Senescence in Aging, Within the Brain and Other Diseases: Mechanisms and Interventions

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Abstract

Aging, shifting demographics, and lifestyle changes are some of the underlying factors contributing to an increase in the incidence and prevalence of age-related disorders. Brain health is correlated with cellular senescence and is an important indicator of physiological aging and several age-related diseases. Examining the current state of knowledge of the underlying mechanisms of senescence as well as prospective therapeutic modalities concerning aging and age-related diseases is thus crucial. The senescence-associated secretory phenotype (SASP) of senescent cells (SnCs) results in a secretome, which is primarily composed of growth factors, cytokines/chemokines, and extracellular matrix (ECM) remodeling proteins secreted by the arrested cells. Increasingly, research suggests a causative role of senescence in various diseases such as osteoporosis, neurodegenerative diseases, cardiovascular diseases, and metabolic dysfunction, among others. SnCs promote age-related diseases by affecting the differentiation and proliferation of stem cells. They do so, in part through disruption of the Wingless-related integration site (Wnt) signaling pathways and Yes-associated protein and its ortholog transcriptional coactivators with a PDZ-binding domain (YAP/TAZ) transcriptional regulation, affecting tissue regeneration and a decreased ability for the body to rejuvenate. Senescent cell-induced immune system dysregulation, e.g., immunosenescence, as well as senescent cell-secreted substances also cause persistent, low-grade inflammation in organisms known as inflamming, which accelerates aging and results in tissue damage. During age-related senescence, key chromatin structural changes take place in the cells that affect nuclear transport, causing genomic instability, changes in nucleosome positioning, post-translational modifications of histones, global histone loss, etc. Elimination of SnCs using senolytics by targeting cellular and molecular pathways has emerged as a potential therapeutic strategy for delaying aging and improving age-related dysfunctions including brain diseases.

Introduction

Population aging together with shifting demographics and related lifestyle alterations are among the underlying causes of an increased incidence and prevalence of age-related disorders. Such disorders include non-communicable diseases, which can pose severe problems, especially in older people. The greater likelihood of disease severity and frequency in old age increases the burden of healthcare costs, including out-of-pocket expenses in the absence of any employer-sponsored health insurance.1,4 Such expenses are further compounded by the rapid advancement of public health in most countries around the world. Global life expectancy is expected to increase, contributing to a significant rise in the number and proportion of older persons worldwide.5,6 It is predicted that between 2015 and 2030, the number of individuals aged 60 and above will rise by 56%, reaching 1.4 billion, or the equivalent of 16.5% of the world’s population.7 An aging demographic augments the pressure on public health care systems to adapt to meet with increasing demand for age-related care and treatment of diseases, underscoring the importance of a 2030 agenda for sustainable development, which necessitates fulfillment of all Sustainable Development Goals (SDGs).8,9 Concerning health, SDGs include encompassing all segments of society, with a special emphasis on the most vulnerable, including the older population.

Keywords: Aging; Senescence; Neurological diseases; Brain disorders; Public health; Senolytics.

Abbreviations: AD, Alzheimer’s Disease; CVD, cardiovascular diseases; CNS, central nervous system; ECM, extracellular matrix; GBM, glioblastoma multiforme; ML1, mixed lineage leukemia gene; mtDNA, mitochondrial DNA; MSCs, mesenchymal stem cells; NE, nuclear envelope; NPCs, nuclear pore complexes; NSCs, neural stem cells; PD, Parkinson’s Disease; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; SIRT1, sirtuin-1; SnCs, senescent cells; TAZ, coactivator with PDZ-binding motif; TBI, traumatic brain injury; TGF-β, transforming growth factor-β; Wnt, Wingless-related integration site; YAP, Yes-associated protein.

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Older persons contribute significantly to social capital

The United Nations (UN) strongly recognizes the diversity of older persons in terms of their capabilities and needs, including wisdom in the form of social capital that they bring to the workforce, and needs that are shaped by their age, including accelerated aging.18 Older persons are often seen as role models and mentors in society, as they have a great deal of experience in their respective fields and provide valuable advice and guidance on difficult issues. Notably, the concept of “old age” is multidimensional, which includes not only chronological age (based on birth date) but also, biological age.11,12 Multidimensional measures reflect the human body’s ability to actively engage in physical activities, which may be affected by factors unrelated to age, like psycho-socioeconomic factors, which often lead to an accelerated aging process that is generally prevalent in low-and-middle-income countries, and results in premature aging.13

Brain health is a critical indicator of aging and aging-related diseases

Significantly, multiple aspects of orchestrated physiological brain aging with marked accelerated deterioration of brain function primarily characterize human aging.14–16 Consequently, the prevalence of dementia globally will dramatically rise due to population aging. Therefore, the burden of neurological disorders associated with aging needs to be limited, along with meeting the growing challenges in preserving brain health among the older population in society.

Brain health is a critical aspect of public health management of age-related diseases

The cost of the economic burden for people with age-related neurological disorders, resulting in physical disability, cognitive or mental disorders, and social dysfunction could be enormous.17,18 Moreover, considering the link between brain health and wider health determinants, public health policies in any country obligate immense importance for maintaining the brain health of the population.19,20 Indeed, brain health is critical for physical and mental health, social well-being, productivity in the workplace, and creativity. In recent times, it is important to highlight that apart from causing severe damage to the physical and mental health of many people, fortunately, the COVID-19 pandemic has compelled a large number of professionals to embrace virtual working environments. Such environments necessitate an enormous amount of adjustments in terms of creative thinking, generating increased opportunities for transdisciplinary collaboration among neurologists, psychiatrists, psychologists, neuro- and socio-behavioral scientists, policymakers, as well as citizens. Such cross-disciplinary interconnectedness fosters brain health.21,22

Between health and diseases, cellular senescence is tightly regulated

Simplistically, senescent cells (SnCs) are cells that have stopped dividing.23–27 In essence, senescence is a physiological process in the form of a cellular response characterized by permanent growth arrest (cell cycle arrest), as a tumor suppressive stress response, to prevent the possible occurrence of cancer cells in older age. Cell cycle arrest occurs in part due to the ineffectiveness of DNA repair mechanisms, among others, such as other phenotypic changes that distinguish senescent cells from young cells, which include a proinflammatory secretome, associated with aging phenotype.28–30

