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Review

The heterogeneity of cellular senescence: insights at the single-cell level

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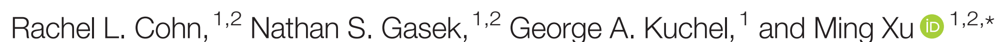

Senescent cells are highly associated with aging and pathological conditions and could be targeted to slow the aging process. One commonly used marker to examine senescent cells *in vivo* is p16, which has led to important discoveries. Recent studies have also described new senescence markers beyond p16 and have highlighted the importance of investigating senescence heterogeneity in cell types and tissues. With the development of high-throughput technologies, such as single-cell RNA-seq and single-nucleus RNA-seq, we can examine senescent cells at the single-cell level and potentially uncover new markers. This review emphasizes that there is an urgent need to investigate senescence heterogeneity and discuss how this could be accomplished by using advanced technologies and sequencing datasets.

Highlights

Currently, senescent cells do not have a known gold standard genetic marker.

Single cell RNA-seq and single-nucleus RNA-seq have emerged as powerful methods for investigating senescence heterogeneity.

It is unknown what cell populations are being targeted by senolytics *in vivo*.

Gaining a greater understanding of senescent cell heterogeneity can have large clinical implications and improve patient treatment.

The importance of understanding cellular senescence heterogeneity

Aging represents the greatest risk factor for common chronic diseases that increase morbidity in late life [1]. The geroscience hypothesis states that strategies designed to slow biological aging will enhance health in older adults by decreasing the onset and progression of multiple chronic diseases [2]. Cellular senescence has emerged as a mechanism that could be targeted to delay the aging process. The discovery of **senolytic** (see Glossary) drugs that specifically eliminate senescent cells has raised interest in aging research which has led to key animal studies and subsequent preclinical and clinical trials in humans [3].

Cellular senescence refers to stable cell cycle arrest following exposure to various stresses [3]. Senescent cells are associated with higher expression of cell cycle regulators such as Cdkn2a (**p16**) and Cdkn1a (**p21**) which are involved in modulating cell cycle arrest**.** A number of p16-based mouse models have been generated and have led to important findings in the field. However, p16 might not be a specific or sensitive marker for cellular senescence since not all p16 highly expressing ($p16^{high}$) cells are necessarily senescent [4] and some senescent cells do not express p16 [5,6]. Studies have begun to reveal the remarkable heterogeneity of cellular senescence in different tissues, highlighting the importance of cellular senescence markers beyond p16 – including Cdkn1a (p21) [7–10], Cdkn2d (p19) [11], **uPAR** [12], and **glycoprotein non-metastatic melanoma protein B** (**GPNMB**) [13] – and emphasizing the urgent need for a better understanding of senescent cell heterogeneity.

In this review we summarize current knowledge of senescence biology, emphasize heterogeneity in senescent cells, and offer insights on using high-throughput datasets to examine senescence. We first discuss what is known biologically about senescent cells and continue with a review of current technologies and analytic approaches used to investigate the heterogeneity of senescent cells, followed by a summary of several studies examining transcriptomes of senescent cells at the single-cell level in diverse tissues. We conclude with future directions, including the generation of new models and application of precision medicine

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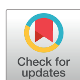

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strategies to target senescent cells. This review also provides additional insights beyond the knowledge from p16-based models.

