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Review

Senescence in Aging and Alzheimer's Disease

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ABSTRACT: Cellular senescence, once considered a protective mechanism against oncogenesis, is now recognized as a key driver of aging and age-related diseases, including Alzheimer's disease (AD). In the central nervous system (CNS), senescence-like states emerge in both proliferative and post-mitotic cells—astrocytes, microglia, oligodendrocyte lineage cells, endothelial cells, pericytes, and even neurons—contributing to chronic dysfunction. Canonical pathways, such as $p16^{INK4a}$-pRB and p53-p21, enforced by persistent DNA damage responses, lead to irreversible cell-cycle arrest. The senescence-associated secretory phenotype (SASP) links intracellular stress to extracellular inflammation, tissue remodeling, and bystander senescence. CNS senescence is triggered by diverse insults, including amyloid-β and tau pathology, oxidative stress, mitochondrial dysfunction, NF-κB and cGAS–STING signaling, impaired proteostasis and autophagy, telomere attrition, and genomic instability. Senescence markers in the CNS are heterogeneous, ranging from p16/p21 expression and lamin B1 loss to lipofuscin accumulation and cell type–specific SASP profiles, highlighting the need for multiplexed detection strategies. Targeting senescence has emerged as a promising therapeutic avenue in AD. Senolytics selectively eliminate senescent cells and improve cognition in preclinical models, while senomorphics aim to suppress harmful phenotypes without inducing cell loss. Early clinical trials suggest feasibility, but challenges remain, including biomarker development, blood-brain barrier penetration, long-term safety, and optimal timing of intervention. This review summarizes recent advances in understanding CNS senescence in aging and AD, explores emerging therapeutic strategies, and outlines future directions emphasizing precision medicine through multi-omic biomarkers, advanced imaging, and stage-specific interventions. Targeting CNS senescence holds potential to delay or alter the course of AD.

Keywords: senescence, aging, Alzheimer's disease, central nervous system

1. Introduction

Cellular senescence is a state of stable cell-cycle arrest accompanied by characteristic morphological and molecular alterations, originally recognized as a tumor-suppressive mechanism that prevents the proliferation of damaged or stressed cells [1]. Senescent cells display persistent activation of DNA damage responses (DDR), chromatin remodeling, metabolic reprogramming, and a distinctive senescence-associated secretory phenotype (SASP) that includes pro-inflammatory cytokines, chemokines, growth factors, and proteases [2, 3]. While transient senescence can contribute to wound healing and tissue remodeling, the chronic persistence of senescent cells is now implicated in tissue dysfunction and age-related diseases across multiple organ systems [4, 5]. In the central nervous system (CNS), evidence suggests that cellular senescence is not limited to proliferative glial and endothelial populations but can also manifest as a "senescence-like" phenotype in post-mitotic neurons, thereby expanding its relevance beyond traditional paradigms [6, 7].

Alzheimer's disease (AD) is the most common cause of dementia worldwide, affecting more than 50 million individuals globally and accounting for approximately 60–70% of dementia cases [8]. Its prevalence is projected

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to triple by 2050 due to the aging population, posing immense personal, social, and economic burdens [9]. Current therapeutic approaches, including cholinesterase inhibitors, NMDA receptor antagonists, and recently approved anti-amyloid monoclonal antibodies, provide modest symptomatic benefits or disease-modifying effects in select patient populations but fail to halt or reverse the neurodegenerative process [10]. The multifactorial nature of AD pathology—encompassing amyloid-β (Aβ) deposition, tau hyperphosphorylation, neuroinflammation, vascular dysfunction, and synaptic failure—underscores the need for novel therapeutic strategies targeting upstream or convergent pathogenic pathways [11].

Aging is the strongest known risk factor for AD, with the incidence doubling approximately every five years after the age of 65 [12, 13]. Age-related molecular alterations such as genomic instability, telomere attrition, mitochondrial dysfunction, epigenetic changes, and loss of proteostasis overlap considerably with the hallmarks of cellular senescence [14, 15]. In the aging brain, these processes are further exacerbated by chronic low-grade inflammation ("inflammaging") and impaired regenerative capacity, creating a permissive environment for neurodegeneration [12, 16]. Recent studies indicate that cellular senescence may represent a mechanistic link between aging and AD by contributing to chronic neuroinflammation, disrupting neuronal and glial homeostasis, and impairing neurovascular integrity [17, 18]. Importantly, the senescence-associated secretome can propagate deleterious signals to neighboring cells, potentially amplifying AD pathology through a feedforward loop of inflammation, oxidative stress, and proteostatic collapse [19, 20].

Given these converging lines of evidence, elucidating the role of cellular senescence in AD pathogenesis has emerged as a critical research priority. Understanding the cellular and molecular mechanisms of senescence in CNS cell types, its triggers in the aging and AD brain, and its functional consequences at the tissue and network levels may reveal novel intervention points. Furthermore, the recent development of senolytic and senomorphic agents raises the possibility of therapeutically targeting senescent cells to modify the course of AD [9, 21, 22]. The following sections will examine the mechanisms and markers of senescence, its triggers in the CNS, cell type-specific manifestations, its contributions to AD pathogenesis, and emerging therapeutic strategies.

2. Markers and Triggers of Cellular Senescence

Identifying and characterizing cellular senescence in the CNS presents unique challenges. Unlike proliferative tissues, the adult brain is composed largely of post-mitotic neurons interspersed with proliferative glia, vascular cells, and oligodendrocyte precursors [23, 24]. Senescence in this context manifests as a spectrum, ranging from canonical proliferative arrest to "senescence-like" states in neurons. Because of this heterogeneity, both markers and triggers of senescence must be carefully defined to enable mechanistic insight and translational targeting in aging and AD [25].

2.1 Classical Senescence Markers

The most widely used senescence markers derive from proliferative cell systems. $p16^{INK4a}$ (CDKN2A) is upregulated in senescent cells and enforces G1 arrest by inhibiting CDK4/6, thereby preventing phosphorylation of the retinoblastoma protein (pRB) [13, 26-28]. Similarly, $p21^{CIP1}$ (CDKN1A), a downstream effector of p53 activation, suppresses cyclin–CDK activity and consolidates growth arrest [29, 30]. Both p16 and p21 are robust indicators of senescence in astrocytes, microglia, endothelial cells, and oligodendrocyte precursor cells (OPCs) [3, 31, 32]. However, in neurons, p16 and p21 are inconsistently expressed, limiting their reliability as universal CNS markers.

Another classical marker is senescence-associated β-galactosidase (SA-β-gal) activity, reflecting lysosomal expansion. SA-β-gal staining has been used to detect senescent astrocytes and microglia in aged and AD mouse brains [33-36]. Yet, its specificity is questionable, as lysosomal activity also increases during non-senescent stress conditions. DNA damage response (DDR) foci, particularly γH2AX and p53BP1 puncta, serve as hallmarks of senescence when persistent. These foci represent unrepaired double-strand breaks or replication-independent lesions, which accumulate in aged neurons and glia [37].

Together, classical markers provide an entry point for identifying senescent cells in the brain, but they lack absolute specificity. Many are transiently induced by acute stress, and none alone can definitively establish a senescent state.

2.2 Emerging and CNS-Specific Markers

To overcome the limitations of classical markers, several emerging indicators have been developed. Senescence-associated heterochromatin foci (SAHF), visible as punctate DAPI-dense nuclear structures, reflect chromatin remodeling that represses proliferation-related genes [38, 39]. Loss of lamin B1, a nuclear envelope protein, has emerged as a robust and relatively specific senescence marker across multiple cell types, including astrocytes and endothelial cells [40].

Metabolic and structural features also provide additional readouts. Lipofuscin accumulation, a pigment composed of oxidized protein–lipid aggregates, increases in senescent neurons and glia, and can be detected histochemically [41-43]. Transcriptomic and proteomic profiling of the SASP further enables cell-type–specific detection. For instance, senescent astrocytes display downregulation of neurotrophic genes (GFAP, S100β) alongside secretion of IL-6, IL-8, and MMP-3, whereas senescent microglia express inflammatory chemokines (CCL2, CXCL10) and complement proteins [44].

CNS-specific innovations include identification of telomere-associated DNA damage foci (TAF) in post-mitotic neurons, which colocalize with tau tangles in AD brains [45-47]. Moreover, "dystrophic microglia," characterized by fragmented processes and elevated p16 expression, are increasingly recognized as a morpho-functional signature of microglial senescence [48]. Collectively, these markers (Table 1) improve sensitivity and specificity for detecting senescence in neural tissues, though multiplexed approaches remain essential.

A comprehensive overview of classical and emerging senescence markers across CNS cell types is presented in Table 1.

Table 1. Senescence Markers in CNS Cell Types.

Marker / Phenotype	Detected in Cell Type(s)	Detection Method / Key Features	Key Refs
$p16^{INK4a}$ / $p21^{CIP1}$	Astrocytes, Microglia, Neurons	Immunostaining, qPCR; correlate with SASP and tau pathology	[17, 32, 192]
SA-β-gal activity	Astrocytes, Microglia	Histochemical staining for β-galactosidase at pH 6.0	[136]
γH2AX / 53BP1 foci	Neurons, Endothelial Cells	Immunofluorescence for DNA damage response	[247]
Lamin B1 loss	Astrocytes, Endothelial Cells	Immunoblot or IF reduction of nuclear envelope integrity	[248]
SAHF formation	Astrocytes, Fibroblasts	DAPI-stained heterochromatin foci, H3K9me3 positivity	[249]
Lipofuscin accumulation	Neurons, Astrocytes	Autofluorescence microscopy (age pigment granules)	[250]
SASP profile (IL-6, IL-1β, MMPs)	Astrocytes, Microglia	Multiplex cytokine assay, ELISA, RNA-seq	[251]
Dystrophic morphology	Microglia	Iba1+ fragmented microglia with reduced branching	[252]
Telomere-associated foci	Neurons, Glia	Co-localization of γH2AX and telomeric DNA damage foci	[66, 253]
Spatial transcriptomic	Astrocytes, Oligodendrocytes, Microglia	snRNA-seq, spatial omics in AD tissue	[196, 254, 255]

2.3 Triggers of Senescence in the Aging and AD Brain

Multiple pathogenic stressors in the aging brain and in AD can induce or exacerbate cellular senescence across diverse CNS cell types [49]. These triggers often act synergistically, initiating canonical senescence pathways, amplifying the SASP, and perpetuating a feedforward loop of neurodegeneration and neuroinflammation.

