physiological decline, or contributing to chronic diseases. Moreover, emerging evidence suggests that senescence is not a single, uniform program but a highly heterogeneous process. It may manifest differently depending on the initiating trigger, its duration, the tissue microenvironment, the cell type affected, and the individual’s age or life stage. Yet, this diversity has been documented primarily in cell culture or animal models, with very limited characterization in human tissues. The absence of a systematic, organ- and cell-type-resolved atlas of senescence in humans represents a major barrier to understanding its biological significance and to developing precise strategies to target senescent cells for therapeutic benefit in aging and disease.

The NIH SenNet consortium aims to build the first comprehensive human reference framework for heterogeneous senescent cell states, defined as “senotypes,” providing the resources and tools needed to finally ask and answer the deep and meaningful questions about how senescent cells influence human aging and disease.[2] Through collaborative efforts of the SenNet’s tissue mapping centers (TMC) and Technology Development and Application (TDA), the consortium has developed innovative tools and technologies to generate a multimodal, multidimensional atlas of senescent cells in multiple human tissues across the lifespan and physiological states.[3] The SenNet publication collection (https://www.cell.

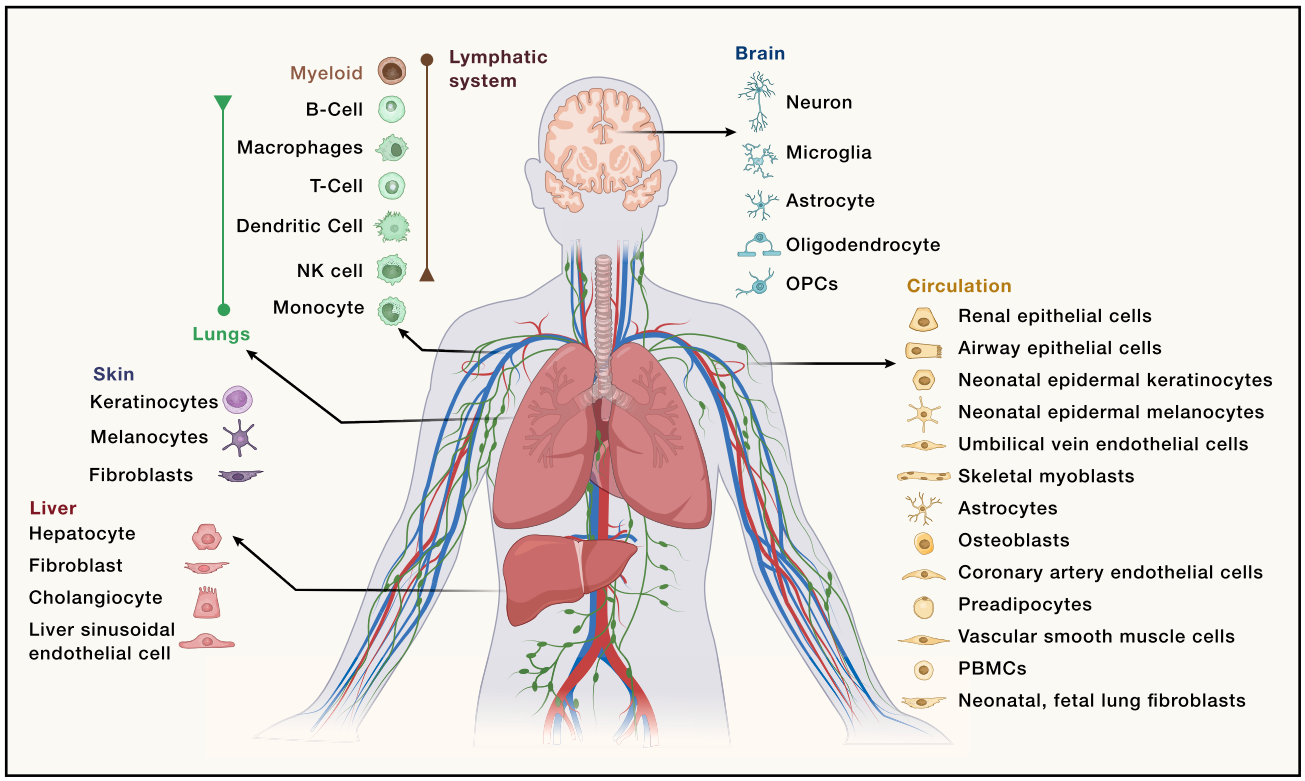

Figure 1. Heterogeneous senescence markers identified across human tissues

Predominant cell types with senescence signatures during healthy aging in lymph nodes, lung parenchyma, prefrontal cortex tissues of the brain, and 14 other tissues; during disease in the fibrotic liver and human chronic wounds from aged skin; and during the COVID-19 pandemic have been identified.