The current consensus on the biology of senescent cells

Cellular senescence as a concept has been known since the 1960s via findings that human fibroblasts cannot divide indefinitely and eventually enter a state of irreversible cell cycle arrest [14]. Research on senescent cells *in vivo* has been greatly stimulated since 2011, when a groundbreaking study showed that clearance of *p16*^{high} cells improves tissue function in progeroid mice [15]. Cells can be induced into senescence through a variety of triggers such as oncogenic stress, telomere attrition, genotoxic drugs, and oxidative stress, amongst others [16]. While the markers of senescent cells are still not precisely defined, there is somewhat of a consensus about certain key senescent cell features (Figure 1). So far, accumulation of senescent cells has been observed in tissues with aging, diseases, or selected physiological responses such as wound healing and embryonic development, while they might be rare in young and healthy tissues. Furthermore, there is evidence that senescent cells could be present in proliferative tissues but they exhibit turnover at different rates under different conditions [17], further adding to our understanding of senescent cell presence. Also, senescent cells produce a characteristic proinflammatory secretome, collectively termed the senescence-associated secretory phenotype (SASP) [16]. In addition, senescent cells have increased cell size and granularity, positive staining for senescence-associated-β-galactosidase (SA-β-gal), and lipofuscin accumulation in lysosomes, the presence of cytosolic DNA, antiapoptotic pathway activation (through senescent cell antiapoptotic pathways; SCAPs), and a number of nuclear changes including loss of lamin B1, telomere shortening, senescence-associated heterochromatin foci, and DNA damage in telomeres (telomere-associated foci, TAF) [3,18]. At the transcript level, p16 and p21 are the two most commonly used markers for senescent cells [3,16]. These features have been extensively used to identify senescent cells in various tissues with aging or other pathological conditions. However, these features might not be conserved in all senescent cells and might not be sufficient or accessible to examine senescence heterogeneity *in vivo*.

Senescence heterogeneity at a glance

Senescent cell heterogeneity was first observed when senescent cells were shown to exhibit varying degrees of susceptibility to senolytics. It is now evident that all current senolytics have

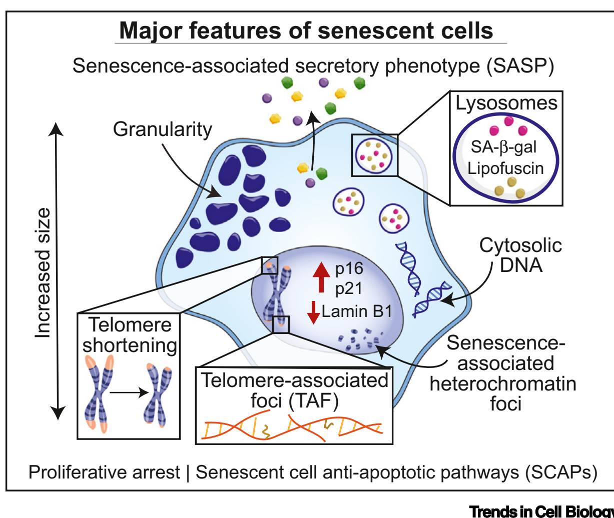

Figure 1. A summary of the current consensus on the biology of senescent cells. Senescent cells accumulate in tissues with aging and disease, and with various physiological conditions. They are in a state of proliferative arrest and use senescent cell antiapoptotic pathways to maintain their prosurvival networks. They have the senescence-associated secretory phenotype (SASP) that can damage the surrounding tissue and have increased expression of the cyclin-dependent kinase inhibitors p16 and p21 and decreased expression of lamin B1. Senescent cells also exhibit increased granularity, cytosolic DNA, senescence-associated-β-galactosidase (SA-β-gal) staining, telomere shortening, telomere-associated foci (TAF), and senescence-associated heterochromatin foci.

Glossary

Bulk RNA-seq: a sequencing method using next-generation sequencing technologies to detect RNA transcripts from pooled cell populations or tissues.

Chimeric antigen receptor (CAR) T cells: a type of immunotherapy where T cells are genetically altered so that they can kill specific cell targets.

Dasatinib/quercetin: a senolytic drug combination of an Src kinase inhibitor (dasatinib) and a flavonoid (quercetin) that kills senescent cells by inhibiting components of their prosurvival networks.

Eigengene: an unbiased method that weights average expression over genes. In the case of senescent cells, the method takes genes that are commonly involved with senescence in different tissue types and weights the average expression of that gene over all other genes in the same gene list. Weights are then optimized with principal component analysis and the mean expression of each eigengene is calculated over all cells.