2.3.1 Amyloid-β and Tau Toxicity

Amyloid-β (Aβ) and hyperphosphorylated tau (hp-tau), the pathological hallmarks of AD, can directly or indirectly trigger senescence programs in glial cells and neurons. Multi-omic analyses show that age-associated oxidative stress, Aβ accumulation, and hp-tau synergistically promote the buildup of senescent glial cells, and that the senescent cell burden correlates with the progression from mild cognitive impairment to advanced dementia [17]. At the neuronal level, a bidirectional relationship between tau and the DDR has emerged: tau perturbs microtubule stability, mitochondrial dynamics, and axonal transport, thereby exacerbating genomic instability and persistent DDR activation, which in turn reinforces tau toxicity in a self-amplifying loop [50]. Furthermore, Aβ fibrils activate innate immune receptors such as TLRs on microglia, driving inflammatory-senescent phenotypes and amplifying SASP output, suggesting that upstream neutralization of these aggregates could mitigate senescence induction [51, 52].

2.3.2 Oxidative Stress and ROS

Oxidative stress is both a hallmark of aging and a prominent feature in AD, arising from mitochondrial dysfunction, impaired antioxidant defenses, and chronic

neuroinflammation. [53] Excess ROS can inflict oxidative DNA lesions, lipid peroxidation, and protein oxidation, all of which can trigger senescence via DDR activation and p38 MAPK signaling, thereby triggering cellular senescence [54]. In neurons, oxidative stress promotes tau hyperphosphorylation and synaptic dysfunction via stress-activated kinases such as JNK/p38 [17]. In microglia, ROS bias the cells toward a pro-inflammatory phenotype, reinforcing the SASP and exacerbating paracrine senescence signaling [55]. Given the high metabolic rate and lipid-rich environment of the brain, oxidative stress represents a particularly potent and pervasive senescence trigger in the CNS.

2.3.3 Inflammation and NF-κB /cGAS-STING Pathways

Chronic low-grade inflammation, commonly known as inflammaging, is a defining feature of the aged brain and is further exacerbated in AD through sustained microglial activation and reactive astrogliosis. This persistent inflammatory state not only arises from age-associated cellular stress but is also perpetuated by the accumulation of senescent cells, which release a SASP rich in cytokines, chemokines, and proteases. Central to this process is NF-κB, which acts as a master transcriptional regulator of SASP gene expression and sustains a self-reinforcing inflammatory loop within the central nervous system [56]. Dysregulated NF-κB signaling in microglia and astrocytes enhances the production of interleukins (e.g., IL-6, IL-1β), tumor necrosis factor-α (TNF-α), and matrix metalloproteinases, thereby disrupting synaptic homeostasis, compromising blood brain barrier integrity, and fueling neurodegeneration [57].

In parallel, mounting evidence implicates the cGAS-STING pathway as a key driver of senescence-associated neuroinflammation [58]. Cytosolic DNA fragments, originating from nuclear envelope instability, telomeric attrition, or damaged mitochondria, can activate cGAS, leading to STING-dependent type I interferon and NF-κB signaling [59]. In glial cells, this pathway promotes reactive and neurotoxic phenotypes, enforces chromatin remodeling, and amplifies SASP output, thereby linking DNA damage and mitochondrial dysfunction to innate immune activation [60]. Experimental evidence demonstrates that inhibition of STING reduces inflammatory phenotypes in human senescent cells and ameliorates age-related cognitive decline in murine models [59]. Conversely, chronic or hyperactive STING signaling drives maladaptive microglial activation, neuronal loss, and synaptic failure, underscoring its pathogenic role in AD progression [60].

Pharmacological suppression of STING in transgenic AD models has been shown to attenuate microgliosis, reduce amyloid and tau pathology, and improve cognitive outcomes, positioning STING as a therapeutic node at the intersection of senescence, inflammation, and neurodegeneration [61]. Together, NF-κB and cGAS–STING form a synergistic inflammatory network that amplifies senescence in the CNS: NF-κB maintains chronic SASP production, while cGAS–STING integrates genotoxic and mitochondrial stress into sustained innate immune activation. Interventions targeting these pathways may therefore hold promise in mitigating inflammaging and senescence-associated pathology in AD [57].

2.3.4 Telomere Attrition and Genomic Instability

Telomeres, the repetitive nucleotide sequences at chromosome ends, are essential for maintaining genomic stability by preventing aberrant DNA repair and chromosomal fusion. With each cell division, telomeres progressively shorten due to the end-replication problem, eventually reaching a critically short length that activates a DDR and induces senescence through the p53–$p21^{CIP1}$ and $p16^{INK4a}$–pRB pathways [62, 63]. Although most neurons are post-mitotic, proliferative neural cell populations—including neural stem/progenitor cells (NSPCs), OPCs, astrocytes, and microglia—are vulnerable to telomere erosion. Shortened telomeres in these populations impair neurogenesis, glial repair functions, and myelin maintenance, thereby accelerating CNS aging [64].

In AD, telomere attrition has been repeatedly observed in peripheral blood leukocytes and neural tissues, correlating with cognitive decline and disease progression [65]. Telomere dysfunction is thought to interact with AD pathology via multiple mechanisms. First, telomere shortening promotes genomic instability and persistent DDR signaling, reinforcing senescence in glia and vascular endothelial cells, which in turn secrete pro-inflammatory SASP factors that exacerbate neurodegeneration [66]. Second, genomic instability induced by telomere dysfunction can amplify the toxic effects of Aβ and tau pathology, for example by facilitating oxidative DNA lesions, somatic mutations, and chromatin remodeling [67]. Third, accelerated telomere shortening has been linked to lifestyle risk factors for AD—including chronic stress, metabolic dysfunction, and systemic inflammation—suggesting that it integrates both genetic and environmental stressors into CNS senescence phenotypes [68-70]. Importantly, emerging evidence suggests that telomerase reactivation or telomere-stabilizing interventions may mitigate cellular senescence and neurodegeneration. Mouse models of telomerase deficiency exhibit premature cognitive decline and neurodegeneration, whereas telomerase reactivation restores hippocampal

neurogenesis and improves memory [71]. These findings raise the possibility that telomere maintenance is not only a marker of cellular aging but also a therapeutic target in AD and related dementias.

Telomere shortening is a well-established driver of replicative senescence in proliferating cells, but evidence suggests it may also contribute to senescence-like states in post-mitotic neurons and glia through telomere dysfunction-induced foci (TIFs). In the aging brain, telomerase activity is reduced, and critically short telomeres are associated with increased microglial reactivity and astrocytic senescence. Moreover, genomic instability induced by oxidative lesions, replication stress in progenitor cells, or defective DNA repair machinery accelerates senescence induction and may synergize with AD-related proteotoxic stress.

2.3.5 Disrupted Autophagy and Proteostasis Collapse

Given the high metabolic activity and limited regenerative capacity of the brain, protein homeostasis, the coordinated regulation of protein synthesis, folding, transport, and degradation, is critical for neuronal health. With aging, proteostasis gradually declines due to impaired autophagy, ubiquitin–proteasome system efficiency, and chaperone function, leading to the accumulation of misfolded proteins and damaged organelles [72, 73]. These disturbances activate senescence programs through persistent DNA damage response, mitochondrial dysfunction, and pro-inflammatory signaling, thereby reinforcing a deleterious cycle of cellular dysfunction in the CNS.

In Alzheimer' s disease, autophagy dysfunction is a central pathological feature, as evidenced by the accumulation of autophagic vacuoles, lysosomal storage defects, and impaired clearance of Aβ and hyperphosphorylated tau [74, 75]. Genetic or pharmacological inhibition of autophagy accelerates Aβ and tau accumulation, whereas restoration of autophagic flux promotes their clearance and ameliorates neurodegeneration in animal models [76, 77]. Defects in lysosomal acidification and membrane integrity further impair the degradation of toxic aggregates, contributing to both neuronal senescence and neuroinflammation via leakage of cathepsins and mitochondrial DNA [78].

Proteostasis collapse is also linked to SASP induction. In glial cells, accumulation of misfolded proteins and dysfunctional mitochondria activates NF-κB and cGAS–STING pathways, driving secretion of pro-inflammatory cytokines that propagate senescence to neighboring cells [79]. In neurons, proteostatic stress promotes aberrant tau aggregation and chromatin remodeling, leading to irreversible alterations in gene expression [67]. Importantly, defective autophagy can amplify oxidative stress by failing to remove damaged mitochondria (mitophagy deficiency), creating a feedback loop that accelerates senescence in both neurons and glia. Recent evidence suggests that therapeutic modulation of autophagy may attenuate senescence in the aging and AD brain. Strategies such as mTOR inhibition (rapamycin), AMPK activation, and caloric restriction mimetics have been shown to restore autophagic flux, reduce protein aggregation, and improve cognitive performance in preclinical AD models [80, 81]. Furthermore, small-molecule enhancers of proteasome activity and chaperone-based therapies are under investigation as approaches to stabilize proteostasis and delay senescence-driven neurodegeneration [82].

2.3.6 Retrotransposon and HERV Reactivation as Novel Triggers of Senescence

In the aging brain and in AD, increasing evidence indicates that activation of retrotransposable elements, particularly long interspersed nuclear elements-1 (LINE-1) and human endogenous retroviruses (HERVs), acts as a previously underappreciated source of genomic stress and senescence [83-85]. Under conditions of DNA damage, nuclear envelope instability, mitochondrial dysfunction, or impaired epigenetic silencing, retroelements become transcriptionally derepressed [86, 87]. The resulting cytosolic DNA or RNA–DNA hybrids activate the cGAS–STING pathway, inducing type I interferon production, NF-κB signaling, and SASP amplification, thereby linking retroelement activation directly to cellular senescence and neuroinflammation [88-90].