com/consortium/cellular-senescence-network) highlights some of the progress made in generating the human cellular senescence atlas during healthy aging of whole lymph nodes, lung parenchyma, prefrontal cortex tissues of the brain, and 14 other tissues; during disease in the liver and human chronic wounds from aged skin; and during the COVID-19 pandemic (Figure 1). Some of the manuscripts highlight the senolytic therapies identified and tested within the SenNet consortium. The SenNet publication collection also covers some of the latest technological advancements made within SenNet, not only technology for acquiring single-cell and spatial omics data to study senescence but also AI-based advances for interpreting these large, complex datasets (Figure 2). We envision that mapping senescent cells across human tissues will enable the development of precise diagnostics and senolytic therapies that selectively target harmful senescence while preserving its beneficial roles, transforming the management of aging and chronic diseases. Such a blueprint could shift healthcare from reactive treatment to proactive maintenance of tissue health, extending healthy lifespan and preventing disease before it manifests.

Senotype during normal aging

During normal aging, distinct senotypes—molecularly and functionally diverse forms of cellular senescence—emerge across different tissues, reflecting variations in triggers, cell types, and microenvironmental contexts. For example, Sloan et al. constructed a spatially resolved atlas of aging and senescence in human dorsolateral prefrontal cortex, revealing highly heterogeneous cell-type- and layer-specific senescence programs, which were highlighted by age-enriched astrocyte and endothelial cell gene modules enriched in the white matter and layer 1 of the cortex.[4] Notably, Lund et al. identified conserved, cell-type-specific senescence-associated molecular signatures in these cells correlated with structural brain changes observed via neuroimaging, linking cellular senescence to region-specific brain aging and potential functional decline.[5] Farzad et al. presented a comprehensive senescence map for human immune organs, focusing on lymph nodes from donors aged 5 to 86 years. Using an integrated single-cell and spatial multiomics approach,[6] the atlas systematically characterized age-associated changes in the proteome, transcriptome, epigenome, and cellular metabolism, revealing both cell-type-specific patterns of senescence and step-by-step focal accumulation of germinal center B cell senescence with age. This resource provides a framework to understand how immune tissue architecture and function are remodeled by senescence over the lifespan.

Senotype during disease

In human disease, cellular senescence may manifest as distinct disease- or aging-associated senotypes representing unique cellular states that can drive pathology or contribute to the development and progression of age-related conditions. For example, Karpova et al. employed single-cell multiome, Xenium spatial transcriptomics, and CODEX imaging to map normal and fibrotic liver