Fisetin: a flavonoid with senolytic properties.

Glycoprotein non-metastatic melanoma protein B (GPNMB): a type I transmembrane protein involved in the invasion and metastasis of a number of cancers.

Imaging flow cytometry: a method that combines flow cytometry with high-content image analysis that can visualize every cell in a sample.

p16: a cyclin-dependent kinase inhibitor that halts the progression of the cell cycle. It is encoded by the *CDKN2A* gene.

p21: a cyclin-dependent kinase inhibitor that halts the progression of the cell cycle. It is encoded by the *CDKN1A* gene.

Senolytics: pharmaceutical treatments specifically designed to target and eliminate senescent cells.

Single-cell RNA-seq: a sequencing method using next-generation sequencing technologies to detect RNA transcripts from individual cells.

Single-nucleus RNA-seq: a sequencing method using next-generation sequencing technologies to detect RNA transcripts of individual nuclei from tissues.

uPAR: a receptor that facilitates the breakdown of extracellular matrix during wound healing, fibrinolysis, and tumorigenesis.

distinct efficacy on diverse senescent cell populations. For example, **dasatinib** is most effective at eliminating senescent preadipocytes, while **quercetin** better targets endothelial cells [19]. Both **fisetin** and navitoclax kill senescent fibroblasts and endothelial cells, yet have limited effect on senescent preadipocytes [20,21]. Even so, there remains a general lack of knowledge about exactly which cell populations are being targeted by senolytics *in vivo* at the single-cell level, limiting their utility in a broader pathological context. Considering the scope of the problem, varied chronic conditions being targeted, and the growing number of ongoing clinical trials, such information is critically important.

Analysis of **bulk RNA sequencing** (**RNA-seq**) data from fibroblasts from both humans (foreskin fibroblasts, epidermal melanocytes) and mice (embryonic fibroblasts, skin microvascular endothelial cells) demonstrate differences in transcriptomic signatures and SASPs based on senescence inducers, cell types, and stages of the senescence process [22], which may contribute to differences in function. Furthermore, individual senescent cells within the same culture of human fibroblasts also demonstrate cell-to-cell transcriptomic variability, as evidenced by single-cell isolation and nanofluidic PCR experiments showing a lack of correlation of gene expression among several senescence-associated genes [23]. Based on these *in vitro* findings, senescent cells *in vivo* are likely heterogeneous as well, which can come from diversity in terms of age and sex as well as varied pathological states, locations of the tissues, microenvironment, and accumulation kinetics. These differences are not well described by the current literature, and more research using high-resolution methods, such as **single-cell RNA-seq, single-nucleus RNA-seq**, or other single-cell resolution techniques, is necessary to uncover the characteristics of senescent cells under different conditions *in vivo.*

Models for understanding senescent cell heterogeneity *in vivo*

Until recently, p16 has predominated as a marker for studying senescence *in vivo* and has helped to determine the causal roles of $p16^{high}$ cells in various age-related conditions. Although other senescence-related markers have been used to confirm senescence, such as SA-β-gal and the presence of SASP factors, emerging evidence has indicated that p16 might be neither a sensitive nor a specific marker for senescence because some $p16^{high}$ cells are not senescent (e.g., pancreatic β-cells [24], macrophages [4], mesenchymal stem cells [25], endothelial cells [26]), while not all senescent cells express high levels of p16 [16]. Moreover, multiple p16-based mouse models [15,26–28] might not target the same $p16^{high}$ cells *in vivo* due to different transgene designs (such as different p16 promoters or transgene locations). Moreover, while senolytics are widely used to examine the role of senescent cells *in vivo*, the exact cell populations targeted by different senolytics remain largely unknown. These technical complications constrain our knowledge of senescence to only a subset of senescent cells *in vivo*.