In AD brains, HERV-K and LINE-1 transcripts are elevated in neurons and microglia and correlate with cognitive decline, tau pathology, and neurodegeneration [84, 91, 92]. Tau accumulation itself can promote LINE-1 derepression and DNA damage, forming a feedforward loop between proteotoxic stress and retrotransposon reactivation [84, 93]. Retroelement activation also promotes oxidative stress, mitochondrial damage, and DNA double-strand breaks, reinforcing senescence-associated DDR and inflammatory pathways [94, 95]. Importantly, a recent first-in-human pilot clinical trial demonstrated that antiretroviral therapy (ART) targeting HERV activity reduced neuroinflammatory markers and stabilized cognition in patients with early AD [96], highlighting retrotransposon suppression as a novel therapeutic avenue intersecting with senescence biology.
Markers and triggers of senescence provide complementary insights: markers enable detection and mapping of senescent populations, while triggers highlight upstream stressors that induce them (Fig. 1). In the aging and AD brain, senescence is rarely caused by a

single insult; rather, proteinopathies, oxidative stress, inflammation, genomic instability and proteostasis failure interact to create a feed-forward senescence niche. Therefore, detection and interpretation of aging in the CNS requires an integrated, multimodal approach that includes histochemistry, transcriptomics, proteomics, and functional imaging. Such strategies will be crucial not only for mechanistic understanding but also for evaluating therapeutic interventions aimed at senescence in neurodegenerative disease.

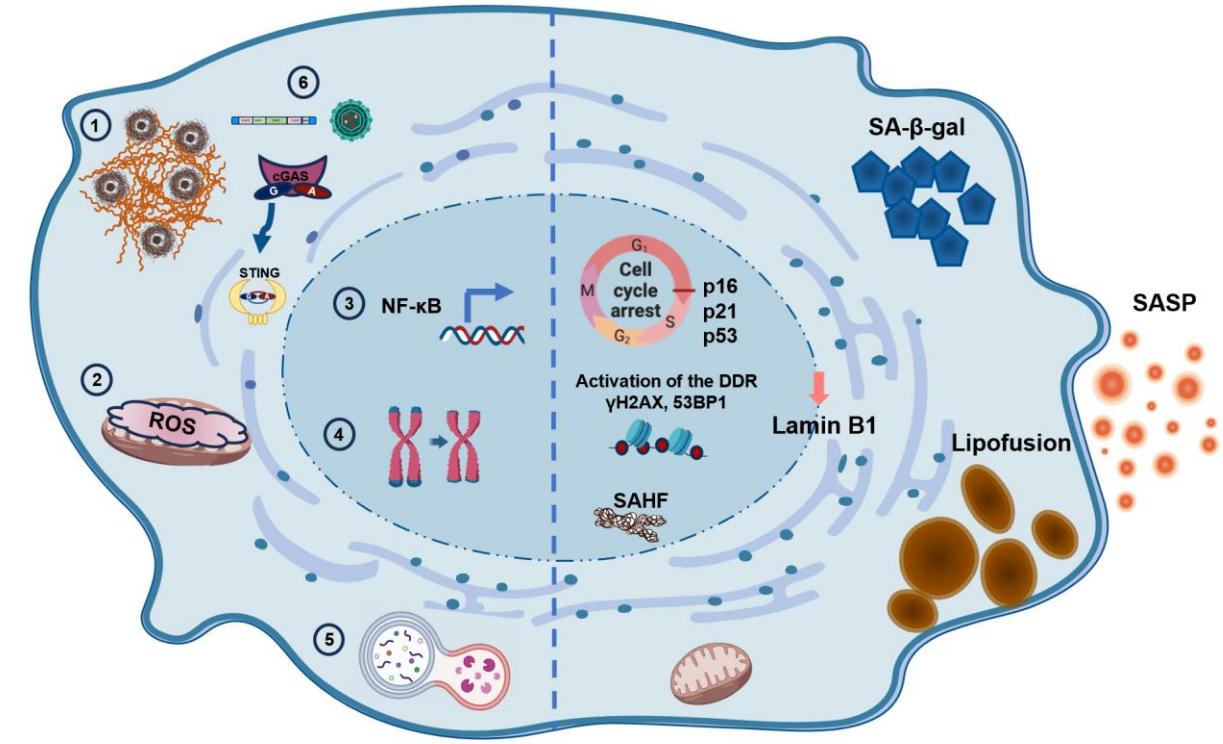

Figure 1. Markers and triggers of cellular senescence in the central nervous system (CNS). Cellular senescence in the CNS can be initiated by diverse upstream triggers, including: ①amyloid-β (Aβ) and tau aggregation, ②oxidative stress and mitochondrial dysfunction, ③chronic inflammation (NF-κB, cGAS–STING activation), ④telomere attrition and genomic instability, and ⑤proteostasis collapse, ⑥ Retrotransposon and HERV. These stressors converge on a central senescence programme, leading to stable cell-cycle arrest and secretory reprogramming. Senescent cells can be detected using classical and emerging markers. Classical markers include upregulation of $p16^{INK4a}$ and p21, senescence-associated β-galactosidase (SA-β-gal) activity, and persistent DNA damage response (DDR) foci such as γH2AX and 53BP1. Emerging markers include loss of lamin B1, lipofuscin accumulation, and senescence-associated heterochromatin foci (SAHF). Together, these readouts highlight both the challenges and opportunities in identifying senescent cells in complex neural tissues.

3. Mechanisms of Cellular Senescence

Cellular senescence is a multifaceted response to diverse stresses, including DNA damage, telomere attrition, oncogene activation, metabolic or mitochondrial dysfunction, and proteostatic collapse, which ultimately culminates in durable cell-cycle arrest and broad transcriptional and functional reprogramming [23]. These outcomes are orchestrated by intersecting modules: $p16^{INK4a}$–pRB and p53–$p21^{CIP1}$ pathways, persistent DNA damage response, and the senescence-associated secretory phenotype; mitochondrial dysfunction, oxidative stress and proteostasis failure act both as upstream triggers and downstream amplifiers of the senescent program [13, 14]. In the context of the CNS, these pathways are not limited to proliferative populations such as astrocytes, microglia, or OPCs, but also extend to post-mitotic neurons and vascular cells, where they contribute to synaptic dysfunction, neurovascular uncoupling, and neuroinflammation in AD [17, 32, 97]. Understanding the canonical and non-canonical mechanisms of senescence is crucial for interpreting its role in aging and AD [6, 15, 98].

3.1 Canonical Pathways: $p16^{INK4a}$–pRB and p53–$p21^{CIP1}$

At the core of senescence induction lie two major tumor suppressor pathways: the $p16^{INK4a}$ /retinoblastoma (pRB) axis and the p53/ $p21^{CIP1}$ axis [24, 26, 27]. Activation of $p16^{INK4a}$ inhibits cyclin-dependent kinases CDK4 and

CDK6, preventing phosphorylation of pRB and thereby enforcing G1-phase arrest [28]. In parallel, p53, which is stabilized by DNA damage or oncogenic stress, transactivates $p21^{CIP1}$ to inhibits cyclin E-CDK2 complexes and reinforces pRB-mediated arrest [29, 30]. These pathways often operate redundantly, ensuring irreversible withdrawal from the cell cycle even if one arm is compromised [99, 100].

Across aging tissues, $p16^{INK4a}$ is a robust indicator of cumulative stress and reduced regenerative capacity; in the CNS, it is most prominent in damaged or activated glial cells and is associated with decreased function [15]. In the AD context, multi-cohort and model studies showed that $p16^{INK4a}$ was upregulated in microglia adjacent to Aβ lesions, and nanoparticle siRNA inhibiting p16 reduced aged microglia proportion, enhanced Aβ clearance and improved memory in 5xFAD mice [101]. With regard to tau pathology, recent human models and in vivo evidence suggest that age-related increases in p16 exacerbate tau-related phenotypes, supporting p16 as a contributor to AD progression [102]. More broadly, accumulation of p16 positive senescent cells and restriction of remyelination were observed in the central white matter injury and demyelination model. Selective depletion of senescent cells can improve repair in young and middle-aged animals, but the effect is limited in aged animals, suggesting that the age context determines the effect window of senotherapy [103]. Collectively, $p16^{INK4a}$ is not only a marker, but its upstream triggers (DDR, inflammation, metabolic stress) and downstream effects (RB-E2F repression, chromatin remodeling, SASP amplification) jointly participate in the AD-related network.

$p21^{CIP1}$ is particularly critical in the early and reversible stages of senescence, followed by a cascade of consolidation and irreversible arrest with $p16^{INK4a}$. Single cell/mononuclear transcriptional profiling and risk allele function studies in aging neurons suggested that Cdkn1a (p21) was significantly induced by tau stimulation in the APOE4 and TREM2 background, accompanied by changes in microglia response state and neuronal vulnerability [104]. Mechanistically, $p21^{CIP1}$ can couple DDR and metabolic/mitochondrial pathways. For example, in rodent cerebral cortex, GDF11 deficiency upregulates $p21^{CIP1}$ via Smad2 pathway and drives excitatory neuronal senescence and brain aging phenotype, while exogenous GDF11 can alleviate this axon-related senescence [105]. In terms of intervention, removal of $p21^{high}$ cells could accelerate tissue repair and reduce inflammation in vivo, supporting the idea of "functional senolysis" targeting $p21^{high}$. Although the evidence for this strategy is stronger in peripheral tissues, it provides a clear direction for CNS/AD precision intervention (safety and specificity needs to be verified in the brain) [106].

3.2 The DNA Damage Response (DDR) as a Central Trigger

A central upstream activator of both p16 and p53 pathways is the DDR, typically triggered by double-strand breaks, replication stress, or oxidative lesions [107, 108]. Persistent DDR signaling, characterized by γH2AX foci, ATM/ATR activation, and recruitment of repair factors such as 53BP1, acts as a hallmark of senescent cells [24, 109]. This persistent DDR stabilizes p53, reinforces p21 expression, and promotes chromatin changes that consolidate senescence [110].

A critical aspect of senescence-associated DDR is the formation of telomere-associated DNA damage foci (TAF). Unlike classical telomere shortening, TAF arise from irreparable telomeric damage and persist even in non-dividing cells such as neurons and cardiomyocytes [37]. This observation has profound implications for the CNS, where post-mitotic neurons accumulate TAF with age, contributing to senescence-like phenotypes independent of replication.

Another mechanism linking DDR to inflammatory signaling is nuclear instability and micronucleus formation, which allow chromatin fragments to access the cytosol and activate the cGAS–STING pathway. This pathway converts cytosolic DNA into a robust type I interferon and NF-κB response, coupling DDR to SASP amplification [111].In neurons and glia, mitochondrial dysfunction and tau pathology can induce such nuclear envelope damage, making DDR a nexus between proteinopathy and chronic inflammation in AD. [112-114].