Senescence, as opposed to being a static endpoint, seems to be the outcome of a succession of evolving and phenotypically varied cellular states that emerge following the initial growth arrest. Given the wide range of processes in which senescence is involved, including embryonic development, wound healing, tissue repair, cancer and aging, it is unclear if the characteristics of the SnCs involved in these processes are fundamentally distinct.31 For instance, acute senescence appears to be primarily involved in tightly controlled biological phenomena (such as wound recovery, recovery from tissue damage, and embryological growth) to stop the growth of specific cells. On the other hand, persistent senescence typically results after chronic stress on cells leading to cell cycle arrest. Moreover, chronic senescence seems to affect all cell types and is not programmed. Some progress has been made in understanding cellular senescence during the last few decades. Researchers have made significant progress in our understanding of the molecular mechanisms underlying senescence because of the finding of the cell replicative senescence phenomena in human diploid fibroblasts 60 years ago, as shown in Table 1.32–53

Characteristics of SnCs

SnCs are unable to divide in the presence of nutrients and growth-stimulating mitogens, despite being viable and metabolically active. SnCs’ senescence-associated secretory phenotype (SASP) permits extensive signaling from the non-proliferating cells to the external environment, resulting in a secretome, which is primarily made up of growth factors, cytokines/chemokines, as well as proteins that remodel the ECM and are secreted by the arrested cells.30,54–56 SnCs typically share signature features like enlarged and flat morphology.56 Members of the p53/p21 confer their non-proliferating ability together with the networks of p16/RB tumor-suppressor that serve to stop proliferation and contribute to the longevity of the senescent condition.57,58

SnCs are linked to embryonic development as well as a wide range of human diseases

Apart from its role in embryonic development, senescence has been shown to play key roles in fibrosis and wound healing.59,60 For example, SnCs prevent liver fibrosis in mice by activating hepatic stellate cells, preventing their proliferations so that ECM cannot be deposited in the fibrotic scar in response to liver damage.61 Additionally, similar to apoptosis, cellular senescence also contributes to embryonic development, in a developmentally programmed manner. Moreover, accumulating research tends to suggest a causative role of cellular senescence in a multitude of diseases such as osteoporosis, frailty, osteoarthritis, https://www.sciencedirect.com/topics/medicine-and-dentistry/frailty/pulmonaryfibrosis, https://www.sciencedirect.com/topics/medicine-and-dentistry/pulmonary-fibrosishttps://www.sciencedirect.com/topics/medicine-and-dentistry/nephropathyrenal diseases, hepatic steatosis, neurodegenerative diseases, cardiovascular diseases, and metabolic dysfunction.62–77 Therefore, given the key roles of senescence in a wide range of age-related diseases, it is crucial to look at both general and underlying disease-specific mechanisms contributing to the etiology and progression of each disease.

Cellular senescence in aging and age-induced diseases: the underlying mechanisms

Simplistically, single-cell dysfunction can potentially harm the...
el inception of SnCs can potentially ameliorate age-induced cell senescence, hastening the aging process. Therefore, it is likely that the regeneration and restoration may be affected by cellular senescence.

Table 1. History of Cellular Senescence and Senotherapy: Some Fascinating Advancements in This Area are Presented

<table>
<thead>
<tr>
<th>Year</th>
<th>Key Finding(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1961</td>
<td>Discovery of replicative senescence in human diploid fibroblasts.</td>
</tr>
<tr>
<td>1965</td>
<td>It is hypothesized that cellular senescence accelerates aging by impairing tissue repair ability.</td>
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<tr>
<td>1970</td>
<td>The age of the donor being biopsied and cell replicative life span are connected.</td>
</tr>
<tr>
<td>1980</td>
<td>Replicative senescence is linked to considerable variation in each individual cell’s capacity to divide both within the population as a whole and within a subpopulation of a clonal cell.</td>
</tr>
<tr>
<td>1995</td>
<td>Discovery of SA-ß-Gal as a marker of senescent cells.</td>
</tr>
<tr>
<td>1996</td>
<td>The master regulator of senescence cell cycle arrest, CDK inhibitor P16&lt;sup&gt;INK4A&lt;/sup&gt; has been identified.</td>
</tr>
<tr>
<td>1999</td>
<td>In terms of protection from external natural hazards, cells arising from species of longer life spans are typically better protected than cells from species of relatively shorter life spans.</td>
</tr>
<tr>
<td>2002</td>
<td>In human atherogenic plaques, senescent endothelial cells are seen.</td>
</tr>
<tr>
<td>2004</td>
<td>Use of SA-beta-gal and P16&lt;sup&gt;INK4A&lt;/sup&gt; as biomarkers to identify SnCs in aged primate and rodent tissue.</td>
</tr>
<tr>
<td>2007</td>
<td>Stochastic heterogeneity in telomere-driven replicative senescence.</td>
</tr>
<tr>
<td>2008</td>
<td>Identification of SASP in SnCs.</td>
</tr>
<tr>
<td>2010</td>
<td>The primary function of DNA damage response (DDR) for maintaining the state of profound cellular senescence.</td>
</tr>
<tr>
<td>2011</td>
<td>Senolysis; the elimination of senescent cells, extends the lifespan of mice.</td>
</tr>
<tr>
<td>2014</td>
<td>Many senescent cells are highly resistant to the induction of apoptosis.</td>
</tr>
<tr>
<td>2015</td>
<td>It turns out that senescent cells are advantageous for growth, development, wound healing, and tissue repair.</td>
</tr>
<tr>
<td>2016</td>
<td>Discovery of the senolytic properties of BCL-2 family inhibitors. Atherosclerosis has been demonstrated to be inhibited by SnCs clearance using genetic and pharmacological methods.</td>
</tr>
<tr>
<td>2017</td>
<td>The therapeutic benefit of senolysis in the management of osteoarthritis has been demonstrated.</td>
</tr>
<tr>
<td>2019</td>
<td>Senescent cells consist of non-canonical MHC molecule like human leukocyte antigen E (HLA-E) that binds to inhibitory receptors present on NK cells along with CD8 cells, resulting in reduced immune clearance. Senolysis has been shown to improve the course of diabetes resulting from accelerated pancreatic beta-cell aging.</td>
</tr>
<tr>
<td>2020</td>
<td>An analysis of 279 human genes implicated in cellular senescence reveals that these genes statistically overlap with genes associated with short life spans rather than those associated with long life spans.</td>
</tr>
</tbody>
</table>