A number of new studies have examined senescent cells expressing markers other than p16 *in vivo*. In 2021, a p21-Cre transgenic mouse model was generated, containing a p21 promoter driving an inducible Cre. This model targets p21 highly expressing ($p21^{high}$) cells *in vivo*, which comprise 1–10% of cells in various tissues in aged mice, and are distinct from $p16^{high}$ cells, with both displaying a number of key characteristics of senescence [9]. Remarkably, clearance of $p21^{high}$ cells reduces senescence markers, improves physical function in aged mice [9], and alleviates metabolic dysfunction in obese mice [10]. In another study, urokinase plasminogen activator receptor (uPAR)**,** was identified as a unique senescence marker by comparing differentially expressed genes in bulk RNA-seq datasets of three known mouse models of senescence, and was validated by flow cytometry [12]. Elimination of uPAR-expressing cells with **chimeric antigen receptor (CAR) T cells** specifically kills senescent cells both *in vivo* and *in vitro*, and extends the lifespan of mice with lung adenocarcinoma [12]. Additionally, a separate study investigated

the transcriptomes of vascular endothelial cells and identified GPNMB, a cell-surface protein, as a marker for senescent cells, which was evidenced by its enrichment in senescent vascular endothelial cells compared with non-senescent cells in both human patients and mice with atherosclerosis. Genetic elimination of GPNMB-positive cells reduces the senescent cell burden and alleviates metabolic irregularities in obese mice. Vaccination against GPNMB also improves a number of conditions associated with aging [13]. These exciting findings are just beginning to shed light on the role of various senescent cell populations *in vivo*. In addition, as evidenced by the different senescence markers discovered earlier, it is possible that one marker may not be enough to define senescent cells as a whole, and that a combination of many markers and features will ensure that cells are in a senescent state. The discovery of new senescent markers and the generation of new mouse models have numerous implications for examining senescence heterogeneity as well as the design of new senolytic therapies.

Current high-throughput technologies for examining senescent cells at the single-cell level

The current knowledge gap pertaining to senescence heterogeneity highlights the need to improve technologies to more accurately identify and characterize senescent cells. With technological advancements, single-cell/nucleus RNA-seq methods are among the most powerful tools for investigating senescence heterogeneity (Table 1). These methods have advantages in looking at individual cells at the molecular level and defining transcriptomic characteristics [29]. Although single-cell RNA-seq remains the most comprehensive method for capturing the transcriptome of individual cells, due to high sequencing depth, it may miss capturing cells that are large or sensitive to dissociation, which likely include some senescent cells due to their enlarged size and physical fragility [18]. Conversely, single-nucleus RNA-seq can potentially capture all cell types while the sequencing sensitivity might be lower due to lower mRNA abundance in the nuclei. Spatial transcriptomics is another newly developed method which allows for transcriptomic detection in small tissue sections by RNA-seq while maintaining the histological information of these sections [30]. With future improvements in resolution at the single-cell level (the current resolution is ~55 μm, one to ten cells per section), it could be particularly useful because it will capture all the cell types and provide critical spatial information on senescent cells, which cannot be acquired by single-cell/nucleus RNA-seq. These powerful RNA-seq-based methods can detect thousands of transcripts at the same time, a feature that is essential for discovering new senescent cell markers. However, the sequencing depth of current methods remains relatively low, and only up to 50–60% of transcripts can be sequenced and detected in each cell. This could be a particular challenge for mapping senescent cells due to their low abundance *in vivo*. Enrichment

Table 1. Overview of select technologies for examining senescence heterogeneity

Technique	Single-cell resolution?	Average gene targets	Potential cell type loss	RNA/protein	Spatial	Cell enrichment	Detection sensitivity
Single-cell	Yes	>2000	Yes	RNA	No	Yes	Low
Single-nucleus	Yes	>1000	No	RNA	No	Yes	Low
Bulk RNA-seq	No	>5000	No	RNA	No	No	High
Spatial transcriptomics	No	>1000	No	RNA	Yes	No	Low
mABI	Yes	~50	No	Protein	Yes	No	High
mFISH	Yes	~150	No	RNA	Yes	No	High
Imaging/standard flow cytometry	Yes	~12	Yes	Protein	No	Yes	High

of senescent cells through cell sorting by flow cytometry or other technologies might be advantageous to improve the sequencing sensitivity, but requires robust senescence markers.

