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A Model for Defining Senescence

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ABSTRACT: Our understanding of the causes and effects of cellular senescence in tissues and organs, as well as how this process might be used for human health, are still limited due to the variety of senescent cells. Here, we selected five major areas that would advance the discipline.

KEYWORDS: SENESCENCE REGULATION AND VALIDATION, BIOMARKERS, SENESCENT CELL DETECTION, ISS, SPACEFLIGHT

I. INTRODUCTION

Cellular senescence, a persistent hypo-replicative state characterised by a specific type of permanent cell-cycle arrest in previously replication-competent cells, is brought on by a variety of stress signals, including telomere dysfunction, oxidative stress, changes in chromatin architecture, mitochondrial dysfunction, mitotic stress, and proteotoxicity (He and Sharpless, 2017). Quiescence and senescence differ significantly in that quiescence is characterised by a reversible cell-cycle arrest without any cellular damage or a distinctive secretory phenotype, whereas senescence is characterised by an irreversible cell-cycle arrest linked to macromolecular damage and a secretory phenotype (He and Sharpless 2017). Surprisingly, senescent cells are capable of completing some of the same tasks as their parent replication-competent cells while having their cell cycle paused and being metabolically active (Lee and Schmitt, 2019). The production of anti-proliferative molecules, macromolecular damage, activation of damage-sensing signalling pathways, the secretory phenotype known as senescence associated secretory proteins (SASPs), and unregulated metabolism are hence characteristics of cellular senescence (He and Sharpless, 2017; Gor-goulis et al., 2019). Although Hayflick reported in 1961 that cultivated normal human fibroblasts had a limiting proliferative capability (Hayflick and Moorhead, 1961), the phenomenon was neglected for many years and was not widely acknowledged until recently since it was largely thought to be an in vitro artefact. Furthermore, the biological significance of senescence has emerged in numerous physiologically normal states as well as in a number of diseased diseases (Campisi et al., 2019; Childs et al., 2017; Rhinn et al., 2019; Hou et al., 2019; Khosla et al., 2020). Cellular senescence is necessary, for example, for tissue remodelling during embryogenesis, for the healing of wounds, and to avoid malignant trans-formation of damaged cells (Lee and Schmitt, 2019; Rhinn et al., 2019). The excessive accumulation and activity of senescent cells is also linked to many chronic diseases of ageing, including atherosclerosis, cancer, cardiac and kidney dysfunction, neurodegeneration, pulmonary fibrosis, and many others. This is in contrast to their involvement in these normal physiological processes. Additionally, post-mitotic cells such as cardiomyocytes, osteocytes, osteoclasts, adipocytes, and neurons have been found to have "senescent-like" characteristics in recent research (Pan'czyszyn et al., 2020). It's interesting to note that the removal of these cell types lengthens the lives of ill and old mice (Raffaele et al., 2020). On the other hand, a recent study showed that acute or continuous elimination of p16^{High} senescent cells in murine models damaged blood-tissue barriers, causing health problems related to fibrotic diseases of the liver and tissues as well as a reduction in longevity (Grosse et al., 2020). Therefore, it will be crucial to characterise the post-mitotic senescent signatures of various cell types and assess the consequences of senolysis for tissue integrity and function in either human tissues or/and murine models. It still needs to be established whether the removal of senescent cells, which is easier accomplished and its effects are easier examined in mice, would have comparable positive and/or negative effects in people. While the importance of senescence for human biology is progressively becoming clear, the difficulty of identifying a "universal" signal for senescent cell identification in vivo has been a significant roadblock. The emerging theory is that a panel of biomarkers may be required to detect possibly heterogeneous senescent cells in vivo

(Campisi et al., 2019; He and Sharpless, 2017; Sharpless and Sherr, 2015). These findings prompt some crucial inquiries.

II. A COMPREHENSIVE APPROACH TO SENESCENT CELL DETECTION AND CHARACTERIZATION

The physiological significance of senescent cells in health and illness is becoming more well acknowledged. The first stages are to recognise and define senescent cells in tissues and organs due to the heterogeneity of these cells. In order to identify opportunities for a potential future Common Fund programme focusing on drivers and consequences of cellular senescence, including the development of tools and technologies to identify tissue heterogeneity, tracing and tracking these cells in vivo, and establishing model systems and perturbation agents to validate in vivo observational studies, NIH recently held workshops to solicit input from the broad scientific community to address these questions. Along with these informational exchanges, we offer our viewpoint on conceptual and technical potential as well as roadblocks that prevent advancement. We really believe that these conversations will benefit the entire community of academics working in the subject of cellular senescence in addition to assisting NIH prioritise research initiatives that are likely to advance this field in the upcoming 5–10 years. Through this exercise, the major areas were found: (1) creation of a multimodal atlas that depicts the heterogeneity and spatial distribution of senescent cells across tissues; (2) identification of trustworthy biomarkers for senescent cell detection in vivo; (3) establishment of tools and model systems susceptible to perturbations; Senescence can be controlled by senolytics and immunotherapy, as well as by improving imaging methods to detect and confirm senescence both at the cellular and systemic levels. We go into further detail on each of these features below. Atlas of Senescent Cells The development of an Atlas of Senescent Cells is a crucial necessity for the research given the significant variability of senescent cells and the notion that they represent a continuum of states. To differentiate between acute and chronic senescent states across the course of a person's lifespan and across developmental timelines, a thorough characterization of these cells in multiple tissues using spatiotemporal resolution is required. Single-cell transcriptomics, genomes and epigenomics, proteomics, metabolomics, and spatial profiling should all be a part of the multimodal mapping efforts. In part of this effort, a "taxonomy" of senescence might be created and annotated to define the host's age, the tissue or cell from which it originated, the causes of senescence, and other characteristics. For this attempt, artificial intelligence and computer methods for large-scale data analytics will be essential. Despite the need for strategic collaboration with other organisations already active in this field (such as HCA, HuBMAP, and HTAN), most cellular atlas datasets at this time may not include senescent cells due to their scarcity and unique appearance. The community as a whole might gain from the creation of a unified platform for data ingestion, processing, and display across various atlasing initiatives.