whole multicellular organism. Thus, nature uses a two-pronged approach to control such events. First, a malfunctioning cell can recognize its dysfunction and limit its ability to grow. Second, fully functional healthy cells rely on their ability to recognize the malfunctioning cell and destroy it. Thus, cellular senescence essentially makes use of these inherent cellular properties to keep human health in good shape and mitigate diseases. For example, when a cell recognizes its dysfunction, it induces a permanent inhibition of the cell cycle by causing cell cycle inhibitors like p16<sup>INK4A</sup> and p21<sup>CIP1</sup> to become active, followed by imparting signals to the immune system, that can then recognize and destroy the often-unwanted SnCs. Aging is associated with the progressive building up of SnCs in the body, which further promotes accelerated physiological aging and age-induced dysfunctions. SnCs may accumulate with age due to a variety of factors, including an aging immune system that fails to effectively remove them from tissues, ineffective SASP released by SnCs, a combination of both, and other factors that are currently unknown. Furthermore, tissue regeneration and restoration may be affected by cellular senescence, hastening the aging process. Therefore, it is likely that the elimination of SnCs can potentially ameliorate age-induced cellular dysfunction and prolong life span, contributing to a better quality of life in old age.

**Senescence promotes age-related diseases by affecting the maturation and growth of stem cells to further exacerbate disease pathology**

Multipotent cells that can self-renew and differentiate are known as mesenchymal stem cells (MSCs). Although there is growing evidence of the therapeutic efficacy of MSCs observed in a variety of clinical settings, MSCs eventually become incapable of regenerating themselves as they get older, which increases cellular dysfunction. Prior to going senescent, MSCs only experience a limited number of population doublings as opposed to endless growth. As a result, it is generally speculated that the age of stem cells and replicative senescence are the primary causes of age-related malfunction of stem cells. Among other mechanisms, physiological levels of reactive oxygen species (ROS) are necessary for cellular growth and maturation, although abundance can potentially elicit senescence in many tissues throughout the body, including in stem cells. How ROS contributes to cellular senescence has been ex-
tensively reviewed elsewhere.\textsuperscript{89}

**The role of Wingless-related integration site (Wnt) Signaling in stem cell senescence**

It is established that Wnt signaling regulates cell proliferation and cell polarity, along with many critical biological processes.\textsuperscript{90, 91} Significantly, stem cell maintenance and proliferation depend on the Wnt signaling pathway. Yes-associated protein (YAP) and its ortholog transcriptional coactivators with a PDZ-binding domain (TAZ) can be regulated by both canonical and noncanonical Wnt signaling.\textsuperscript{92, 93} YAP/TAZ proteins translocate to the nucleus after activation, resulting in a complex formation with transcriptional enhanced associate domain transcription factors, to regulate critical cellular functions like cell proliferation and differentiation.\textsuperscript{94} For instance, in the intestine, YAP has been shown to induce epithelial regeneration.\textsuperscript{94} SnCs can affect stem cell differentiation and proliferation by disrupting Wnt signaling pathways as well as YAP/TAZ transcriptional regulation. The disruption resulted in impaired tissue regeneration and decreased ability of the body to rejuvenate itself over time, presumably by affecting the self-renewal and/or multi-differentiation capability of tissue-resident progenitor and stem cells.\textsuperscript{95, 96}

**Paracrine roles of senescent stem cells in age-related diseases**

There is mounting evidence that dysfunction or unregulated activation of senescence contributes to tumor advancement and malignancy.\textsuperscript{97, 98} In numerous cancer types, including breast cancer, homing of MSCs to tumors has been documented.\textsuperscript{99} By attracting and differentiating additional stromal cells, increasing the proliferation, motility, and invasiveness of cancer cells, and remodeling the ECM to facilitate cancer cell invasion and metastasis, proinflammatory molecules and degrading enzymes in the SASP contribute to the progression of cancer.\textsuperscript{100} For instance, senescent MSCs have been shown to promote the proliferation and metastatic spread of breast cancer cells, modulated by SASP components that mediate through the paracrine signaling, altering ECM and tumor microenvironment, resulting in favorable milieu for tumor progression.\textsuperscript{101} Therefore, a thorough understanding of how paracrine factors from stem cells slow down or stop aging-induced diseases, such as brain disorders, is essential for their future clinical use. For example, adipose-derived mesenchymal stem cells have a strong paracrine effect because they can release a variety of cell growth factors and chemokines that promote angiogenesis, endogenous stem cell activation, inflammation control, and wound healing.\textsuperscript{102} In addition, exosomes produced and released by stem cells are increasingly recognized as essential components of intracellular communication, metabolic clearance, tissue regeneration at distant sites, and the immunological response.\textsuperscript{103, 104} As such, they may play crucial roles in reducing the adverse effects of aging-related brain disorders.

**Cellular senescence mediates brain aging and exacerbates brain-related diseases by affecting stem cells, and transplantation of stem cells can potentially ameliorate diseases**

Aging is a complex phenomenon that not only affects many aspects of the human body and disease development but can also have detrimental effects. For instance, on the progression of brain disorders, in part, through alteration of the quantity and quality of endogenous stem cells such as neural stem cells (NSCs).\textsuperscript{105–108} Resident stem cells that maintain a self-renewal and proliferative capacity to produce new neurons, astrocytes, and oligodendrocytes over time can be found in the central nervous system (CNS) of adults.\textsuperscript{109} The ability of CNS stem cells to self-renew and regenerate themselves decreases with aging, leading to a progressive loss of function. Physiologically aging is therefore associated with a progressive loss of function and a decline in the self-renewal and regenerative capacities of CNS stem cells.\textsuperscript{109} For example, NSCs found in neurogenic niches, undergo progressive loss of proliferation along with differentiation and maturation with the advancement of age, primarily due to a progressive hostile microenvironment causing extensive DNA damage.\textsuperscript{110} Additionally, many studies seem to suggest the importance of donor age negatively affecting the quality of stem cells in terms of differentiation, in vivo or ex vivo expansion, and immunogenicity, together with a noticeable loss of reprogramming efficiency of stem cells to be transplanted.\textsuperscript{110, 111}