In addition to these high-throughput methods, high-sensitivity detection methods are equally valuable. For example, multiplexed antibody-based imaging (mABI) technologies such as imaging mass cytometry (IMC) [31] and codetection by indexing (CODEX) [32] can detect 20–50 selected genes simultaneously in each cell at the protein level, which is a useful complement to transcript-based detection – especially given the potential for poor correlation of transcriptomic and proteomic data sets implicated with senescent cells [33]. Multiplex fluorescence *in situ* hybridization (mFISH) [34,35] is another effective approach to detect senescent cells, which can detect more than 100 selected genes at single-molecule resolution. These high-resolution methods are important for validating targets identified by single-cell/nucleus RNA-seq as well as assessing the surrounding microenvironment of senescent cells.

Another useful technology for examining senescent cells is **imaging flow cytometry**, which has been used to examine senescent cells *in vivo* [9,10,36]. The major advantage of this method is that it allows for protein-level detection of several senescence markers or reporters along with assessment of several senescence features at the single-cell level in a relatively high-throughput manner. These features include SA-β-gal staining, cell size, proliferation, DNA damage foci, and cytosolic DNA presence, all of which are currently not measurable by sequencing-based methods. One method that has yet to be used to study senescence is single-cell mass spectrometry, including single-cell proteomics and single-cell metabolomics which provide protein (including post-translational modification) and metabolite identification on a large scale [37] and could have enormous implications for studying senescent cells.

High-throughput RNA-seq approaches are important to gain a deeper understanding of senescent cells, but analytic methods are equally important. Several methods are discussed in Box 1. They are just a sampling of ways to analyze senescent cells from large datasets. These methods, along with other newly developed ones, could contribute to a more unified understanding of senescent cells.

Senescent heterogeneity in tissues (single-cell/nucleus level)

The current knowledge of senescence heterogeneity is insufficient. To begin to fill this gap, we review several high-resolution studies examining senescent cells at the single-cell level, and indicate the need to leverage these powerful datasets to find markers other than p16 and p21.

Box 1. Examples of analytic methods for investigating senescent cells

- One study analyzed transcriptome data of 50 human tissues in the Genotype-Tissue Expression Project (GTEx) in bulk and single-cell RNA sequencing data sets [45]. While the full computational analysis is detailed elsewhere, it accounted for aged tissues and integrated both bulk and single-cell RNA-seq data sets when generating senescent gene coexpression modules and networks. The study was able to identify over 50 senescence genes that were conserved across multiple human tissues [45]. This valuable data set can be applied to single-cell and other high-resolution data sets going forward and can help to define characteristics of cells across multiple tissue types.
- Another useful method is the eigengene method [11] which takes genes that are commonly involved with senescence in different tissue types and weights the average expression of that gene over all other genes in the same gene list. Weights were optimized with principal component analysis (PCA), and the mean expression of each eigengene was calculated over all cells. Senescent cells were defined if the level of eigengene expression was greater than the mean expression over all the other cells plus three times the standard deviation. Overall, this method allows for detection of senescent cells using an unbiased approach and may be useful for identifying new markers.
- Using publicly available datasets of single-cell as well as bulk RNA-seq, one group created a more comprehensive list of senescent markers (SenMayo) which consists of 125 genes, primarily SASP factors [46]. These genes were found to be highly correlated with age, the level of p16 and p21, and the burden of senescent cells in both mouse and human tissues, which could be a valuable resource for identifying senescent cells.

