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REVIEW ARTICLE

Role of Cellular Senescence in Neurodegeneration: Mechanisms and Therapeutic Implications

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Abstract: Cellular senescence leads to irreversible cell cycle arrest and changes in gene expression that influence several cellular processes within the central nervous system. This review comprehensively examines the impact of cellular senescence on various cell types like neurons, microglia, astrocytes and oligodendrocytes and how the accumulation of senescent cells leads to neurodegeneration. The senescence associated secretory phenotype of these cells leads to chronic neuroinflammation through the secretion of pro-inflammatory cytokines and chemokines. Senescence also impairs adult neurogenesis and myelin repair processes. With age, the numbers of senescent cells increase due to telomere shortening and mitochondrial dysfunction resulting oxidative stress. This causes a decrease in brain volume and loss of cognitive functions. Senescent vascular cells compromise the blood-brain barrier integrity exacerbating neuroinflammation. Targeting the removal of senescent cells and modulating their secretory phenotype offers new therapeutic avenues to mitigate neurodegeneration and age-related cognitive decline.

Keywords: Cellular senescence; Neurodegeneration; Neuroinflammation; Blood-brain barrier; Adult neurogenesis; Myelin repair; Mitochondrial dysfunction

1. Introduction

Neurodegeneration refers to the gradual deterioration and loss of structure and function of neurons in the central nervous system. It underlies several devastating neurological disorders that have a devastating impact on individuals and cause a tremendous economic burden. Some of the major neurodegenerative diseases include Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Huntington's disease (HD) and multiple sclerosis (MS). These disorders are characterized by selective vulnerability and progressive death of specific neuronal populations in distinct regions of the brain and spinal cord. [1-5] The prevalence and incidence of neurodegenerative diseases rise exponentially with advancing age. Age is recognized as the strongest risk factor, with most cases developing after the age of 60 years. According to some estimates, the number of people living with neurodegenerative diseases will double in the next 25 years owing to increased life expectancy and aging of the population worldwide. [6-11] Although aging is a complex biological process influenced by both genetic and environmental factors, cellular senescence appears to play a key role in modulating the aging process and predisposing to age-related diseases. [12-14]

Cellular senescence refers to an irreversible proliferation arrest of somatic cells in response to various stresses like telomere shortening, oxidative stress, oncogene activation or DNA damage. It is an important tumor suppression mechanism that prevents uncontrolled cell division. [15-18] However, the accumulation of senescent cells interferes with tissue homeostasis and contributes to aging and age-related pathologies. Senescent cells develop distinct molecular and phenotypic alterations collectively referred to as senescence-associated secretory phenotype (SASP). The SASP involves the secretion of pro-inflammatory cytokines, chemokines, proteases, growth factors and extracellular vesicles by senescent cells that disrupt tissue microenvironment. Increased senescent cell load has been detected in various tissues during aging and in association with age-related diseases. [19-24] Transplantation of minimal numbers of senescent cells into young mice is sufficient to induce accelerated aging phenotypes. Conversely, removal of p16INK4a-positive senescent cells using genetic clearance techniques has shown to notably delay age-related deterioration and increase healthspan in several mammalian models. This highlights the causal role of cellular senescence in biological aging and age-related dysfunction and diseases. [25-29]

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In the central nervous system, the accumulation and persistence of senescent neurons, glia and neural progenitor cells with advancing age could have profound implications by interfering with distinct neurobiological processes like neurogenesis, myelination, brain plasticity and blood-brain barrier integrity. [30-34] The aim of this review is to provide a comprehensive assessment of the current knowledge regarding the mechanistic involvement of cellular senescence in driving neurodegeneration. A special focus will be given to discussing the detrimental role of SASP factors secreted by senescent glia in promoting chronic neuroinflammation. Potential therapeutic strategies targeting senescent cell clearance or SASP modulation will also be explored with their translational significance for mitigating neurodegeneration.