3.3 The Senescence-Associated Secretory Phenotype (SASP)

A defining feature of senescent cells is their ability to secrete a complex pro-inflammatory and tissue-remodeling milieu known as the SASP. Its composition includes interleukins (IL-6, IL-1β), chemokines (CCL2, CXCL10), growth factors (VEGF, GM-CSF), and proteases (MMP-1, MMP-3) [44, 115]. SASP factors are regulated at multiple levels: transcriptionally by NF-κB and C/EBPβ, translationally by mTOR-mediated selective translation, and epigenetically through chromatin remodeling. Additionally, stabilization of GATA4 under conditions of autophagy inhibition provides a key node linking DDR to NF-κB–driven SASP induction [116].Importantly, SASP is not static but evolves over time. "Early SASP" waves are dominated by IL-1α and pro-inflammatory cytokines, while "late SASP" phases

include growth factors and matrix-remodeling enzymes [44]. This temporal heterogeneity underscores the dual role of SASP: transient SASP can recruit immune cells for clearance, while chronic SASP drives paracrine senescence and tissue dysfunction.

In the CNS, SASP displays distinct cell-type–specific profiles. Astrocytic SASP is enriched in IL-6 and CCL2 and disrupts neuronal support and BBB integrity; microglial SASP enhances complement activation and promotes synapse loss; endothelial SASP contributes to vascular leakage and neurovascular uncoupling [15]. In AD, these SASP-driven interactions amplify amyloid and tau pathology, neuroinflammation, and synaptic dysfunction [117-119].

Box 1. Terminology of Senescence in CNS.

In proliferative cell types such as astrocytes, microglia, and oligodendrocyte precursor cells, cellular senescence denotes an irreversible cell-cycle arrest accompanied by persistent DNA-damage response signaling, up-regulation of $p16^{INK4a}$/$p21^{CIP1}$, and secretion of SASP factors.

In contrast, senescence-like states occur in post-mitotic neurons and other non-dividing cells that display sustained DNA damage, mitochondrial dysfunction, or SASP-like secretory changes without classical cell-cycle arrest.

Functional senescence represents a broader physiological decline in repair and homeostatic capacity, such as reduced synaptic plasticity or impaired neurovascular coupling, that shares molecular hallmarks with canonical senescence but does not necessarily entail permanent proliferation arrest.

Collectively, these terms describe a continuum of stress-adaptation states across CNS cell types rather than discrete, mutually exclusive categories.

3.4 Non-Canonical Mechanisms: Mitochondrial Dysfunction, Proteostasis Failure, and Epigenetic Remodeling

Beyond canonical pathways, senescence is reinforced by non-classical mechanisms that converge on metabolic stress, protein homeostasis, and chromatin architecture [120]. These processes not only sustain the senescent state but also amplify neurodegenerative pathology in AD.

Mitochondrial dysfunction underlies a distinct phenotype termed mitochondria dysfunction–associated senescence (MiDAS). MiDAS is characterized by elevated reactive oxygen species (ROS), altered mitochondrial dynamics, and release of mitochondrial DNA into the cytosol, which activates the cGAS–STING pathway and sustains SASP [121]. A hallmark of MiDAS is altered NAD^+/NADH ratios, linking mitochondrial metabolism to chromatin and transcriptional reprogramming [122]. Notably, MiDAS-associated SASP is characterized by reduced IL-1α but increased interferon-stimulated genes, highlighting a shift from canonical inflammatory SASP to innate immune–driven signatures [122, 123]. In the CNS and AD, MiDAS is particularly relevant because neurons and glia exhibit early mitochondrial defects, including decreased complex I activity, impaired mitophagy, and ROS accumulation before overt Aβ or tau pathology [124-126]. These findings suggest that MiDAS is a metabolically driven, DDR-independent form of senescence that complements classical models and may represent an early upstream event linking metabolic failure to chronic inflammation and neurodegeneration in AD.

Loss of proteostasis contributes to senescence by impairing autophagy and lysosomal clearance, leading to accumulation of misfolded proteins and damaged organelles [127]. In AD, defective autophagy-lysosomal flux exacerbates tau aggregation and amyloid accumulation, which in turn reinforce senescence-associated DDR and SASP [25].

Epigenetic remodeling further stabilizes the senescent state. Hallmarks include loss of lamin B1, enrichment of heterochromatin marks such as H3K9me3 and H3K27me3, and the formation of senescence-associated heterochromatin foci (SAHF). These changes repress proliferation-related genes while sustaining SASP transcription. In the CNS, lamin B1 loss has been observed in aging astrocytes and is proposed as a marker of senescence in human hippocampus [40].

Together, these canonical and non-canonical mechanisms amplify and stabilize the senescence program, providing multiple points of intersection with neurodegenerative pathology (Fig. 2).

4. Cell Type–Specific Senescence in the CNS

Cellular senescence in the central nervous system manifests differently across distinct cell populations due to their developmental origin, proliferative capacity, metabolic demands, and functional roles. In AD and aging, these cell type-specific senescence programs contribute in unique yet interconnected ways to neurodegeneration, neuroinflammation, and vascular dysfunction.

4.1 Neurons: Senescence-like States and Functional Vulnerability

Although neurons are traditionally regarded as post-mitotic and therefore outside the canonical framework of

senescence, a growing body of evidence demonstrates that they can adopt a senescence-like phenotype during aging and in AD [128]. This phenotype is defined not by proliferative arrest, but rather by a persistent DDR, chromatin remodeling, mitochondrial dysfunction, and secretion of pro-inflammatory mediators. These features indicate that neuronal senescence represents a qualitatively distinct but biologically relevant adaptation to chronic stressors in the CNS [129].

Neuronal senescence is often initiated by proteotoxic stress, notably from Aβ accumulation and hyperphosphorylated tau. These aggregates induce oxidative DNA damage, impair nuclear architecture, and promote mitochondrial dysfunction. Persistent DNA breaks marked by γH2AX and 53BP1 foci accumulate in aging neurons, activating p53–$p21^{CIP1}$ signaling and epigenetic remodeling that resembles canonical senescence pathways [130]. In addition, the high metabolic demand of neurons renders them vulnerable to ROS-mediated damage, further perpetuating DDR activation and reinforcing senescence signaling cascades. Importantly, DDR activity in neurons is not transient: studies in both human AD brains and transgenic mouse models show long-lasting DDR foci that co-occur with synaptic dysfunction and altered neuronal excitability [131].

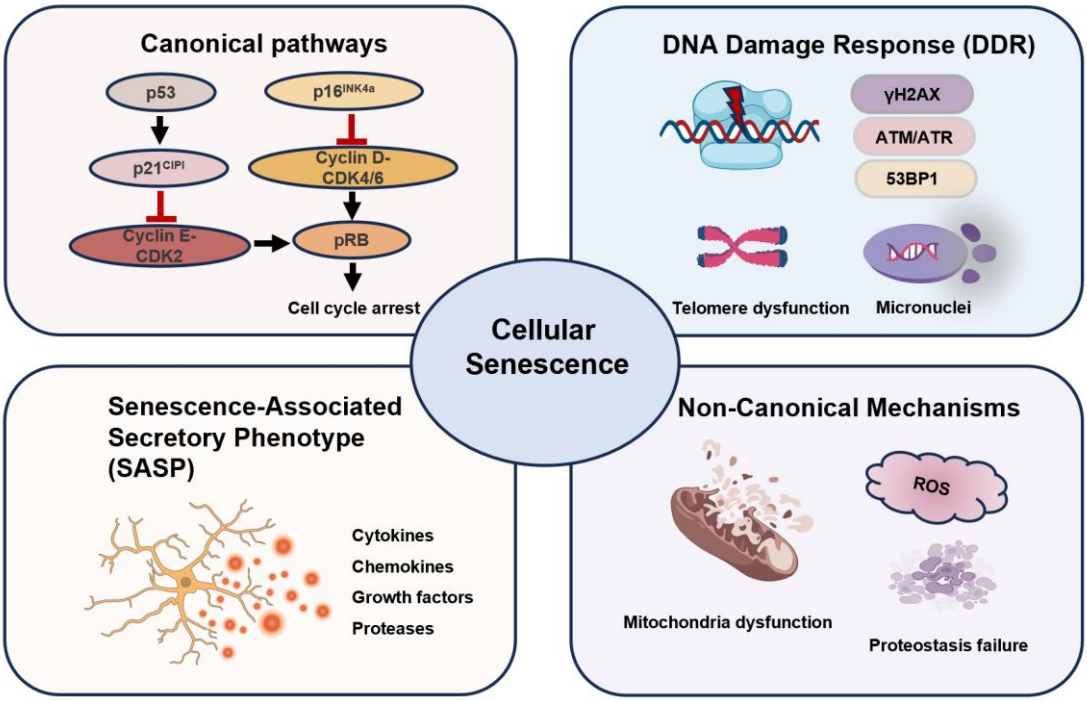

Figure 2. Mechanisms of cellular senescence in the CNS. Cellular senescence arises from diverse upstream stressors, including DNA damage and telomere dysfunction, metabolic and mitochondrial defects, proteostasis collapse, and chronic inflammation. Canonical signaling pathways involve the $p16^{INK4a}$–pRB and p53–$p21^{CIP1}$ tumor suppressor axes, which enforce durable cell-cycle arrest, while persistent DNA damage response (DDR) and telomere dysfunction reinforce senescence even in post-mitotic neurons. The senescence-associated secretory phenotype (SASP), driven by NF-κB, C/EBPβ, and cGAS–STING signaling, propagates inflammation, paracrine senescence, and neurotoxicity. Non-canonical amplifiers include mitochondrial dysfunction (MiDAS), autophagy impairment, proteostasis failure, and epigenetic remodeling, which stabilize the senescent state. In the CNS, these mechanisms converge in astrocytes, microglia, oligodendrocyte precursor cells, endothelial cells, and stressed neurons, thereby linking senescence to amyloid and tau pathology, neuroinflammation, and cognitive decline in AD.

The functional consequences of neuronal senescence extend beyond the cell-intrinsic level. Senescent neurons exhibit synaptic protein loss (e.g., decreased PSD-95, synaptophysin), dendritic spine retraction, and impaired calcium homeostasis, contributing directly to circuit dysfunction and cognitive decline [130]. In parallel, senescent neurons secrete a SASP-like profile, including pro-inflammatory cytokines (IL-6, TNF-α), chemokines (CCL2), and matrix metalloproteinases, which can activate surrounding microglia and astrocytes. This paracrine signaling fosters a feed-forward loop of neuroinflammation, further amplifying neurodegenerative cascades [132].