Adipose tissue

One study leveraged single-cell RNA-seq amongst other technologies to examine both *p21*^{high} and *p16*^{high} cells in adipose tissues from obese mice [10]. They showed that *p21*^{high} and *p16*^{high} cells are two distinct cell populations in terms of cell types, tissue location, accumulation kinetics, and physiological roles. Similar discrepancies were recapitulated in aged mice [9]. Notably, adipose *p21*^{high} cells showed a number of key senescence features (assessed by imaging flow cytometry) in the contexts of both aging and obesity. Moreover, by performing single-cell RNA-seq on adipose-derived mesenchymal stem cells isolated from young and aged mice, another study demonstrated that *p21*^{high} cells accumulate more with aging and exhibit a number of altered pathways commonly seen in senescent cells induced *in vitro*, including upregulation of SCAPs, SASP, NF-κB, HMGB1, and FOXO pathways [8]. While these studies showcased a novel population of senescent cells, it is important to recognize that – like p16 – p21 might not be a specific marker for senescent cells.

Brain

In aged mice, single-nucleus RNA-seq and single-cell RNA-seq have shown that both *p16*^{high} and *p21*^{high} cells accumulate more in microglia, oligodendrocyte progenitor cells (OPCs), and oligodendrocytes in aged mouse hippocampus with certain degrees of heterogeneity [38]. In human brains, a single-nucleus RNA sequencing study using an **eigengene** approach found that p19/CDKN2D was the most significant marker of senescent cells in postmortem brains from patients with Alzheimer's disease (AD), and also defined a unique group of senescent cells in human AD brains [11]. p19 upregulation was further validated by mFISH and mABI in human AD brains and additional experiments confirmed that p19-expressing cells had several key features, including larger nuclei and more lipofuscin-positive cells than non-p19-expressing cells. The senescent cells found in this dataset were mostly excitatory neurons with tau pathology commonly seen with AD. This high-resolution study also revealed some of its limitations. For example, some SASP genes were used to identify senescent cells, but their expression levels were also upregulated in cells showing no common senescent hallmarks. This further emphasizes the need to develop a more comprehensive and accurate way to define senescent cells.

Liver and kidney

A recent study examined *p16*^{high} cells by single-cell RNA-seq in liver and kidney using p16-Cre mouse models [28]. In healthy and young mouse livers, *p16*^{high} cells are mostly endothelial cells and a few Kupffer cells. In mouse livers with non-alcoholic steatohepatitis (NASH), *p16*^{high} cells are mainly macrophages along with other cell types. In healthy and young kidneys, p16^{high} cells are mainly epithelial cells. Gene ontology (GO) analysis on *p16*^{high} cells showed highly heterogeneous pathway changes among different cell types and conditions. Although exciting, it remains unclear whether these *p16*^{high} cells show any other senescence features.

Eye

Another study leveraged gene set variation analysis (GSVA) to analyze single-cell RNA-seq datasets of mouse retinas with proliferative retinopathies; it revealed that certain cell types, including astrocytes, pericytes, endothelial cells, and glial cells, showed expression of senescence-related genes from two published senescence-related gene-sets [39,40]. They identified a subset of senescent endothelial cells in the retina, which highly express Col1a1, that can be specifically eliminated by a senolytic drug [41]. This study took advantage of known senescence gene lists to identify senescent cells, including a senolytic-responsive subset, and to determine a novel senescence marker other than p16 and p21.

Other tissues

Tabula Muris Senis, or Mouse Ageing Cell Atlas, is a single-cell RNA-seq database, completed in 2020, that contains sequencing data from 23 mouse tissues across the lifespan [42]. One component of this large database was an examination of senescence in older mouse populations which showed that p16 expression increased significantly with aging as did E2f2, Lmnb1, Tnf, and Itgaf [42]. To note, E2f2 and Lmnb1 are typically downregulated in senescent cells [43]. Nevertheless, this invaluable database provides a comprehensive large-scale study to understand senescent cells with aging. With the rapid advances in sensitivity of single-cell RNA-seq, this database could be improved to better understand senescence heterogeneity *in vivo*.