2. Cellular senescence

2.1. Cellular senescence and molecular signatures

The major molecular signatures of cellular senescence include permanent cell cycle arrest regulated by tumor suppressor pathways involving p53-p21-Rb and p16INK4A-Rb. The p16INK4A-Rb pathway is considered as the major effector involved in establishing and maintaining senescence by inhibiting cyclin-dependent kinases CDK4 and CDK6. [35-39] Senescent cells also exhibit senescence-associated β-galactosidase activity at pH 6, which serves as a biomarker for senescence. Another distinctive feature is the senescence-associated secretory phenotype (SASP) where senescent cells secrete various pro-inflammatory cytokines, chemokines, growth factors, proteases and extracellular vesicles mediating paracrine senescence induction in surrounding cells. The SASP is dependent on several signaling pathways involving NF-ϰB, IL-1α and p53. [40-44] Cellular senescence is also associated with mitochondrial dysfunction, impaired autophagy and accumulation of damaged mitochondria leading to increased oxidative stress. Senescent cells also show increased lipofuscin deposition and metabolic shift towards glycolysis. These molecular signatures (detailed in Table 1) contribute to the establishment and maintenance of senescence phenotype. [45-49]

Table 1. Senescence Signatures and Biomarkers for different Neural Cell Types

Cell Type	Senescence Signatures	Key Senescence Biomarkers
Neurons	Permanent cell cycle arrest, mitochondrial dysfunction, increased ROS, elevated inflammatory genes	Increased p16Ink4a, p53, nucleocytosolic blebbing, lipofuscin deposits
Astrocytes	Enlarged and flattened morphology, activation of p16-pRB pathway, SASP factors secretion	SA-β-gal activity, elevated IL-6, CCL2, TNFα expression
Microglia	Impaired phagocytic ability, pro-inflammatory phenotype, reduced neurotrophic support	Annexin A1 downregulation, increased CD11b and CD68 surface markers
Oligodendrocytes	Defective myelination, reduced migration/proliferation, mitochondrial defects	Lower proliferation marker Ki67, elevated lipocalin 2, activated p38-MAPK pathway
Endothelial Cells	Disrupted tight junctions, abnormal morphology, higher MMP secretion	Elevated p21, vWF, ICAM1 proteins, disrupted ZO-1 tight junction expression

2.2. Role of Cellular senescence in neurodegeneration

The accumulation and persistence of senescent cells in the aging brain can influence neurodegeneration through multiple mechanisms [50]:

- Senescent neuronal cells show permanent cell cycle arrest hindering the self-renewal capacity of neurons. This leads to a gradual loss of neurons contributing to neurodegeneration. [51, 52]
- Microglia and astrocyte senescence results in chronic neuroinflammation through increased secretion of pro-inflammatory factors as part of SASP. This inflammatory environment induces bystander senescence in surrounding glial cells generating a vicious cycle of neuroinflammation. [53-55]
- Oligodendrocyte senescence impairs myelin repair and remyelination processes in demyelinating conditions like multiple sclerosis. Persistent demyelination makes neurons vulnerable to damage and cell death.[56-58]
- Senescent endothelial cells and pericytes disrupt the blood-brain barrier integrity through increased MMPs secretion. This allows infiltration of peripheral immune cells and inflammatory molecules worsening neuroinflammation. [59-62]
- Accumulation of senescent neural progenitor cells decreases the innate regenerative capacity of the brain by impairing adult neurogenesis and reducing production of new neurons from progenitor cells in the hippocampus and SVZ. [63-67]
- Mitochondrial dysfunction and increased oxidative stress in senescent cells promotes neurodegeneration by causing oxidative damage to lipids, proteins and DNA in neurons. [68-70]