An additional hallmark is the accumulation of lipofuscin, an autofluorescent pigment that reflects defective lysosomal clearance. Lipofuscin buildup correlates with mitochondrial impairment and protein aggregation, and has been proposed as a histological marker of neuronal senescence in aging and AD brains [133]. Collectively, these changes suggest that neuronal senescence is not a passive marker of cellular stress but an active contributor to network-level dysfunction.

Preclinical studies have shown that selective clearance of senescent neurons, or pharmacological attenuation of their SASP, improves cognitive outcomes in mouse models of AD. For example, senolytic approaches (e.g., BCL-2 family inhibitors) or senomorphics targeting NF-κB signaling reduce neuroinflammation and partially restore synaptic integrity [17]. These findings underscore the translational relevance of neuronal senescence: while neurons may not divide, their adoption of a senescence-like state is sufficient to drive pathology and represent a viable therapeutic target. However, challenges remain in specifically distinguishing senescent neurons from transiently stressed but recoverable neurons, highlighting the need for multi-marker and functional readouts.

4.2 Astrocytes: Senescence as an Inflammatory Amplifier

Astrocytes are the most abundant glial cells in the CNS and play indispensable roles in synaptic homeostasis, neurotransmitter recycling, BBB regulation, and metabolic support. However, with aging and in AD, astrocytes undergo profound functional remodeling, including a transition into a senescence-like state. This shift is characterized by cell-cycle arrest, persistent DNA damage response signaling, mitochondrial dysfunction, and secretion of a proinflammatory SASP. These changes not only compromise astrocytic homeostatic functions but also actively contribute to neuroinflammation and neurodegeneration [17, 134].

Astrocyte senescence can be triggered by extrinsic insults, including Aβ deposition, tau pathology, and systemic inflammatory cues, as well as intrinsic stressors such as oxidative stress and telomere attrition. In vitro studies demonstrate that exposure of human astrocytes to Aβ oligomers induces DDR foci (γH2AX, 53BP1), upregulation of $p16^{INK4a}$ and $p21^{CIP1}$, and impaired mitochondrial function [135, 136]. Transcriptomic profiling of senescent astrocytes further reveals activation of NF-κB–dependent SASP networks, including IL-6, IL-1β, and MMP-3, all of which amplify tissue-level inflammation [119]. Another emerging mechanism is activation of the cGAS–STING pathway in astrocytes. Cytosolic DNA fragments released from damaged nuclei or dysfunctional mitochondria activate cGAS, leading to STING-mediated type I interferon and NF-κB signaling. This axis has been shown to reinforce SASP programs in astrocytes, linking nuclear instability with inflammatory amplification [25].

Senescent astrocytes lose essential homeostatic and neuroprotective functions. They display impaired glutamate uptake due to reduced expression of excitatory amino acid transporters (EAAT1/GLAST, EAAT2/GLT-1), predisposing neurons to excitotoxicity [137]. They also downregulate key neurotrophic factors (BDNF, GDNF), weakening neuronal resilience to stress.

In parallel, astrocytic SASP promotes chronic neuroinflammation, recruiting and activating microglia while also compromising BBB integrity. Matrix metalloproteinases secreted by senescent astrocytes degrade extracellular matrix and tight junction proteins, exacerbating vascular permeability and facilitating peripheral immune infiltration [138]. Recent spatial transcriptomics from human AD brains confirm that astrocytic senescence markers are enriched in regions of Aβ plaques and tau tangles, implicating them directly in the propagation of neuropathology [139, 140].

Mounting evidence suggests that senescent astrocytes are not merely bystanders but drivers of AD pathology. In transgenic AD mouse models, clearance of senescent astrocytes (and microglia) using senolytic drugs (dasatinib + quercetin) reduces neuroinflammation, lowers tau pathology, and improves cognitive outcomes [141]. Similarly, genetic ablation of $p16^{INK4a}$ positive astrocytes ameliorates Aβ burden and restores synaptic function [17]. These findings underscore astrocytic senescence as a therapeutic node linking neuroinflammation, proteostasis collapse, and cognitive decline.

Given their abundance and central role in CNS homeostasis, targeting senescent astrocytes offers unique therapeutic opportunities. Senolytic strategies (e.g., BCL-2 inhibitors) and senomorphics (agents that suppress SASP without killing cells) are being explored in preclinical models. Notably, inhibition of NF-κB or cGAS–STING signaling in senescent astrocytes attenuates SASP and reduces microglial activation [142, 143]. However, a key challenge is the heterogeneity of astrocytic responses: while some astrocytes adopt a pro-inflammatory senescent phenotype, others may retain neuroprotective functions. Thus, precision strategies that selectively target deleterious astrocytic senescence while sparing adaptive responses will be essential for translation.

4.3 Microglia: Senescence and Loss of Immune Competence

Microglia, the resident immune cells of the CNS, are essential for maintaining homeostasis through surveillance, synaptic pruning, and response to injury. With aging and in AD, however, microglia undergo profound phenotypic remodeling, including the adoption of senescence-like states characterized by impaired phagocytic function, chronic pro-inflammatory signaling, and the secretion of SASP factors [144]. Senescent microglia not only lose their neuroprotective capacity but also actively exacerbate neuroinflammation, synaptic dysfunction, and neurodegeneration [145].

Multiple intrinsic and extrinsic stressors converge to induce senescence in microglia. Chronic exposure to Aβ aggregates has been shown to induce DDR signaling, mitochondrial dysfunction, and upregulation of $p16^{INK4a}$ and $p21^{CIP1}$ in microglia [146, 147]. Transcriptomic studies from human AD brains confirm the presence of senescence-like microglial populations enriched near Aβ plaques, marked by lipofuscin accumulation, lamin B1 loss, and elevated SASP genes [148]. Oxidative stress is another potent driver. Microglia exposed to ROS or mitochondrial dysfunction exhibit NF-κB activation, persistent DDR foci (γH2AX, 53BP1), and impaired clearance of cellular debris [149]. Importantly, senescent microglia display reduced ability to phagocytose Aβ, thereby perpetuating plaque accumulation and neurotoxicity.

The cGAS–STING pathway has recently emerged as a crucial signaling axis linking genomic instability to microglial senescence. Cytosolic DNA fragments, originating from nuclear or mitochondrial sources, activate cGAS and subsequently STING, driving a robust type I interferon and NF-κB–mediated inflammatory response. Hyperactivation of this pathway in microglia promotes chronic neuroinflammation, synaptic loss, and cognitive decline [58, 59]. Pharmacological inhibition of STING in aged or AD mouse models attenuates microglial reactivity and restores neuronal function [25].

The hallmark of senescent microglia is the transition from protective surveillance to maladaptive inflammation. Normally, microglia phagocytose apoptotic cells and amyloid aggregates, limiting neurotoxicity. However, in senescent states, microglia lose this clearance capacity, leading to persistent accumulation of Aβ and dystrophic neurites [150].Instead, senescent microglia secrete a pro-inflammatory SASP, including IL-6, TNF-α, and CCL2, which propagate neuroinflammation and recruit peripheral immune cells across a compromised blood–brain barrier. At the same time, SASP factors act in a paracrine manner to induce senescence in neighboring astrocytes and neurons, amplifying CNS dysfunction. Morphologically, senescent microglia display dystrophic features—fragmented processes, cytoplasmic beading, and reduced motility—observable in both aged and AD brains [151]. These changes correlate with impaired surveillance capacity, further exacerbating synaptic vulnerability.

Microglial senescence contributes directly to both early and late stages of AD pathology. In early disease, impaired clearance of soluble Aβ oligomers facilitates plaque deposition, while chronic SASP secretion drives tau hyperphosphorylation and synaptic dysfunction. In late stages, senescent microglia adopt a "disease-associated microglia (DAM)" phenotype, characterized by high expression of ApoE, Trem2, and Cst7, but fail to resolve pathology [152, 153]. Instead, they reinforce inflammatory loops that worsen neuronal loss and cognitive decline. Compellingly, experimental clearance of senescent microglia in AD mouse models rescues synaptic integrity and improves cognitive performance. Senolytic therapies targeting $p16^{INK4a}$ positive microglia, or interventions modulating NF-κB and STING signaling, reduce both amyloid burden and neuroinflammation [25]. These results place microglial senescence as a central node in the pathophysiological cascade of AD.

Targeting microglial senescence is an attractive therapeutic strategy. Senolytic drugs such as dasatinib plus quercetin have been shown to selectively clear senescent microglia and astrocytes, reducing tau pathology and improving cognition. Senomorphics, including NF-κB inhibitors and STING antagonists, attenuate SASP and restore microglial phagocytic capacity without killing the cells [154]. Another emerging approach is immune checkpoint modulation, where targeting inhibitory receptors on senescent microglia restores immune function [143].

Given the heterogeneity of microglial states, a precision approach is essential: while senescent microglia are deleterious, certain DAM-like populations may retain partial protective functions. Thus, future therapies will likely combine selective senescence clearance with reprogramming strategies that restore homeostatic microglial activity.

4.4 Oligodendrocyte Lineage Cells: Impaired Remyelination Capacity

Oligodendrocyte lineage cells, including OPCs and mature oligodendrocytes, are indispensable for maintaining CNS integrity by producing myelin sheaths and supporting axonal health. Unlike neurons, OPCs retain proliferative capacity throughout life, enabling remyelination after injury and adaptive myelin plasticity. However, during aging and AD, oligodendrocyte lineage cells exhibit features of cellular senescence, including DDR, telomere shortening, mitochondrial dysfunction, and SASP secretion, which collectively impair myelin maintenance and regeneration [155, 156]. Dysfunction of

these cells contributes not only to white matter degeneration, a recognized hallmark of AD, but also to cognitive decline, given the critical role of myelin in neuronal circuit synchronization [157].

Aging OPCs show accumulation of DNA damage and telomere attrition, leading to increased expression of $p16^{INK4a}$ and $p21^{CIP1}$, hallmarks of senescence [158, 159]. Transcriptomic profiling of aged human and mouse white matter has identified a population of senescent OPCs with upregulated inflammatory pathways and downregulated myelination-related genes [160-162]. These cells also display reduced responsiveness to growth factors, diminished proliferation, and impaired differentiation into mature oligodendrocytes, thereby limiting remyelination capacity [163].