Another study used single-cell RNA-seq to compare transcriptomic differences in the kidney, lung, and spleen between aged and young mice [44] and found that various cell types express unique genes with aging, and similar cell types exhibit similar aging trajectories in terms of gene enrichment, while dissimilar cell types have distinct trajectories. The study did show common genes differentially expressed with age among the three tissues studied, including decreased expression of genes in SRP-dependent protein translation and upregulated expression of genes related to inflammation [44].

In summary, in most of these studies, senescent cells are distributed in various cell populations rather than forming specific clusters, further demonstrating heterogeneity. Known senescence markers (p16 or p21) were used for senescent cell identification. Due to the limitations of these markers, assessment of other senescence features is necessary to better understand these cell populations. Moreover, these powerful datasets can be leveraged to discover new senescence markers and examine senescence biology with better computational analysis pipelines.

Concluding remarks

Due to the multilayered complications of senescence biology that we have discussed here, there is an urgent need to investigate the heterogeneity of cellular senescence, find new and more specific markers for senescent cells, and develop models and technologies to improve their detection in both healthy and diseased tissues. Additionally, the tissue-specific differences in senescent cells described in this review suggest that a combination of many markers, rather than just one marker, could more accurately detect senescent cells. Single-cell/nucleus RNA-seq as well as other high-throughput sequencing methods have provided valuable insights into the heterogeneity of senescent cells. However, these just scratch the surface, and more elaborate and comprehensive studies are urgently desired (see Outstanding questions).

Given all of the above challenges and complexities, the National Institutes of Health (NIH) Common Fund's Cellular Senescence Network (SenNet) Program was established to systematically identify and characterize heterogeneity in senescent cells involving different healthy human and mouse tissues across the lifespan[i]. SenNet aims to provide publicly accessible atlases of senescent cells, highlight differences among them, and identify secreted molecules across different tissues. It also aims to develop innovative tools and techniques to better detect and examine these rare cells. Hopefully, SenNet will significantly advance senescence research by achieving these goals.

Due to the high therapeutic value of targeting senescent cells, understanding the heterogeneity of senescence will also play a major role in improving precision medicine approaches for older populations. For example, finding conserved and sensitive senescence markers could improve senescent cell detection and would also permit the assessment of senolytic efficacy; knowing the dynamic nature of senescent cells will help to determine better timing of senolytic treatments;

Outstanding questions

Is there a universal signature for senescent cells across all tissues? And are there tissue-specific or disease-specific senescent cell signatures?

Are there unique signatures of senescent cell populations considered to be pathologic versus those that may be beneficial?

Is it feasible to design different senolytics based on heterogeneity to more precisely target diseases?

Do senescent cell signatures change over time?

Does senescence burden in one tissue correlate with that in other tissues within the same individual?

What are the precise senescent cell populations targeted by senolytics?

What are the unintended effects of senolytics on non-senescent cells?

What is happening in the surrounding tissue area when cells are targeted by senolytics?

What are the p16^{high} and p21^{high} cells targeted by various transgenic mouse models?

What is the optimal way to analyze senescent cell data?

information on tissue-specific senescent cells can develop new senolytic delivery methods to improve drug potency; understanding of disease-specific senescent cells can improve treatment efficacy and reduce side effects; and data regarding individual-specific senescent cells can guide selection of more effective senolytics, thereby improving drug responsiveness and clinical outcomes.

In sum, a better understanding of senescence heterogeneity can be very informative to design interventions to more accurately target diseased and aging tissues, which can potentially revolutionize the patient care system in aging communities.

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Declaration of interests

M.X. has a financial interest related to senolytics. Patents on senolytic drugs (including PCT/US2016/041646, filed at the US Patent Office) are held by Mayo Clinic.

Resources

[i]http://commonfund.nih.gov/senescence

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