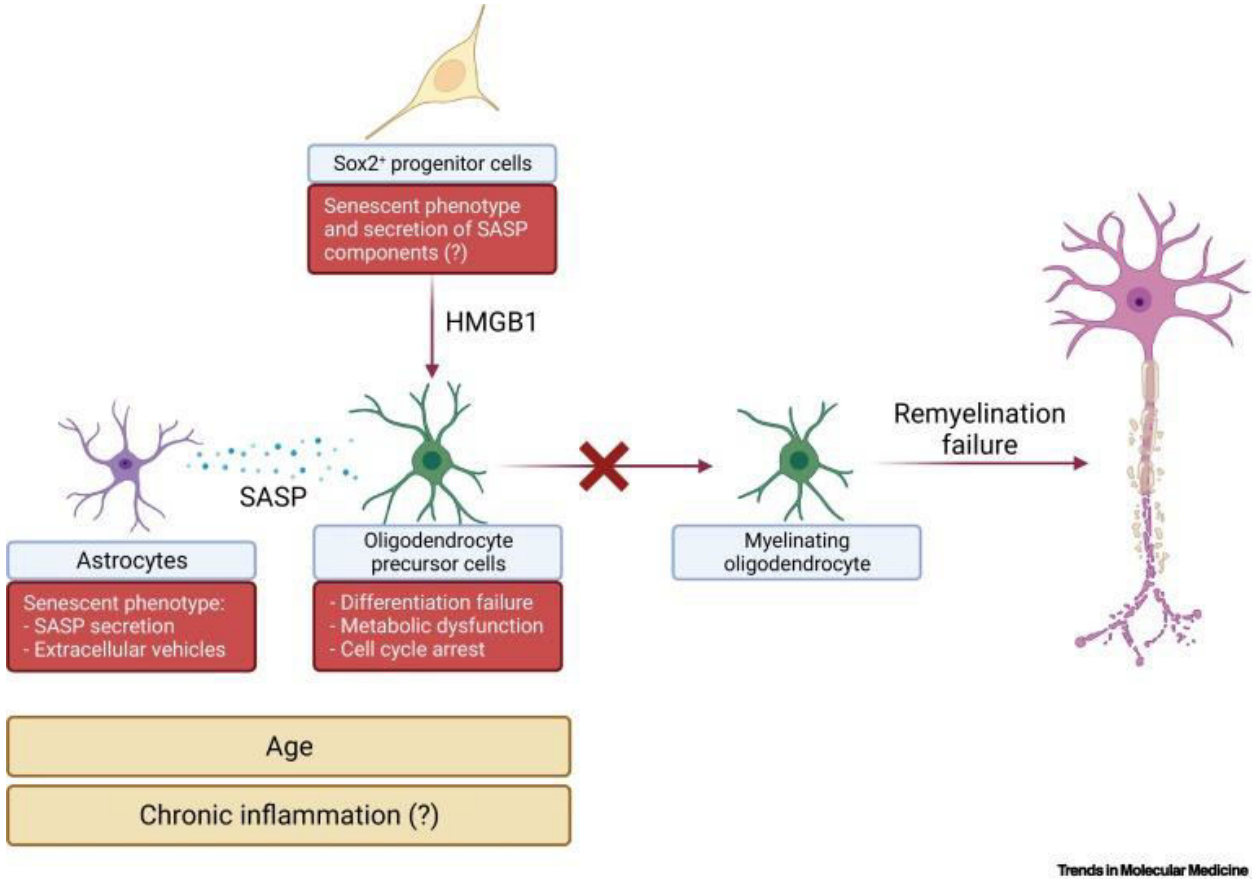

Figure 1. Cellular senescence in the neurons (Image source: © Christopher Nelke, Christina B. Schroeter, Marc Pawlitzki, Sven G. Meuth, Tobias Ruck, Cellular senescence in neuroinflammatory disease: new therapies for old cells?, Trends in Molecular Medicine, Volume 28, Issue 10, 2022, Pages 850-863)

2.3. Cellular senescence and neuroinflammation

A hallmark of aging brain is increased neuroinflammation characterized by elevated circulating pro-inflammatory cytokines and chronic microglial activation. [71-74] This is thought to be mediated by SASP factors secreted by age-accumulated senescent cells in the brain. Some of the major SASP factors implicated in neuroinflammation include:

- IL-6: Increased IL-6 levels are found in aged brains as well as AD patients. IL-6 can directly damage neurons and oligodendrocytes exacerbating neurodegeneration. [75-80]
- IL-1β: Microglia and astrocyte secreted IL-1β induces neuronal damage and synaptic dysfunction contributing to age-related cognitive impairments. [81-84]
- TNF-α: Upregulated TNF-α amplifies neuroinflammatory response by activating microglia and promoting secretion of other pro-inflammatory mediators. [85-87]
- CCL-2: Increased CCL-2 attracts peripheral macrophages into the brain worsening neuroinflammation and amyloidosis in AD. [88-90]
- MMPs: Matrix metalloproteinases like MMP-9 secreted via SASP disrupt the blood-brain barrier integrity and promote neuroinflammation [91]

3. Neurogenesis

Neurogenesis and myelin repair are important endogenous regenerative mechanisms in the adult central nervous system. Cellular senescence has detrimental effects on both these processes:

3.1. Adult Neurogenesis

Accumulation of senescent neural stem/progenitor cells in the subventricular zone and dentate gyrus decreases the pool of available progenitors for adult neurogenesis. [92]