Mitochondrial dysfunction and oxidative stress are additional drivers of senescence in oligodendrocyte lineage cells. Oligodendrocytes are metabolically demanding due to their requirement for lipid synthesis during myelination. Excessive ROS production, mitochondrial DNA damage, and impaired mitophagy in aged or AD brains promote proteostasis collapse and senescence induction [164, 165]. Recent studies implicate neuroinflammatory signaling as a major extrinsic driver of oligodendrocyte senescence. Activated microglia and astrocytes release SASP factors such as IL-1β, TNF-α, and CCL2, which can reinforce senescence in OPCs via NF-κB–dependent transcriptional reprogramming [103, 166]. This paracrine induction of senescence suggests that oligodendrocyte lineage cells may act as secondary amplifiers of inflammaging in AD.

White matter degeneration is a consistent finding in both aging and AD, manifested as myelin thinning, nodal disruption, and oligodendrocyte loss [167]. Senescent OPCs fail to proliferate and differentiate in response to demyelinating insults, leading to remyelination failure and impaired axonal conduction. Functional imaging studies in AD patients demonstrate early white matter abnormalities, particularly in regions such as the corpus callosum and hippocampal connections, which correlate with memory deficits and cognitive impairment [168]. Moreover, senescent oligodendrocytes themselves adopt a SASP phenotype, secreting pro-inflammatory cytokines, matrix metalloproteinases, and extracellular vesicles that further compromise axonal integrity [169]. This positions oligodendrocyte lineage cells not only as victims of the senescence process but also as active contributors to neurodegeneration. Importantly, single-nucleus RNA sequencing of AD brains has revealed disease-associated oligodendrocytes with signatures of stress responses, senescence, and immune activation, particularly enriched in proximity to amyloid plaques and tau pathology [170]. These findings highlight the potential role of oligodendrocyte senescence in integrating amyloid, tau, and inflammatory insults into structural white matter decline.

Targeting oligodendrocyte senescence represents a promising but underexplored avenue for AD therapy. Preclinical studies indicate that senolytic interventions, such as dasatinib plus quercetin, can reduce senescent glial populations and restore remyelination efficiency [11]. Senomorphics, particularly NF-κB inhibitors and mitochondrial stabilizers, have shown potential in preserving OPC function under stress conditions [171]. Additionally, strategies aimed at enhancing OPC regenerative capacity—including growth factor supplementation (e.g., PDGF-AA, IGF-1), epigenetic modulators, and metabolic reprogramming are being investigated as complementary approaches [172, 173]. Given the dual role of oligodendrocyte lineage cells as both targets and amplifiers of senescence, future therapies may require combined senolytic and regenerative strategies to restore white matter integrity in AD.

4.4 Endothelial Cells and Pericytes: Vascular Senescence and Barrier Dysfunction

The neurovascular unit (NVU) is essential for maintaining cerebral homeostasis, consisting of endothelial cells, pericytes, astrocytic endfeet, and basement membrane components. Among these, cerebral endothelial cells (ECs) and pericytes play critical roles in forming and regulating the BBB, controlling vascular tone, nutrient delivery, and clearance of metabolic waste, including Aβ. With aging and in AD, both ECs and pericytes undergo senescence-like changes, characterized by DDR, mitochondrial dysfunction, inflammatory reprogramming, and impaired barrier function [174, 175]. Their dysfunction accelerates cerebrovascular pathology, exacerbates neuroinflammation, and synergizes with neuronal and glial senescence to drive disease progression.

Cerebral ECs are particularly susceptible to oxidative stress and inflammatory insults, which activate $p16^{INK4a}$ and $p21^{CIP1}$ pathways, inducing cell cycle arrest and senescence [176]. Senescent ECs display reduced nitric oxide bioavailability, increased ROS production, and pro-thrombotic properties, leading to vascular rigidity and hypoperfusion [177]. Importantly, senescent endothelial cells secrete SASP factors, including IL-6, IL-8, and MMPs, which disrupt tight junction proteins, such as claudin-5 and occludin, leading to BBB disruption [3]. Single-nucleus RNA sequencing of aged and AD human brain tissue has revealed transcriptional signatures of endothelial dysfunction, including upregulation of inflammatory and antigen presentation pathways and downregulation of transport and barrier genes [178]. Moreover, EC senescence has been shown to impair Aβ.

clearance across the BBB via reduced expression of LRP1 and P-glycoprotein transporters, thereby enhancing amyloid deposition [179, 180].

Pericytes, mural cells embedded within the capillary basement membrane, are indispensable for maintaining BBB stability and regulating cerebral blood flow. Pericyte loss is an early and consistent feature in AD pathology [181]. With aging, pericytes exhibit telomere shortening, mitochondrial damage, and SASP induction, leading to compromised contractility and increased capillary leakage [182]. Experimental models demonstrate that pericyte deficiency or senescence results in BBB leakage, hypoperfusion, and neurodegeneration, independent of amyloid pathology [183]. Pericytes also regulate clearance of toxic proteins via the glymphatic system and transcytotic pathways; their senescence impairs these mechanisms, amplifying protein aggregation stress in the parenchyma. Additionally, pericyte SASP contributes to the pro-inflammatory NVU microenvironment, activating astrocytes and microglia. This crosstalk amplifies chronic neuroinflammation and promotes neuronal vulnerability in AD [184].

Given their central role in neurovascular homeostasis, targeting senescence in ECs and pericytes represents a promising avenue for AD intervention. Senolytic therapies have shown efficacy in clearing senescent vascular cells and restoring BBB function in preclinical models [185]. For example, dasatinib and quercetin reduce endothelial SASP factors, attenuate vascular leakage, and improve cognition in aged mice [186, 187]. Alternative approaches include senomorphics such as NF-κB inhibitors or antioxidants that modulate SASP without eliminating the cells. Enhancing pericyte survival via PDGFRβ signaling or mitochondrial protection strategies has also been proposed to preserve BBB integrity [182]. Importantly, emerging vascular-targeted interventions, such as LRP1 upregulation and pericyte regenerative therapies, may synergize with anti-amyloid or anti-tau strategies to provide multimodal benefits in AD.

Taken together, these cell type-specific manifestations of senescence emphasize the systemic nature of the senescent burden in the CNS. Each cell type not only suffers functional decline but also propagates stress signals to other CNS compartments, amplifying neurodegenerative cascades. This interconnectedness provides multiple potential intervention points for therapeutic strategies aimed at mitigating senescence in AD.

5. Senescence in AD Pathogenesis

Cellular senescence has increasingly been recognized not as a passive correlate of aging but as an active contributor to AD pathogenesis. By integrating chronic DNA damage responses, dysfunctional proteostasis, and inflammatory secretory programs, senescent cells in the CNS influence nearly every stage of AD progression—from the initiation of Aβ and tau pathology to amplification of neuroinflammation, vascular dysfunction, and large-scale network disintegration.

5.1 Contribution of Senescent Cells to Amyloid and Tau Pathology

Senescent cells in the CNS, particularly astrocytes, microglia, and endothelial cells, actively modulate Aβ deposition and tau pathology. Senescent glial cells exhibit impaired proteostasis and lysosomal dysfunction, leading to reduced clearance of extracellular Aβ aggregates [17]. Senescent microglia show diminished phagocytic capacity, limiting the removal of soluble and insoluble Aβ species, while astrocytes demonstrate lower expression of Aβ-degrading enzymes, including neprilysin and insulin-degrading enzyme (IDE), which further promotes amyloid accumulation [188, 189]. In addition, the SASP indirectly enhances amyloidogenesis. Pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF-α, secreted by senescent cells stimulate β-secretase (BACE1) and γ-secretase activity, increasing Aβ production [190, 191]. Tau pathology is similarly influenced; SASP factors activate kinases like glycogen synthase kinase-3β (GSK-3β) and cyclin-dependent kinase 5 (CDK5), driving tau hyperphosphorylation and tangle formation [192]. Conditioned media from senescent astrocytes accelerate tau aggregation in primary neurons, highlighting paracrine propagation of pathology. In vivo, pharmacological clearance of senescent glia reduces tau burden and alleviates cognitive deficits in transgenic mouse models, confirming the pathogenic contribution of senescent cells.

5.2 SASP as a Driver of Neuroinflammation

The SASP constitutes a diverse pro-inflammatory and matrix-remodeling secretome, which in the CNS fuels chronic neuroinflammation. Senescent astrocytes and microglia release IL-6, IL-8, CCL2, VEGF, and MMP-3, all of which not only disrupt local homeostasis but also recruit and prime immune cells [32]. SASP factors compromise synaptic integrity by enhancing aberrant microglial pruning and weakening astrocytic glutamate uptake, thereby lowering the threshold for excitotoxic damage [193]. Endothelial senescence contributes further by releasing VEGF and adhesion molecules, promoting leukocyte infiltration and BBB breakdown [194]. Importantly, SASP signaling is self-amplifying. Paracrine senescence induces neighboring cells, including neurons, glia, and vascular elements, to adopt senescence-like

phenotypes, thereby propagating dysfunction through the brain parenchyma [195]. The chronicity and heterogeneity of SASP thus transform focal lesions into tissue-wide inflammatory states, a process tightly aligned with the progressive course of AD.

5.3 Feedforward Loop between AD Pathology and Senescence

Amyloid and tau pathology not only result from senescence but also reinforce it, forming a pathological feedforward loop. Aβ oligomers and tau aggregates induce DNA damage, mitochondrial dysfunction, and oxidative stress in neurons and glia, thereby triggering senescence pathways [196]. In turn, SASP-driven inflammation accelerates amyloidogenic processing of APP and tau hyperphosphorylation, closing a vicious cycle [10, 197]. Recent single-cell RNA-seq studies reveal that AD brains harbor senescent astrocyte and microglial subpopulations enriched for SASP gene signatures that spatially correlate with amyloid plaques and tau tangles [198]. Moreover, senescent endothelial cells contribute to vascular dysfunction and BBB breakdown, which enhances Aβ influx and neuroinflammation [184]. These findings indicate that AD pathology and cellular senescence are locked in a reciprocal amplification loop that drives disease progression. This feedforward loop provides a mechanistic explanation for the progressive and irreversible nature of AD.