**Aging neural stem cells underlie the development of brain diseases**

The quality and quantity of NSCs can be significantly influenced by age-related cellular senescence. Over time, NSCs lose their capacity to enter the cell cycle effectively. p16\textsuperscript{INK4A}, a marker for senescence and a negatively regulates cell cycle, is highly elevated with aging in the brain comprise of subventricular zone, which may be responsible for the concurrent drop in new neuron development mediated by the inhibition of cell cycle of NSCs and NPCs.\textsuperscript{112–114} It is likely that inhibition of this cell cycle is mediated by p16\textsuperscript{INK4A} causing senescence. Indeed, p16\textsuperscript{INK4A} overexpression leads to relicative senescence (irreversible loss of cell proliferation and altered cell behavior) in ESC-derived NSCs.\textsuperscript{113, 114} On the other hand, NSCs expansion and cognitive improvement can be facilitated by the induction of pro-cell cycle regulators including the Polycomb family member BMI-1 (PCGF4) and cyclin-dependent kinases.\textsuperscript{115, 116} BMI-1 is known to be a transcriptional negative regulator of cell cycles, and overexpression of this gene in hippocampal NSCs induces self-renewal.\textsuperscript{117} Furthermore, a transgene delivered by lentivirus in vivo boosted hippocampus neural growth and reversed some facets of age-linked cognitive deterioration in older mice (16-month-old pups) by co-overexpressing cyclin D1 and CDK4 in the NSCs present in the hippocampus.\textsuperscript{118} Furthermore, the removal of SnCs that express p16\textsuperscript{INK4A} delays the onset of age-related diseases.\textsuperscript{119}

**The role of neural stem cells in the management of cerebrovascular diseases**

One of the main mechanisms behind many cardiovascular diseases (CVD) is cellular senescence.\textsuperscript{120} A distinct secretory phenotype, activation of tumor suppressor pathway, a persistent growth arrest, and resistance to apoptosis are all characteristics of the stress or damage response associated with senescence.\textsuperscript{121–123} CVD, such as stroke is the major etiology of prolonged morbidity and the second greatest cause of death globally.\textsuperscript{124} However, to date, there are only two Food and Drug Administration (FDA)-approved therapies; tissue plasminogen activator, and thrombectomy. The usefulness of such therapies is limited by the fact that they can only be applied to acute patients, encompassing only a small number of CVD patients.\textsuperscript{125–127} Additionally, the majority of recent therapeutic trials have mostly aimed to manage apoptosis, immunological and inflammatory responses, and excitotoxicity—late-onset secondary damage mechanisms—with little to no success. Interestingly, in addition to NSCs’ ability to repair tissue damage in the initial stag-
es of disease development, they also have the ability to respond continuously to environmental cues, along with the ability to secrete paracrine growth factors and signaling factors in the right quantities. This results in a tailored long-term cellular response against stroke-related injuries, allowing NSCs to slow the progression of early cerebrovascular insult. This is in sharp contrast to conventional drug therapies used for the treatment of stroke. Thus, despite the numerous challenges associated with repairing neural damage, such as the fact that neurons are highly differentiated terminal cells, which restricts their capacity for regeneration, the likelihood that they secrete less than optimal levels of neurotrophic substances like BDNF (brain-derived neurotrophic factor) and the overproduction of inflammatory substances like cytokines, in principle, NSCs could provide a novel and effective alternative therapy for the management of stroke. The promotion of extension and growth of synapses, which results in synaptic plasticity and the regeneration of axons, together with relief from the creation of brain scars at the location of injuries are among the potential benefits of NSC transplantation in stroke patients.

Neural stem cells can improve brain functions after catastrophic head injury

One of the most common reasons for hospitalization, disability, and death worldwide is traumatic brain injury (TBI). TBI affects about 10 million people annually and results from extensive brain tissue damage brought on by a variety of external forces, including direct head impacts from car accidents, blast waves from explosions, etc. Recent studies point to DNA damage-induced cellular senescence as a potential cause of sequelae associated with mild TBI. Post-TBI complications such as visual impairment, long-term cognitive dysfunction, hearing loss, etc., can affect patients and their families to a great extent. The underlying mechanisms of TBI are manifold including degradation of the blood-brain barrier; induction of marked neural inflammation, along with impaired neuronal degeneration. A growing body of evidence appears to point to a critical role of NSCs in hippocampus-induced learning and memory processes, as well as in the proper functioning of olfactory systems in the brain. Additionally, following TBI, greater neurogenic regeneration capacity has been observed in a variety of animal brain damage models as well as in a limited number of human studies. That said, solid evidence of neurogenesis induced by TBI in the human brain is limited, to date, primarily due to hurdles of obtaining human brain samples, together with inherent technical difficulties, in order to be able to effectively address the detailed underlying mechanisms of de-novo neurogenesis through retrospective birth dating of NSC in patients. Further challenge is associated with the limiting amount of endogenous NSCs that demands supplementation of exogenous NSCs through transplantation to the damaged brain tissue in a targeted manner for successful post-traumatic nerve cell regeneration. Apart from replacing the damaged neural cells, it is conceivable that the secretion of exogenous stem cells can further alleviate the proinflammatory reaction at the injury site to assist with the overall healing process, and to improve brain health post-injury.

The potential impact of MSCs on cellular senescence-induced neurodegenerative disorders

It is speculated that cellular senescence contributes significantly to the physiological aging process and aging-induced diseases, such as Alzheimer’s Disease (AD) and Parkinson’s Disease (PD). Senescent astrocytes, microglia, endothelial cells, and neurons have been seen in the brains of AD patients and AD animal models. AD, which is characterized by the accumulation of β-amyloid peptides in the ECM between neurons, also known as amyloid plaques, and the development of neurofibrillary tangles within the cells as a result of tau protein hyperphosphorylation in neurons, is the primary cause (50–70%) of dementia cases worldwide. The aforementioned factors cause progressive neuronal loss due to neuroinflammation and oxidative stress. In 2015, nine individuals with mild to moderate AD underwent the first phase of a clinical trial using MSCs from human umbilical cord blood. Due to the lack of any adverse reactions observed in the patients, MSCs were stereotactically injected into the hippocampus and anterior hippocampus, indicating the viability and safety of the stem cell administration. Since that time, a variety of clinical trials are still being conducted on AD patients and are registered on ClinicalTrials.gov under the trial numbers NCT01547689, NCT02672306, NCT02054208, and NCT02600130.