SASP factors secreted by senescent glial cells like IL-6 and TNF-α create a pro-inflammatory microenvironment inhibiting the proliferation and differentiation of neural progenitors into neurons. Mitochondrial dysfunction and oxidative stress in senescent progenitors induces DNA damage reducing their self-renewal capacity and survival. Microglia and astrocyte senescence leads to disrupted neurogenic niche due to impaired structural and functional support for neurogenesis. [93]

3.2. Myelin Repair

Senescent oligodendrocyte precursors have reduced proliferation and differentiation potential needed for remyelination in demyelinating lesions. Increased MMPs in SASP degrade myelin sheets and inhibit migration of precursor cells into lesion sites hindering repair. [94] Pro-inflammatory environment due to SASP deters precursor cell maturation and impairs recruitment of supportive cells like microglia for efficient remyelination. Mitochondrial dysfunction in senescent oligodendrocytes decreases ATP production required for extensive membrane wrapping during myelination. [95]

3.3. Impact on blood-brain barrier integrity

The blood-brain barrier (BBB) forms the interface between the peripheral blood circulation and the central nervous system. It maintains brain homeostasis by regulating the transport of molecules into and out of the brain parenchyma. BBB breakdown leads to neuroinflammation which contributes significantly to the pathogenesis of various neurological disorders. Cellular senescence of brain endothelial cells and pericytes compromises the integrity of BBB. Endothelial cells form the structural and functional core of the BBB by linking together through tight junction complexes which restrict the paracellular diffusion of solutes. Aging is associated with upregulation of senescence markers like p16INK4a and p21 in brain endothelial cells. [96-97] A progressive loss of tight junction proteins including claudin-5, occludin and ZO-1 occurs with endothelial cell senescence disrupting the barrier function. Senescent endothelial cells undergo morphological changes exhibiting an enlarged and flattened phenotype compared to their younger counterparts. This alters the proper apposition of endothelial cells compromising the integrity of tight junctions. [98]

Pericytes wrapped around endothelial cells maintain their functional integrity and regulate vascular tone and blood flow within the brain. Aging results in accumulation of senescent contractile pericytes characterized by increased lipofuscin deposits and senescence-associated β-galactosidase activity. Senescent pericytes demonstrate impaired contraction-relaxation ability and reduced barrier-supporting capabilities through secreting pro-inflammatory mediators. The SASP of pericytes contains factors such as inflammatory cytokines (IL-6, IL-1β, TNF-α), metalloproteinases (MMP-2, MMP-9), and reactive oxygen species which cause direct disruptive effects on BBB. The increased presence and activity of MMPs, especially MMP-2 and MMP-9 are hallmarks of BBB breakdown under pathological conditions as well as normal aging. Studies have shown upregulation of these MMPs in both endothelial cells and pericytes during cellular senescence. [99] MMP-2 and MMP-9 secreted in the SASP cleave tight junction proteins and basal lamina components like laminin, collagen IV which are crucial for maintaining the structural and functional integrity of the neurovascular unit. This promotes opening of tight junctions, detachment of pericytes from the vascular wall and leakage of the BBB. Mitochondrial dysfunction and elevated oxidative stress are characteristic features of senescent endothelial cells and pericytes. This leads to production of excessive reactive oxygen species that oxidatively modify tight junction proteins and basal lamina components deteriorating BBB properties over time. Infiltration of peripheral monocytes and T-cells in the brain is also seen with aging which secrete inflammatory mediators exacerbating endothelial senescence and further BBB damage. Thus, senescence of the neurovascular unit contributes prominently to BBB breakdown during normal brain aging by secreting proteinases and pro-inflammatory factors that disrupt intercellular interactions. This facilitates transcytosis of plasma components into the brain extracellular fluid making neurons susceptible to damage and loss of function. Targeting cellular senescence mechanisms could help maintain the inherent properties of the BBB and limit age-related neuroinflammation.Implications of senescent cell accumulation in the brain [100-102]