5.4 Functional Consequences at the Network and Circuit Levels

Beyond molecular pathology, senescence has profound consequences on brain networks and circuits. Senescent astrocytes lose their capacity to maintain glutamate homeostasis and potassium buffering, leading to excitotoxic stress and impaired synaptic plasticity [199]. Senescent microglia exhibit exaggerated pro-inflammatory responses and diminished synaptic pruning, resulting in aberrant connectivity and impaired learning circuits [200]. Senescence-induced vascular dysfunction compromises cerebral blood flow, exacerbating hypometabolism and network hypoactivity [201]. Recent in vivo calcium imaging and electrophysiological studies reveal that regions enriched in senescent glia display disrupted oscillatory activity and impaired long-range communication between hippocampal and cortical circuits, correlating with memory decline [202]. Thus, senescence not only drives molecular hallmarks of AD but also translates into systems-level dysfunction.

Taken together, cellular senescence is not a bystander but a central amplifier of AD pathogenesis. Senescent astrocytes, microglia, OPCs, and endothelial cells converge to impair proteostasis, propagate inflammation, and destabilize neuronal circuits. The resulting senescence niche sustains pathology through self-reinforcing loops that couple molecular lesions to network dysfunction. Conceptually, this positions senescence as both a driver and an integrator of AD, bridging triggers such as Aβ and tau with downstream manifestations of cognitive decline. Therapeutic strategies that target senescent cells or their SASP therefore hold promise not merely to slow aging but to modify the course of neurodegeneration itself.

6. Potential Therapeutic

The recognition of cellular senescence as a driver of AD pathology has spurred the development of therapeutic strategies aimed at targeting senescent cells or modulating their deleterious effects. These interventions broadly fall into two categories: senolytics**,** which selectively eliminate senescent cells, and senomorphics**,** which suppress the harmful SASP without killing the cells. Both approaches hold promises for modifying the trajectory of neurodegeneration, yet they present distinct opportunities and challenges in translation to the CNS.

6.1 Senolytics

Senolytic therapies, which selectively eliminate senescent cells by exploiting their reliance on senescent cell anti-apoptotic pathways, have emerged as a promising strategy to counteract neurodegenerative processes in AD [203]. At present, several classes of senolytic agents have been investigated, including BCL-2 family inhibitors such as navitoclax (ABT-263), the dasatinib–quercetin (D+Q) combination, and peptide-based therapies such as FOXO4-DRI [204, 205]. Navitoclax effectively eliminates senescent cells but is limited by dose-dependent hematological toxicities, notably thrombocytopenia. Recent approaches to overcome these limitations include targeted prodrug formulations (e.g., Nav-Gal) and proteolysis-targeting chimera (PROTAC)-based BCL-xL degraders, which enhance tissue selectivity and may improve tolerability [206, 207]. Intermittent administration of D+Q effectively reduced senescent cell load, suppressed neuroinflammation, and improved cognitive deficits in aged and transgenic mouse models [11, 208]. Importantly, early-phase clinical studies in age-associated diseases such as idiopathic pulmonary fibrosis and diabetic kidney disease have reported safety and feasibility of D+Q administration, and an ongoing Phase I feasibility trial (NCT04685590) is now testing this approach in individuals with mild AD. Another line of senolytic development involves FOXO4-

DRI, a peptide that disrupts the FOXO4–p53 interaction, thereby releasing senescent cells from a survival lock; recent structural refinements have enhanced its specificity, although its translational relevance for AD remains to be determined [209]. Despite these advances, several challenges remain. On-target toxicities of current senolytics require careful dosing strategies and may necessitate CNS-specific delivery routes to minimize systemic exposure. Furthermore, the therapeutic window during the course of AD remains unclear, as senescence may play both protective and pathological roles depending on disease stage. Translational progress will depend on integrating biomarkers of senescence and SASP activity into trial design, monitoring pharmacodynamic responses in cerebrospinal fluid and imaging modalities, and considering combination approaches in which senolytics are paired with disease-modifying anti-amyloid or anti-tau agents. Collectively, these advances underscore the potential of senolytic therapies as a novel disease-modifying strategy in AD, while also highlighting the need for refined tools to target senescent cells in a temporally and cell type–specific manner.

6.2 Senomorphics

Senomorphics aim not to kill senescent cells but to reprogramme or suppress their harmful phenotypes, principally by attenuating SASP output, restoring proteostasis and mitochondrial health, or blocking innate-immune amplification loops that lock senescent cells into a pro-inflammatory state. In the brain this approach is especially attractive because many CNS cell types (astrocytes, endothelial cells, OPCs) retain functional roles that one would prefer to preserve, so long-term modulation of their secretory and metabolic profiles may be safer and more practicable than wholesale cell ablation. Mechanistically, three therapeutic levers have emerged from recent preclinical and translational work. Firstly, direct inhibition of the SASP transcriptional program by inhibiting NF-κB, JAK/STAT and p38-MAPK signaling pathways consistently reduced the secretion of IL-6, IL-1β, TNF-α and matrix metalloproteinases in senescent glial and endothelial cells, and suppressed paracrine senescence and local inflammation [59, 61, 210]. Pharmacological inhibitors of IKK/NF-κB and JAK1/2 show robust SASP suppression in vitro and reduce neuroinflammatory readouts in vivo, arguing that targeted anti-inflammatory senomorphics can decouple senescence from its tissue-damaging sequelae without removing the cell [44, 211]. Second, restoring proteostasis and mitochondrial quality control via the mTOR–AMPK–autophagy axis or NAD^+ augmentation has been shown to blunt the ROS→DDR→SASP feed-forward loop that sustains senescent phenotypes. mTOR inhibitors (rapamycin and rapalogs) enhance autophagic flux, promote clearance of aggregated proteins and improve cognition in several AD mouse models; ongoing clinical efforts are now testing rapamycin paradigms in humans for cognitive endpoints, although temporal and dose dependencies require careful calibration [212, 213]. Parallel strategies—activation of AMPK (e.g., metformin) or supplementation with NAD^+ precursors (nicotinamide riboside, NMN)—improve mitochondrial function, reduce inflammatory signaling, and in some preclinical and early clinical studies show signals consistent with modulation of ageing biology relevant to AD risk, making them promising senomorphic candidates for longer-term disease modification [214-216]. Third, blocking innate immune amplifiers that transduce cytosolic DNA into a persistent inflammatory program has recently gained traction: the cGAS–STING axis is a central node that links nuclear/mitochondrial damage to type I interferon and NF-κB-driven SASP. Genetic or pharmacological inhibition of STING reduces microglial reactivity, lowers brain inflammation and preserves cognitive function in aging and AD models, and several brain-penetrant STING antagonists (for example H-151 in preclinical studies) are progressing as candidate CNS senomorphics [22, 217, 218]. Together these approaches act at complementary points in the senescence network: NF-κB/JAK/p38 inhibitors reduce SASP transcription; mTOR/AMPK/NAD^+ interventions restore intracellular housekeeping and limit the upstream generation of damage signals; and cGAS–STING blockade prevents damaged DNA from converting into a chronic interferon/SASP amplifier.

Translating senomorphics to AD therapeutics requires overcoming several hurdles. BBB penetration is critical, as many systemic modulators have limited central exposure [213]. SASP's heterogeneity across cell types and disease stages demands multiplexed biomarker panels in CSF and plasma (cytokines, interferon signatures, metalloproteinases), imaging modalities (e.g., neuroinflammation PET, BBB integrity MRI), and ideally fluid or tissue transcriptomics to confirm on-target engagement [22]. Safety concerns are significant: chronic suppression of NF-κB or interferon signaling could impair host immunity [59]. Timing also matters; senomorphics may be most effective when administered during early or prodromal stages of AD (before irreversible neuronal loss), whereas late-stage disease may respond less favorably. Nevertheless, the promise is real: rapamycin and rapalogs are advancing in AD-focused prevention trials [212]; NAD^+ precursors are being tested in early human studies [216]; and brain-penetrant STING inhibitors offer a direct, CNS-relevant target [217]. Looking forward, combination strategies—using

senolytics to acutely reduce senescent cell burden followed by chronic senomorphic maintenance—are an attractive translational approach [219]. By reprogramming maladaptive signaling instead of eliminating cells, senomorphics may safely attenuate neuroinflammation, slow amyloid/tau propagation, and stabilize neural circuits in AD.

Emerging evidence also suggests that retrotransposons and human endogenous retroviruses (HERVs), once silenced in the genome, become derepressed during aging and senescence, generating cytosolic DNA that further activates cGAS–STING, exacerbating neuroinflammation in AD [85]. Recent clinical findings, such as the study by Sullivan et al., provide human evidence for HERV activation contributing to AD progression and highlight its potential as a therapeutic target [220].

A structured summary of senescence-targeted therapeutic strategies, including senolytics and senomorphics, is provided in Table 2.

Table 2. Therapeutic strategies targeting cellular senescence in AD.

Strategy	Representative Agents	Mechanism of Action	Clinical Status / Trial No.	Major CNS Challenges	Key Limitations	Key Refs
Senolytics	Dasatinib + Quercetin (D+Q)	Inhibit BCL-2/BCL-xL, induce apoptosis of senescent cells	Phase II (NCT04685590)	BBB penetrance; off-target toxicity	Thrombocytopenia, immune suppression	[205]
	Navitoclax (ABT-263), Nav-Gal (prodrug)	BCL-xL inhibition	Oncology Phase II; CNS use preclinical	Platelet toxicity	Poor selectivity for brain senescent cells	[256, 257]
	FOXO4-DRI peptide	Disrupt p53–FOXO4 survival signaling	Preclinical	Delivery to CNS	Stability and specificity	[258, 259]
Senomorphics	Rapamycin / Rapalogs	mTOR inhibition → ↑Autophagy, ↓SASP	Ongoing prevention trials (MET-FINGER; NCT04200911)	Dose-dependent BBB penetration	Metabolic/immune side effects	[260-262]
	Metformin, AMPK activators	Restore mitochondrial function, inhibit NF-κB/SASP	Multiple epidemiological and early cognitive trials	BBB variability	Lactic acidosis (rare), metabolic heterogeneity	[214, 263, 264]
	NAD^+ precursors	Enhance mitochondrial NAD^+, improve proteostasis	Early Phase (NCT04228666)	Bioavailability, long-term safety	Unknown optimal dosing	[265-267]
	cGAS–STING inhibitors (H-151)	Block cytosolic DNA sensing → ↓Type I IFN/SASP	Preclinical AD models	Achieving CNS exposure	Off-target immunomodulation	[268-270]
	JAK inhibitors (ruxolitinib, baricitinib)	Block SASP cytokine signaling (IL-6/IFN axis)	Approved for systemic use; pilot repurposing for neuroinflammation	CNS selectivity	Immune suppression	[271]
Combination	Senolytic–Senomorphic combo ("debulk and maintain")	Intermittent senolytic clearance followed by chronic senomorphic suppression	Conceptual/ preclinical	Sequential drug timing and delivery	Unknown cumulative toxicity	[272]
	MAGL inhibitors (e.g., JZL184, ABX-1431)	Increase 2-AG levels, reduce pro-inflammatory eicosanoids, activate PPAR-γ to suppress SASP	Preclinical AD and TBI models	Target engagement in glia, BBB permeability	Behavioral side effects, dosing precision	[246, 273]
	Telomerase activators (TA-65, GRN510)	Stabilize telomere length, reduce DDR-induced senescence	Preclinical; limited human data	Off-target proliferation	Potential tumorigenicity	[274, 275]