On the other hand, substantia nigra’s dopaminergic neuron loss in PD patients characteristically manifests as a typical movement problem. In theory, it might be possible to convert MSCs into astrocytes and neuron-like cells in the culture before transplanting those cells back into the patients. As an alternative, the astrocytes in PD patients can be transdifferentiated (direct differentiation) to produce dopamine-releasing neurons endogenously or through an intermediate formation of NSCs, by adjusting the environmental cues, which regulate the origin of neurons by specifying a targeted developmental pathway. Having said that, to fully understand NSCs or MSCs’ potential in treating neurodegenerative illnesses, more research is required in this field.

The function of cellular senescence in the growth and progression of brain tumors

Cellular senescence in cancer is brought on by a variety of stressors, such as DNA damage, oncogene activation, therapeutic drugs, or reactive oxygen species. The primary malignant brain tumor that affects adults most frequently is glioblastoma multiforme (GBM). However, it is still resistant to systemic therapy. Senescent cell removal has become a potentially effective new cancer treatment strategy. SnCs are identified in patients and mouse GBMs. After partial elimination of p16INK4A-expressing malignant SnCs, which make up less than 7% of a tumor, female mice with GBM have improved survival. By integrating single-cell and bulk RNA sequencing, immunohistochemistry, and genetic knockdowns, this study identifies nuclear factor erythroid 2-related factor 2 transcription factor as a determinant of the senescent phenotype.

The potential benefits of stem cells and mechanisms of action in the management of brain tumors

Interestingly, adult stem cells may potentially be a powerful tool and could offer a great therapeutic resource for the management of brain tumors. NSCs and MSCs both migrate extensively towards and could offer a great therapeutic resource for the management of brain tumors. The potential benefits of stem cells in the management of brain tumors include their ability to target tumors effectively, enabling the delivery of cytotoxic substances and signals, such as apoptosis-inducing proteins, anti-angiogenic factors, nanoparticles, oncolytic viruses, cell cycle modulators, and inducers of cellular differentiation, among others, to the tumour cells while sparing healthy cells. The immunomodulatory qualities of the transplanted stem cells may suppress tumor growth by altering the tumor microenvironment in addition to their potential impact on cancer stem cells; an area that warrants further research.
further investigation.\textsuperscript{153-156} Prior to being effectively translated into clinical settings, the adoption of relatively new therapeutic technologies, such as genetically engineered stem cells that give anti-tumor capabilities, would necessitate a more thorough understanding of underlying mechanisms. Nevertheless, human tissue-derived MSCs are generally regarded as one of the most promising approaches in delivering therapeutics and preventing the critical loss of cells in the brain, due to the abundance of MSCs available, especially from adipose tissue and/or bone marrow, together with easy isolation and \textit{ex vivo} expansions for clinical use and fewer ethical concerns. Moreover, recent studies tend to show that transplanted MSCs can even disrupt the blood-brain barrier and target damaged tissue, where they can exert therapeutic effects through multidirectional differentiation, execute paracrine effects along with the release of extracellular vesicles, and even transfer mitochondria to the damaged neurons through tunneling nanotubes, improving syntactic function and enhancing higher-order cognitive functions.\textsuperscript{157,158} However, to produce fully functional exogenous sources of neural cells that can be easily grafted into damaged neural tissue in the face of hostile environments caused by insults such as brain injury, more research is required to precisely decipher the \textit{in vivo} mechanisms that guide NSC differentiation to functional neurons. Also, more thorough pre-clinical and clinical research is urgently needed to accurately determine the safety and efficacy of stem cell therapy by considering the effects of aging on stem cells and the transplant recipients to preserve brain health and to ameliorate a wide range of brain disorders. In addition to the functional dysregulation of stem cells mediated by cellular senescence, it would be interesting to explore the specific immune and molecular pathways that drive age-related diseases.

\textbf{SnCs-mediated dysregulation of the immune system aggravates age-related diseases by inducing immunosenescence and inflamming}

The progressive decline of the physiological characteristics and dysregulation of the immune processes with age, as a result of immune cell senescence, which is known as immunosenescence, is believed to cause reduced elimination of SnCs in the body.\textsuperscript{159,160} SnCs accumulate as a result of decreased senescent cell clearance and surveillance due to the lower numbers of immune cells, such as macrophages together with their dysfunctions. Additionally, aging causes an imbalance between immunological and inflammatory responses that lower immune response effectiveness and produce an immunosuppressive microenvironment.\textsuperscript{161} As a compensatory response, inflammatory mediators like regulatory T (Treg) cells and M2 macrophages, which are immunosuppressive, while promoting myelopoiesis by releasing immunosuppressive substances like transforming growth factor-β (TGF-β), ROS, and interleukin-10 (IL10).\textsuperscript{162,163} The promotion of growth and activation of M2 macrophages and Treg cells are then further aided by IL10.\textsuperscript{164} In fact, a few of these substances inhibit specific immune system components and accelerate immunosenescence. TGF-β, for example, may inhibit helper T (Th) cell development, reduce the cytotoxicity of CD8 T cells and NK cells, and diminish the immunological response of B cells, all of which can result in immune paralysis, a chronic immune system dysfunction.\textsuperscript{165,166} Significantly, immunosenescence along with secreted factors from SnCs, additionally results in a chronic low-grade inflammatory response known as “inflamming” in organisms, which promotes aging and causes tissue damage.\textsuperscript{167,168} The factors released from SnCs such as proinflammatory cytokines and chemokines normally attract and induce immune cells for the destruction of SnCs. However, an impaired immune system fails to resolve these inflammatory signals due to immune cell senescence, causing inflammation to be further intensified together with the establishment of a chronic inflammatory cycle, resulting in a greater accumulation of SnCs. Chronic inflammation can interfere with physiological functions, and play a role in the development and/or progression of diseases such as atherosclerosis, type II diabetes, and osteoporosis. Furthermore, it is conceivable that the aging brain might reduce the efficacy of transplanted stem cells due to increased neuroinflammation associated with aging.\textsuperscript{169,170}