3.4. Telomere shortening and mitochondrial dysfunction in cellular senescence

Telomeres are protective DNA-protein complexes located at the ends of eukaryotic chromosomes that prevent DNA degradation and instability during cell division. With each cell division, telomeres become shortened due to the end-replication problem. When telomeres reach a critical short length, cells enter a state of irreversible growth arrest known as replicative senescence. Telomere attrition has been shown to mediate cellular senescence in various brain cell types with aging and under chronic stress conditions. Short telomeres induce DNA damage response and p53/p21/p16 signaling driving cells into senescence. [103, 104] Accelerated telomere shortening also occurs in neurodegenerative disorders causing early onset of senescence in neurons and glia. Mitochondria play a central role in cellular senescence by generating reactive oxygen species (ROS) that damage cellular proteins, lipids and mitochondrial DNA. This creates a vicious cycle of mitochondrial dysfunction, ROS generation and senescence. Studies have reported increased mitochondrial fragmentation, impaired dynamics and electron transport chain deficiencies in senescent neural cells. Failure to clear damaged mitochondria through mitophagy leads to accumulation of dysfunctional mitochondria propagating oxidative stress and driving more cells into senescence. Thus, telomere erosion and mitochondrial dysfunction jointly play critical roles in the pathophysiology of neurodegeneration through induction and maintenance of cellular senescence in the brain.

4. Therapeutic strategies targeting senescent cells

Clearance of senescent cells: Genetic ablation of p16Ink4a-positive senescent cells has been shown to alleviate aging phenotypes and extend healthspan in various mouse models. Drugs like senolytics specifically induce apoptosis in senescent cells by disabling their anti-apoptotic mechanisms. Certain natural compounds like quercetin, navitoclax and dasatinib are promising senolytic agents able to selectively eliminate senescent cells from various tissues including the brain, slowing aging and improving health. [105-110]

4.1. Modulating SASP

Inhibiting the NF-kB and MAPK signaling pathways which regulate SASP factor expression/secretion can suppress the deleterious paracrine effects of SASP. Drugs like aspirin exert neuroprotective effects through SASP modulation. Anti-inflammatory therapies targeting specific SASP factors like IL-1β, TNFα and CCL-2 may also hold potential. [111-114]

4.2. Mitochondria-targeted approaches

Agents improving mitochondrial function and biogenesis, scavenging ROS and stimulating mitophagy show promise in reducing cellular senescence accumulation, neuroinflammation and neurodegeneration. These strategies to selectively clear senescent cells or temper their pro-ageing secretory activities could significantly delay neurological aging and mitigate multiple neuropathologies. Combination therapies may offer maximum benefits warranting further investigation. [115-118] The potential senolytic agents and their mechanism of action. Potential Senolytic Agents and their mechanism of action is shown in Table 2

Table 2 Potential Senolytic Agents and their Mechanism of Action

Agent	Mechanism of Action	Senescent Cell Types Cleared
Dasatinib and Quercetin	Inhibitory effects on senescence-associated secretory phenotype	Fibroblasts, endothelial cells, hepatocytes, neural stem cells
Navitoclax	Antagonizes Bcl-xL and Bcl-2 proteins controlling mitochondrial apoptosis	Lung fibroblasts, vascular smooth muscle cells
Piperlongumine	Induces ROS-dependent DNA damage and p53 activation	Mouse embryonic fibroblasts
Fisetin	Inhibits mTOR and NF-κB signaling to disrupt SASP	Mouse embryonic fibroblasts
A1331852	Disrupts anti-apoptotic protein BFL-1	Liver oval cells, endothelial cells
FOXO4-DRI	Acts via FOXO4 transcriptional factor	Human mesenchymal stem cells

5. Conclusion

In summary, cellular senescence, characterized by permanent cell cycle arrest and SASP acquisition, emerges as a key mediator of neurodegeneration during aging. Accumulation of senescent cells in the brain disrupts tissue homeostasis by impairing neurogenesis, myelination, BBB integrity and driving chronic neuroinflammation. Telomere erosion and mitochondrial dysfunction causally link the biology of aging to senescence induction and maintenance in neural cells. Targeting senescence removal and modulation holds immense potential for delaying neurological aging and mitigating neurodegenerative disease progression. Further research unraveling the interactions between aging, senescence, and the neurodegenerative process will enable the development of novel therapeutic strategies for improved treatment and management of aging individuals.

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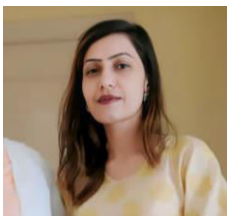

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As a pharmacist-turned-researcher, Im interested in pharmaceutical research, blending scientific accuracy with recent advances