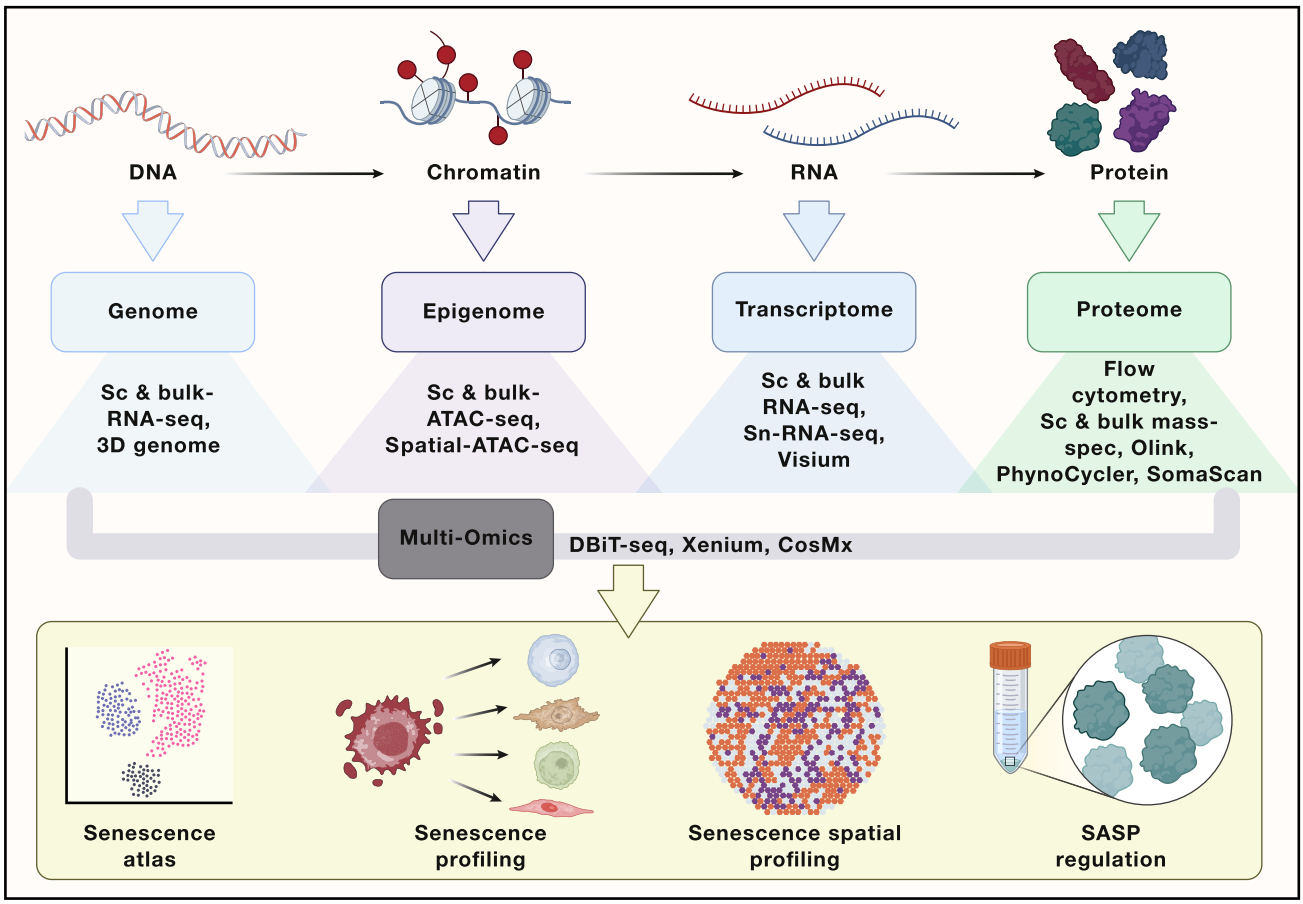

Figure 2. Techniques used to identify distinct senescent cell populations

Single-cell and spatial multi-omics tools profile molecular layers of DNA, chromatin, RNA, and protein with their readouts (genome, epigenome, transcriptome, and proteome) to organize our assays. The analysis spans four aims: senescence atlas, senescence heterogeneity profiling, senescence spatial profiling, and SASP regulation. Representative technologies are listed beneath each layer: single-cell/bulk RNA-seq for genomic analysis; spatial/single-cell/bulk ATAC-seq for epigenomic analysis; single-cell/spatial/bulk RNA-seq, snRNA-seq, and Visium for transcriptomic analysis; and flow cytometry, mass spectrometry, Olink, PhenoCycler, and SomaScan for proteomic analysis. We also note multi-omics approaches such as DBiT-seq, Xenium, and CosMx.