\textbf{Immunosenescence is exacerbated by age-related telomere shortening}

The immune system is particularly vulnerable to the effects of aging because its cells adaptively respond to immunological challenges with massive proliferation and constriction. Telomeres have drawn attention since they have proven to be a great indicator of proliferative history and replicative reserve.\textsuperscript{171,172} Age-related declines in lymphocyte telomerase activity and average telomere length are both observed in the immune system.\textsuperscript{173} Telomere shortening might result in DNA deterioration and cell cycle arrest, which would impair immune cell function and make pathogen removal less effective.\textsuperscript{174} Telomerase affects immunological activation, differentiation, and immunosenescence by regulating critical immunomodulatory proteins such as NF-κB and β-catenin.\textsuperscript{175} The immune response is negatively impacted by the downregulation of telomerase activity, which also activates ageing cells to exacerbate age-related immune dysfunctions.\textsuperscript{176}

\textbf{Immunosenescence is exacerbated by an age-related metabolic decline}

In the course of research, it has been clear that nutritional metabolism has a significant impact on immune function. Age causes a decline in glycolytic metabolism as well as aberrant mitochondrial energy metabolism, which affects T and B cell activation.\textsuperscript{177} Co-enzyme NAD+ catalyzes metabolic processes in the cell and transforms into NADH. Age-related decreases in NAD+ are caused by a decrease in production. Furthermore, age-related decreases in NAD+ metabolism activate NLRP3 inflammasomes, which may be the cause of inflammatory disorders.\textsuperscript{178} Inflammatory and SnCs seen in aged tissue contribute to metabolic failure, exacerbating the immunological dysfunction linked to immunosenescence.\textsuperscript{179}

\textbf{Chromatin architectural changes regulate aging and exacerbate age-related diseases}

During physiological aging and senescence, prominent chromatin structural changes take place resulting in alterations: (1) in the nuclear envelope that affects nuclear transport; (2) genomic instability such as DNA damage and telomere attrition; (3) changes in nucleosome positioning; (4) post-translational modifications of histones; (5) global histone loss together with loss of heterochromatic regions and; (6) chromatin spatial interaction changes together with large-scale chromatin rearrangements.\textsuperscript{180–189}

\textbf{Nuclear envelope dysfunctions lead to aging-related diseases}

Aging affects nuclear transport by disrupting the structure and function of the nuclear envelope (NE). As we age, NE becomes...
more fragile and less effective at keeping nucleic acids and proteins within the tight compartment of the nucleus, since in eukaryotic cells the NE serves as a communication link between the cytoplasm and nucleus.\textsuperscript{190} The nuclear lamina, a bilayer membrane, and the nuclear pore complexes (NPCs) make up the majority of the NE dynamic cellular compartment and are primarily composed of three components: the nuclear lamina, a double membrane, and the NPCs.\textsuperscript{191} The double membrane, which is made up of the inner nuclear membrane and the outer nuclear membrane, is divided by the perinuclear space. When these two membranes link at various points, supramolecular structures called NPCs are produced. These structures act as channels for the selective import and export of macromolecules. These protein complexes are structurally made up of nucleoporins (Nups), which are essential functional elements of the diffusion barrier and transport channels. When any of the three components of NE become damaged or lose their integrity with age, NE becomes dysfunctional and eventually ruptures, leading to aberrant nuclear transport. Importantly, a defective NE can impair the transport of proteins and other molecules, including transcription factors, across the NE, resulting in flaws in DNA repair mechanisms, changing the expression of numerous age-related genes, and causing cellular senescence or even cell death.

**Genomic instability associated with aging promotes aging-related diseases**

Endogenous DNA damage, especially DNA double-strand breaks, is considered a major marker of genomic instability.\textsuperscript{192} As a compensatory response, when DNA is damaged, the DNA damage response and cell cycle checkpoint pathways, such as the p53/p21 and p16\textsuperscript{INK4a}/pRb pathways, are activated to block the cell cycle and prevent the transmission of damaged genetic material to progeny cells.\textsuperscript{193,194} Importantly, previous studies seem to suggest that compared to the general population, centenarians exhibit fewer somatic and germ cell mutations, which suggests that their DNA repair mechanisms are more effective at maintaining genomic stability, underscoring its importance in age-related diseases. Nuclear DNA damage foci that persist has been observed in SnCs.\textsuperscript{195} This is further compounded by the fact that in addition to DNA damage, mitochondrial DNA (mtDNA) is highly susceptible to age-related DNA damage, as it contains only exons together with other histones, making them key regulators of nucleosome dynamics, succinylation, and malonylation have the potential to change the interactions between histone and DNA as well as histone and other histones, making them key regulators of nucleosome dynamics, affecting large varieties of gene expression including aging-related genes.\textsuperscript{203-205} For example, histone methylation and histone acetylation are increasingly being considered prominent histone modification methods by which epigenetic changes are mediated during aging.\textsuperscript{206} These modifications can potentially serve as therapeutic targets in the pursuit of rejuvenation.\textsuperscript{207}

**The role of post-translational modifications of histones comprising of chromatin in age-related diseases**

Although a definite causal relationship has not yet been shown with certainty, posttranslational modifications (PTMs) of histones, whether spontaneous or physiological/pathological, are emerging as significant indicators of aging and aging-related diseases.\textsuperscript{202} The best-studied modifications are acetylation, methylation, phosphorylation, ubiquitylation, and ADP-ribosylation. PTMs are the consequence of chemical changes that can be dynamically added and removed by chromatin-modifying enzymes. These marks, along with other more recently recognized modifications like crotonylation, succinylation, and malonylation have the potential to change the interactions between histone and DNA as well as histone and other histones, making them key regulators of nucleosome dynamics, affecting large varieties of gene expression including aging-related genes.\textsuperscript{203-205} For example, histone methylation and histone acetylation are increasingly being considered prominent histone modification methods by which epigenetic changes are mediated during aging.\textsuperscript{206} These modifications can potentially serve as therapeutic targets in the pursuit of rejuvenation.\textsuperscript{207}