6.3 Preclinical and Clinical Progress

A growing body of preclinical evidence underscores the therapeutic potential of both senolytic and senomorphic strategies in AD models. In diverse transgenic mouse models harboring Aβ or tau pathology, intermittent administration of D+Q has been shown to reduce senescent glial burden, attenuate neuroinflammation, and improve cognitive outcomes, even in aged animals [208]. Similarly, selective elimination of $p16^{INK4a+}$ senescent

cells in tauopathy models reduces tau phosphorylation, diminishes synaptic deficits, and enhances performance in spatial memory tasks [17]. On the senomorphic front, systemic inhibitors of mTOR (e.g., rapamycin) or activators of AMPK (e.g., metformin) improve autophagic flux, restore mitochondrial function, reduce neuroinflammatory markers, and rescue cognition across multiple AD models, often outperforming standard anti-amyloid approaches [212, 221, 222]. Most notably, pharmacological blockade of the cGAS–STING pathway has demonstrated robust suppression of microglial activation, a reduction in pro-inflammatory cytokines, and preservation of cognitive function in both normal aging animals and AD model mice [59, 217]. Together, these preclinical findings establish proof-of-concept that both senolytic and senomorphic treatments can modify key pathological features of AD by targeting cellular senescence mechanisms.

These foundational preclinical successes have led to early-stage clinical efforts. Rapamycin (and its analogs) is currently being evaluated in preventative cognitive decline trials, such as the MET-FINGER study, which integrates mTOR inhibition with metabolic modulation to delay progression in at-risk populations [215]. Early-phase trials testing NAD^+ precursor supplementation (e.g., nicotinamide riboside, nicotinamide mononucleotide) have demonstrated safety and ITT feasibility, with preliminary signals suggesting possible enhancement of mitochondrial and inflammatory biomarkers [216]. Several clinical projects are exploring D+Q in aging-related disorders (e.g., idiopathic pulmonary fibrosis, diabetic kidney disease), with AD-targeted feasibility trials now underway to assess CNS penetration, tolerability, and biomarker engagement (NCT04685590). Parallel drug development efforts are advancing brain-penetrant STING inhibitors and selective BCL-xL degraders into preclinical stages, with the intention of later AD-targeted translation [141, 223, 224]. An emerging translational strategy involves a "debulk-and-maintain" model: intermittent senolytic administration to reduce high-burden senescent cell niches, followed by chronic senomorphic therapy to suppress residual SASP and maintain CNS homeostasis. This combinatorial framework, informed by rigorous preclinical modeling, offers a mechanistically grounded path toward clinical translation—promising disease modification with mitigated long-term toxicity risk.

6.4 Translational Barriers and Future Directions

Despite substantial progress, significant translational barriers remain. First, most senolytic and senomorphic agents exhibit poor BBB permeability, necessitating alternative delivery strategies or molecular redesign [225]. Second, current animal models do not fully recapitulate sporadic AD or immune aging, limiting predictive validity [226]. Third, senescent cells are heterogeneous across CNS cell types, and their roles evolve during disease progression, complicating therapeutic timing [227]. Fourth, biomarker development is limited. While $p16^{INK4a}$, SA-β-gal, and SASP profiling provide valuable cellular-level evidence, they cannot currently be used for patient stratification or longitudinal monitoring. Emerging epigenetic clocks, including DNAm PhenoAge and GrimAge, quantify biological age and correlate with systemic inflammation and cognitive decline [228, 229]. However, their application to CNS aging remains limited because most clocks were derived from peripheral blood and do not fully capture neuron- or glia-specific methylation dynamics. Recently developed brain-specific clocks, such as the CorticalClock and BrainAgeClock, show enhanced sensitivity to neuronal aging, tau pathology, and neuroinflammatory signatures [230, 231]. Although these CNS-targeted models require further validation, they may become valuable tools for quantifying senescence burden and tracking therapeutic response in future AD trials. In addition, circulating cell-free mitochondrial DNA, CSF cytokines, telomere-associated foci, and advanced imaging techniques such as TSPO-PET or senescence-targeted PET ligands are being explored as potential senescence biomarkers [232].

Importantly, recent translational experience has highlighted the complexity of bringing senolytic therapies to the clinic. For instance, UNITY Biotechnology's Phase I trial of UBX1325 (a BCL-xL inhibitor) revealed limited efficacy and dose-dependent adverse events, underscoring the need for improved CNS-targeted senolytics and better patient selection (NCT04537884). Such outcomes emphasize that senescence modulation, while mechanistically sound, demands rigorous safety evaluation, temporal precision, and robust biomarkers to guide dosing and target engagement.

Finally, sex differences represent an underappreciated but critical factor in senescence and AD. Females exhibit higher AD prevalence and faster epigenetic aging in the brain. Estrogen regulates telomerase activity, mitochondrial dynamics, and inflammatory pathways; its decline during menopause may accelerate microglial senescence and SASP expression [233, 234]. Conversely, androgens modulate oxidative stress and DNA repair in male brains [235-237]. Future therapeutic strategies must therefore consider sex-specific pathways and hormonal modulation. Altogether, combined approaches, such as initial senolytic "debulking" followed by long-term senomorphic maintenance, along with biomarker-guided, stage-specific, and sex-informed interventions, are likely to offer the most effective path toward clinically meaningful

modification of AD progression. These sex-specific molecular pathways also have critical clinical implications, underscoring the need for sex-stratified trial designs that account for hormonal status, differential metabolic responses, and potential interactions between hormone replacement, metabolic therapies, and senotherapeutic efficacy.

7. Perspectives

7.1 Limitations in Models and Detection Tools

Despite encouraging progress, major challenges remain in modeling and detecting cellular senescence in AD. Traditional transgenic AD mouse models capture amyloid or tau pathology but incompletely recapitulate the complex aging milieu in which cellular senescence evolves [238]. Senescence markers such as $p16^{INK4a}$, SA-β-gal activity, and γH2AX foci are widely used but neither specific nor consistently expressed across CNS cell types [24]. Moreover, their expression can be transient in response to acute stress, complicating interpretation. Novel single-cell and spatial transcriptomics approaches are beginning to resolve senescent subpopulations in human AD brain tissue [239], but these methods remain costly and technically demanding. The absence of validated CSF or plasma biomarkers specific for CNS senescence further complicates early diagnosis and trial readouts. Development of multiplex biomarker panels, integrating soluble SASP components with senescence-related microRNAs or extracellular vesicle signatures, will be essential for moving beyond histological surrogates.

7.2 Understanding Temporal and Spatial Dynamics of Senescence in AD

Senescence in the CNS is increasingly understood as a dynamic, context-dependent program rather than a fixed endpoint. Its contribution to AD pathogenesis appears to vary across disease stages and brain regions. Early in AD, astrocytic and microglial senescence may contribute to neuroinflammation and synaptic dysfunction, whereas in later stages, OPC senescence impairs myelin maintenance and repair [11]. The spatial distribution is also heterogeneous: hippocampus and entorhinal cortex show stronger senescent signatures compared to primary motor regions [240]. Temporal mapping of senescence trajectories in both animal models and human brain tissue will be critical to identify therapeutic windows. Integrating longitudinal imaging (e.g., TSPO-PET), fluid biomarkers, and post-mortem single-nucleus datasets may help distinguish when senescence transitions from adaptive to maladaptive, thereby informing stage-specific interventions.

7.3 Precision Medicine Approaches Targeting Senescence

Given the heterogeneity of senescence phenotypes, precision medicine approaches will be necessary. SASP composition differs between astrocytes, endothelial cells, and microglia, suggesting that therapies may need to be cell-type or pathway-specific [241]. For example, patients with predominant neuroinflammatory phenotypes may benefit more from NF-κB/JAK inhibitors, whereas those with mitochondrial/metabolic dysfunction may respond better to NAD^+ augmentation or AMPK activation. Genomic and epigenomic profiling, along with polygenic risk scores, could help stratify individuals more likely to exhibit senescence-driven pathology [242]. In the long run, adaptive clinical trial designs using biomarker-guided patient selection could accelerate the identification of responsive subgroups and reduce the risk of failure in heterogeneous AD populations.

7.4 Translational Prospect and Future Research Directions

Translating senescence-targeted strategies to the clinic faces multiple hurdles. BBB penetrance limits the CNS delivery of many promising senotherapeutics [204]. Long-term safety is another concern: chronic suppression of NF-κB or STING signaling could impair immune surveillance, increase infection risk, or promote tumorigenesis [243]. In parallel, regulatory frameworks for aging-modifying therapies remain in their infancy, making it challenging to define appropriate trial endpoints and approval pathways.

Beyond these obstacles, novel opportunities are emerging, including inhibition of monoacylglycerol lipase (MAGL), a central enzyme in 2-AG degradation. MAGL inhibition elevates 2-AG levels, reduces pro-inflammatory eicosanoid production, and activates PPAR-γ–dependent signaling that suppresses COX-2 and NF-κB–driven SASP activity [244-246]. Within the CNS, this mechanism promotes anti-inflammatory and homeostatic glial phenotypes, aligning with senomorphic strategies that reprogram maladaptive signaling without eliminating cells.

Looking forward, research priorities should include the development of brain-penetrant and reversible senotherapeutics; combinatorial strategies such as senolytic "debulking" followed by chronic senomorphic maintenance, potentially incorporating MAGL inhibitors; and the use of human-relevant models, including induced iPSC-derived brain organoids. Equally crucial will be biomarker-driven clinical trials that stratify patients by

senescence burden, SASP signatures, and genetic risk factors, paving the way for precision medicine approaches. By integrating mechanistic insights with translational frameworks, the field can move toward rational, stage-specific, and safe interventions that harness senescence biology to modify the course of AD.

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