samples across ages[7] as well as to human colorectal cancer (CRC) liver metastases with and without chemotherapy, complemented by studies in mouse models of liver fibrosis, which uncovered heterogeneous populations of senescent cells, including CDKN1A$^+$ hepatocytes, SERPINE1$^+$ age-associated hepatocytes, CXCL12+ fibroblasts, and CXCR4$^+$ immune cells, variably distributed across fibrotic and normal tissue, as well as CDKN2A$^+$ hepatic progenitor and cholangiocyte populations with secretory phenotypes in CRC patients, highlighting potential therapeutic targets. Wyles et al. developed a chronic wound model to investigate skin cellular senescence,[8] and the team is currently working toward constructing a map of cellular senescence in normal human skin and chronic wounds using spatial transcriptomics (CosMx) and spatial proteomics (Phenocycler-Fusion), finding that chronic wounds contained elevated SASP factors (IL-6, CXCL9/10, and IFN-γ) and cytotoxic T cells. Enriched p16$^+$ γH2AX$^+$ PCNA$^-$ senescent cells are associated with matrix remodeling and chemokine signaling and formed tight clusters with immune cells and the more spatially dispersed but less abundant p21$^+$ PCNA$^-$ senescent cells exhibiting antioxidant and metabolic gene signatures. Together, these studies reveal the heterogeneity of human senescent cells across tissues, disease states, and aging, providing a foundation for developing cell- and context-specific senotherapeutics, such as targeted treatments for chronic wounds or fibrotic liver disease.

Senotypes in action: From senotype mapping to potential biomarkers and therapies

Biomarkers

In order to further catalog senotypes and define health implications, investigators of the SenNet consortium developed a multi-omic (transcriptome and proteome) senescence catalog (SenCat) in over 30 senescent cell models, including 14 cell types, each with 2 or more senescence-inducing stimuli.[9] This database was used to train new machine-learning-based senescence signatures with improved ability to identify and discriminate senescent cells in culture and *in vivo*. The proteomics component of SenCat was used to train tissue-specific senescence signatures in plasma that were evaluated in two large independent aging

studies: the Baltimore Longitudinal Study on Aging and InCHIANTI, an Italian aging cohort.[10–12] Cell-type-specific circulating senescence signatures were associated with diverse and tissue-specific clinical phenotypes. For example, renal epithelial senescence was the strongest predictor of kidney disease. Immune cell senescence signatures were notably found to be associated with current diabetes status and frailty. Moreover, immune cell senescence signatures were linked with future onset of diabetes mortality, highlighting the role of circulating senotype-specific biomarkers of senescence as predictors of future health outcomes.[12]

Senolytics

Clearing senescent cells has been demonstrated as a viable therapeutic strategy for improving aging. Eliminating senescent endothelial cells alleviated metabolic dysfunction and glucose intolerance in obese mice.[13] Senescent cell screening identified α-eleostearic acid and its methyl ester as lipid senolytics that selectively kill diverse senescent cells, lower tissue senescence, and extend healthspan in mice by triggering ferroptosis via the ACSL4-LPCAT3-ALOX15 axis rather than apoptosis or necrosis.

Advances in computational informatics, machine learning, and artificial intelligence (AI) are essential for analyzing the increasingly large and complex datasets required to identify senescence at single-cell resolution and to spatially map senescent cells within tissues.[14] For example, DESeq2 has been identified as a robust statistical approach for differential gene expression (DGE) analysis, showing invariance to sample size, sparsity, and proportion of truly differentially expressed genes.[15] However, potential false positives or negatives remain, particularly in characterizing rare senescent cells, highlighting the need for AI-driven DGE methods and integrative computational frameworks that can more accurately detect senescent cell populations, capture their heterogeneity, and link senotypes to functional and clinical phenotypes.

Conclusion

The NIH SenNet consortium aims to systematically map human senescence across tissues, ages, and disease states, generating high-resolution atlases that capture the full heterogeneity of senescent cells. By leveraging cutting-edge single-cell and spatial multi-omics technologies along with novel computational and integrative analytics, SenNet has created a rich set of resources (https://data.sennetconsortium.org) including datasets, tissue atlases, and analytical frameworks that serve as a foundational knowledge base for the field. These efforts provide unprecedented insight into the mechanisms that distinguish beneficial from deleterious senescence, reveal the diversity of senescent cell states in humans, and identify new senolytic targets. Ultimately, this comprehensive mapping of senescence in humans has broad implications for understanding the biology of aging, identifying predictive biomarkers, and developing targeted interventions to improve healthspan and treat age-related diseases.

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DECLARATION OF INTERESTS

The University of Minnesota has filed several patent applications on senotherapeutic compounds developed in P.R.'s laboratory. P.R. is also co-founder of Itasca Therapeutics, developing novel senotherapeutic compounds to treat age-related diseases and disorders. R.F. is co-founder of and scientific advisor to IsoPlexis, Singleron Biotechnologies, and AtlasXomics.

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