**Epigenetic alterations of heterochromatin and global histone loss mediate aging and associated diseases**

Heterochromatin is further divided into constitutive and facultative types. Constitutive heterochromatin describes stronger heterochromatin domains that are primarily found in telomeric regions and contain transposable elements along with satellite sequences. These areas densely packed constitutive heterochromatin state prevents damaging chromosomal rearrangements that could lead to genomic instability by suppressing double-strand breaks and nonallelic homologous recombination (NAHR), especially during meiosis.\textsuperscript{208} On the other hand, a DNA sequence may be found in euchromatin in one cell but facultative heterochromatin in another.\textsuperscript{209} Reactive oxygen species continuously wreak havoc on cellular genomes through a multitude of mechanisms. There is evidence that higher-order condensed chromatin structures shield DNA from both radiation- and hydroxyl radical-induced DNA double-strand breaks, underscoring the importance of heterochromatin in increasing the need for cellular defense with aging to prevent the induction of oxidative DNA damage. Thus large-scale heterochromatin loss during aging can result in the unwanted transcriptional
activation of aging-related genes together with increased susceptibility to DNA damage. Importantly, loss of heterochromatin also occurs during senescence. SnCs have facultative heterochromatin domains known as senescence-associated heterochromatin foci, which silence genes that typically promote cell division.\textsuperscript{210,211} Additionally, nucleosome loss has been shown to cause global transcriptional upregulation and genomic instability during yeast aging.\textsuperscript{214}

**Spatial chromatin architectural alterations and large-scale chromatin rearrangements confer to aging events**

The arrangement of higher-order chromatin has received a lot of attention lately. With the introduction of high-resolution nuclear microscopy and chromosomal conformation capture (3C) methods, our understanding of chromatin organization has advanced dramatically.\textsuperscript{212,213} The introduction of 3C has additionally provided advanced insight into how alterations of chromatin occur with aging and cellular senescence. ATP-dependent nucleosome remodeling complexes can regulate the nucleosome distribution with aging and cellular senescence. \textsuperscript{221} remodeler ISW2 in budding yeast extends life span in a target of rapamycin (TOR)-independent way.\textsuperscript{215} The nucleosome remodeling and deacetylase that has been linked to aging, is an additional ATP-dependent remodeling complex, albeit its precise molecular mechanism of action is yet unknown.\textsuperscript{216} The link between chromatin arrangement, aging, and the underlying mechanisms of cellular senescence has been investigated recently.

After examining the immunological and molecular mechanisms that underlie age-related diseases, it is critical to consider whether and how therapeutic interventions using pharmacological approaches would stop the emergence and further propagation of age-related diseases.

**The anti-aging properties of senolytics may potentially improve the health of older persons, and prevent aging-related diseases**

Senolytics are substances that can be used to specifically kill SnCs as a result of accumulating research that strongly suggests the primary role senescence in physiological aging and age-induced illnesses in model organisms.\textsuperscript{217-219} Such evidence is in tune with the Geroscience Hypothesis, which contends that by pharmacologically delaying the development or severity of several chronic diseases by targeting fundamental aging mechanisms, common underlying risk factors for these diseases will be reduced.\textsuperscript{220} Two methods are utilized to find senolytics: drug library screening on several senescent cell types in vitro, and senescent cell anti-apoptotic pathways (SCAPs) for drug development.\textsuperscript{221} SnCs have been demonstrated to build up with aging in a variety of tissues and contribute to a wide range of chronic illnesses, including diabetes, cancer, osteoarthritis, and Alzheimer’s disease, among others.\textsuperscript{222} Furthermore, it has been demonstrated that removing SnCs via genetic methods might reduce a number of illnesses linked to senescence, and delay the development of age-associated disorders. As a result, in order to cure a variety of age-related diseases and improve health and longevity, efforts to promote senolyis are therefore a realistic option. According to class, senolytics reported to date are: (1) ABT-263 (Navitoclax), A-1331852, A-1155463, and ABT-737, which are BCL-2 family inhibitors, (2) Inhibitors that inhibit HSP90 such as 17-DMAG (Alvespimycin), Geldanamycin, 17-AAG (Tane

**Senolytics in stem cell rejuvenation**

Senolytics, which selectively eliminate senescent cells, have been found to enhance stem cell activity and induce tissue regeneration in recent research. Senolytics can create a more favorable environment for stem cells to function and preserve tissue homeostasis by eliminating these damaging cells. MSCs are prone to replicative senescence and senescence-associated functional decline, which limits their application in regenerative medicine.\textsuperscript{223} Senescent MSCs may be removed using senolytics during in vitro expansion or bio-processing for transplantation.\textsuperscript{224,225} Some investigated chemicals examined in vitro are found to play a significant effect in the senescence, rejuvenation, and transplanting of MSCs. Study identified the long-term expansion capacity of MSCs, as well as effects on telomere attrition, SA-β-gal staining, and senescence-associated DNA methylation alterations, are molecular markers for replicative senescence. The four compounds that could have senolytic effects.

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included navitoclax (ABT-263) nicotinamide riboside, quercetin, and danazol.\textsuperscript{236,237} Only ABT-263, one of the four tested medicines, had a senolytic impact on MSCs of human origin, and therapy using this substance did restore telomere length or other critical signatures of aging cells such as epigenetics, among others, in MSCs. Therefore, senolytics are indeed in the early stage of development, necessitating greater efforts to find more effective senolytic drugs. Furthermore, senolytics have been shown to increase the capacity of elderly mice’s bone marrow MSCs to produce bone.\textsuperscript{238} Additionally, the pharmacological elimination of senescent cells with acute systemic administration of the senolytic drug ABT-263, which improves learning and memory in middle-aged mice, caused a rapid increase in NPC proliferation and neurogenesis.\textsuperscript{239} Hippocampal NPCs are also stimulated by the genetic ablation of SnC{s}.\textsuperscript{240}