III. BIOMARKERS

There is a shortage of knowledge regarding the cells that senesce in vivo. The ability to generate a collection of "gold standard" biomarkers to detect senescent cells in vivo, based on both molecular and physiological features, is a crucial component of creating a comprehensive atlas of cellular senescence. SASPs, metabolic fingerprints, and cell surface and intracellular markers are a few examples, but not all. These indicators would also enable a more accurate description of senescence and create a common language for the society. The creation of an exhaustive atlas will make it easier to complete this difficult but crucial phase. The difficult topic of whether senescent cells accurately represent human states in animal models is still open. To investigate, benchmark, and computationally simulate the causative effects of various genetic or pharmacological perturbations, however, a suitable, quickly ageing, but relevant model system is required. Other systems could include human organoid and explant platforms for lineage tracing, characterization of senescent cell accumulation, and their features across different timescales and disease contexts to provide a baseline resource for the community in addition to animal models (e.g., murine, non-human primate). These systems will be essential for comprehending the vulnerabilities of various senescent cell types, which probably differ depending on the tissue of origin, the cell type within a given tissue, and the host's health. Using animal models would also make it possible to quantify the long-term impacts of senescent cells in various tissues as well as the consequences of their removal on the long-term host's physiology. To use immunological treatment and senolytics to remove the cells, it is critical to identify these various vulnerabilities. Finally, these systems would make it possible to evaluate the role of immune cells in regulating the survival and persistence of senescent cells as well as the use of immunotherapy as a complementary treatment to senolytic drugs. Future studies will also require computational and/or predictive attempts to model senescence in vivo in addition to experimental systems. Computational modelling could be useful in

the near future for predicting the occurrence and identifying such cells in health and in other pathological diseases, as it may take a lot of work and time to create a comprehensive atlas of all tissue-resident senescent cells. Tools for Visualization and Imaging Senescent cell tracking and identification in vivo are extremely challenging undertakings, but they are required to validate results from the atlas and biomarker development initiatives. As a result, there is a need for better methods and instruments to visualise individual senescent cells as well as the burden of senescent cells, such as whole-body live imaging (for example, non-invasive imaging such as computer tomography or PET) to identify a specific metabolic reaction specific to senescent cells as well as dynamic changes brought on by therapeutic interventions. Further, there is still debate over the organisation of senescent cells in vivo, with experimental data favouring either clumped or mosaic models. As a result, longitudinal imaging of senescent cells for lineage tracing in vivo is crucial and would change the course of research in this area. Additionally, imaging using intracellular metabolic alterations, cell-surface biomarkers, or other variations is advised. The visualisation tools that must be created for the scientific community's usage in showing imaging data must be taken into account. To accomplish these goals, computational biologists, experts in artificial intelligence, and modellers must collaborate with data producers.

IV. SENESENCE REGULATION AND VALIDATION

It will be necessary to validate the biomarker panels, model systems, and imaging technologies through demonstration projects that generate, remove, or modulate senescence while analysing the effects of those perturbations on health and disease. For instance, sliced transplant tissues from healthy and diseased donors could be used to assess the effects of combining senolytic medicines with additional geroprotectors or disease-specific medications. Senescent cells and the immune system interact, therefore it is important to take this into account when employing immunotherapy to remove them or when activating the host immune system (for example, by using a combination of senolytics and anti-inflammatories). For instance, after CAR-T cell therapy, T cells experience cellular depletion, which is somewhat comparable to senescence. Research in this field may aid in the treatment of senescence-related diseases as well as cancer (Amor et al., 2020). Finally, to demonstrate and validate any senolytic technique in a pertinent experimental model system, lineage tracking and real-time monitoring of clearing as a result of perturbing senescent cells by senolytic therapies will also be key capabilities. Finally, a one-size-fits-all strategy may not be effective in all healthy or pathological circumstances since different senescent cells may respond differently to various senolytic techniques.

As per the opinion from researchers, the moment is appropriate to start addressing the causes and effects of cellular senescence as well as investigating methods to recognise, track, and disturb senescent cells in pertinent experimental model systems. The community can use a senescence cell atlas to investigate acute and chronic senescent states across developmental timescales and lifespan in normal physiological and pathophysiological conditions, but the creation of multimodal maps of senescent cells in different tissues is crucial to this quest.

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