Targeting epigenetic regulators of senescence as potential therapeutics

One of the potential approaches for the epigenetic intervention of senescence is the inhibition of the SASP.\textsuperscript{241} Several investigations have found that the SASP is specifically driven by epigenetic mechanisms that can be targeted by therapeutic means. For example, sirtuin-1 (SIRT1) has been found to directly regulate the expression of the SASP.\textsuperscript{242} Another study found that SIRT1 knockdown or its reduced expression, which normally happens during senescence, causes increased acetylation of H3K9 and H4K16 at the promoter of IL6 and IL8. This results in the transcriptional activation of these cytokines.\textsuperscript{243} Moreover, in addition to directly regulating SASP expression, epigenetic factors can also activate the pro-inflammatory signaling that drives SASP activation. For example, during senescence induction, the mixed lineage leukemia gene (MLL1) protein increases the activation of cell cycle genes related to proliferation, resulting in hyper-inflammatory stress and the susceptibility of DNA to a damage response.\textsuperscript{244} This results in the sensitization of the NF-kB signaling pathway linked to pro-inflammatory response, which augments the expression of the SASP.\textsuperscript{245} Additionally, this study reveals that inhibition of MLL1 downregulates SASP gene expression without allowing senescent cells to evade proliferative restriction, suggesting the therapeutic effect associated with the intervention of MLL1. Furthermore, as cells age, DNA damage response induces epigenetic modifications that activate the SASP.\textsuperscript{246,247} The G9a and G9a-like protein histone methyltransferases are degraded by proteasomes as part of the DNA damage response of G9a-like protein (GLP).\textsuperscript{247} This causes a decrease in H3K9 dimethylation, an indicator of transcriptional repression, imprinted at the promoter of SASP, leading to enhanced gene expression. Importantly, following chromatin remodeling, the DNA damage response can also stimulate and strengthen the SASP without causing actual DNA breaks.\textsuperscript{248} The expression of osteopontin, a crucial pro-inflammatory SASP component, has been shown to rise specifically in response to histone deacetylase 1 (HDAC1) inhibition, which results in hyperacytlation of histone and non-histone proteins.\textsuperscript{249} As a result, HDAC1 inhibition causes the development of a protumorigenic milieu and tumour growth in vivo by abrogating senescence. Tetramethylpyrazine has also been shown to effectively decrease the senescent phenotype of cells by influencing EZH2, which catalyzes tri-methylation of the histone H3 protein’s 27th lysine residue.\textsuperscript{249,250} Also, increasing mitochondrial NAD+ levels by overexpressing nicotinamide nucleotide transhydrogenase and nicotinamide mononucleotide adenyltransferase 3 and delaying replicative senescence can more effectively reprogram aged MSCs.\textsuperscript{251}

Challenges associated with senolytics intervention

Senescent cells have been shown to be essential for processes like wound healing and parturition; however, this comes with a caveat and complications when using senolytics. In principle, senescent cells can be removed by senolytics on an irregular schedule as they develop with aging or disease. Senolytics can be administered sporadically, together with the fact that they can be discontinued for various reasons for patients’ safety in cases such as pregnancy, wound healing, and other disorders. More importantly, other than lysing and removal of senescent cells, no senolytic strategy should interfere with the systems or pathways that govern the physiological processes like cell cycle or senescence that may trigger the abnormal growth of tumor cells, leading to cancer. Other approaches for reducing pathological consequences and limiting the number of senescent cells associated with aging include regulating the immune clearance of senescent cells. Senescent cells tend to overexpress specific cell surface proteins compared to other cell types, which led to the development of Chimeric Antigen Receptor T cells, vaccinations, and antibody-drug conjugates that specifically target these cell surface markers.\textsuperscript{252,253} Although they are not fully specific in their removal of senescent cells, in certain instances they also inactivated macrophages and other non-senescence cell types. On the contrary, small-molecule senolytics may be more advantageous as compared to vaccinations or Chimeric Antigen Receptor T cell therapy, since senolytic therapy can be stopped whenever senescent cells are needed, such as during wound healing, tissue remodeling, or pregnancy.\textsuperscript{254,255}

Future directions

The fascinating field of aging research, and more specifically how intervention in aging-related mechanisms may be able to potentially reverse the pathological consequences of aging cells to improve the quality of life in older age, is still a relatively underexplored area of research. There are many open questions and it is essential to continuously track the new knowledge, however, incremental it may be, to assist by asking more concise questions. For example, the underlying mechanisms of SASP heterogeneity, which can make a sizeable proportion of senescent cells resistant to clearing by macrophages and may even promote tissue degeneration, including in brain tissues, during chronic cellular stress like that brought on by aging, are largely unknown. Also, it would be intriguing to see if donor-derived MSCs may reach highly resistant senescent cells and transfer their immunomodulatory properties, which might facilitate the immune clearance of the cells. Such an approach is especially important, as cells with SASP do not necessarily possess senescent cell-specific antigens to be targeted by small molecules. Additionally, senolytics’ potential efficacy in selectively eradicating resistant cells also needs to be further investigated. Moreover, a majority of the findings in the literature come from studies of senescence in mice, but whether senescent cells in mice are an accurate representation of those found in humans has to be determined. Therefore, more animal models, senescent cell culture techniques, and additional human translational research are all clearly needed for the field to advance. Also, there is no single phenotype for senescent cells, to date, and epigenetic modifications in senescence are primarily diverse and dynamic. Thus, the continuation of research investigating the histone code, and epigenetic protein/nucleotide interactions might result in the discovery of the epigenetic signature of highly resistant senescent cells together with the origin of SASP, which will improve the efficacy of epigenetic drugs to selectively target senescent cells. Last, due to invasive methods required by our present methodology to get tissue samples,
so much less is known about the true cases of senescence in different diseases. Our understanding of these cells’ molecular signatures by single-cell transcriptomics and epigenomics and SASP patterns is limited. Especially, given the absence of a reliable tool to locate and count senescent cells in dysfunctional tissue, hindering the detailed understanding of SASP patterns in the absence of a robust method to retrieve and quantify senescent cells in diseased tissues.\(^{26}\) Having said that, senolytic research has seen exciting times recently, leading to a greater knowledge of the role senescence plays in human health and diseases, which will help control a wide range of diseases through public health policies globally.

### Conclusion

The removal of senescent cells has become a viable therapeutic approach for preventing, delaying aging, or curing a range of illnesses and age-related dysfunctions. Significant development in this field has been driven by the increased awareness of the role senescence plays in human health and diseases. Our understanding of these cells’ molecular signatures by single-cell transcriptomics and epigenomics and SASP patterns is limited. Especially, given the absence of a reliable tool to locate and count senescent cells in dysfunctional tissue, hindering the detailed understanding of SASP patterns in the absence of a robust method to retrieve and quantify senescent cells in diseased tissues.\(^{26}\) Having said that, senolytic research has seen exciting times recently, leading to a greater knowledge of the role senescence plays in human health and diseases, which will help control a wide range of diseases through public health policies globally.

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### Ethical statement

The research has been conducted ethically.

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