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The Role of Glial Cell Senescence in Alzheimer's Disease

Fadhl Alshaebi[1,2] | Alessia Sciortino[1,2] | Rakez Kayed[1]

[1]Mitchell Center for Neurodegenerative Diseases, University of Texas Medical Branch, Galveston, Texas, USA | [2]Departments of Neurology, Neuroscience and Cell Biology, University of Texas Medical Branch, Galveston, Texas, USA

Correspondence: Rakez Kayed (rakayed@utmb.edu)

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ABSTRACT

Glial cell senescence, characterized by the irreversible arrest of cell division and a pro-inflammatory secretory phenotype, has emerged as a critical player in the pathogenesis of Alzheimer's disease (AD). While much attention has been devoted to the role of neurons in AD, growing evidence suggests that glial cells, including astrocytes, microglia, and oligodendrocytes, contribute significantly to disease progression through senescence. In this review, we explore the molecular mechanisms underlying glial cell senescence in AD, focusing on the cellular signaling pathways, including DNA damage response and the accumulation of senescence-associated secretory phenotypes (SASP). We also examine how senescent glial cells exacerbate neuroinflammation, disrupt synaptic function, and promote neuronal death in AD. Moreover, we discuss emerging therapeutic strategies aimed at targeting glial cell senescence to mitigate the neurodegenerative processes in AD. By providing a comprehensive overview of current research on glial cell senescence in Alzheimer's disease, this review highlights its potential as a novel therapeutic target in the fight against AD.

1 | Introduction

Aging is characterized by a generalized decline in cellular homeostasis, resulting in mitochondrial stress, oxidative stress, metabolic impairments, and DNA damage (Lopez-Otin et al. 2023). The accumulation of DNA damage, increased reactive oxygen species (ROS), telomere attrition, and disruption of metabolic processes all compromise cellular integrity and can trigger the onset of a protective physiological response termed cellular senescence (Figure 1) (McHugh and Gil 2018; Wiley and Campisi 2021). Cellular senescence limits the proliferation of aged and damaged cells, thereby preventing the spreading of dysfunctional cells (de Magalhaes 2024). Thus, it has critical implications, including wound healing and defense against tumorigenesis (de Magalhaes 2024). Despite its beneficial effects, cellular senescence has been recognized as a key factor contributing to aging and age-related diseases (Baker and Petersen 2018).

Abbreviations: AD, Alzheimer's disease; APOE, apolipoprotein E; APP, amyloid precursor protein; APP/PS1, amyloid precursor protein/presenilin 1 (mouse model); ATM, ataxia telangiectasia mutated; ATR, ataxia telangiectasia and Rad3–related; Aβ, amyloid beta; BBB, blood–brain barrier; BCL-2, B-cell leukemia/lymphoma 2 protein; BCL-xL, B-cell lymphoma—extra large; CA1, cornu ammonis 1 (hippocampal subfield); CA3, cornu ammonis 3 (hippocampal subfield); CDK, cyclin-dependent kinase; CNS, central nervous system; Cu/Zn SOD-1, copper/zinc superoxide dismutase 1; Cxcl1, C-X-C motif chemokine ligand 1; Cxcl10, C-X-C motif chemokine ligand 10; DAM, disease-associated microglia; DDR, DNA damage response; DNA, deoxyribonucleic acid; GFAP, glial fibrillary acidic protein; GLB1, galactosidase beta 1; GnRH, gonadotropin-releasing hormone; HIV, human immunodeficiency virus; HMGB1, high-mobility group box 1; HO-1, heme oxygenase-1; IGF-1, insulin-like growth factor 1; IL-1α, interleukin 1 alpha; IL-1β, interleukin 1 beta; IL-6, interleukin 6; iNOS, inducible nitric oxide synthase; JAK, Janus kinase; Ki-67, proliferation marker protein Kiel 67; LRP1, low-density lipoprotein receptor-related protein 1; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; mTOR, mammalian target of rapamycin; NFTs, neurofibrillary tangles; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NGF, nerve growth factor; NLRP3, NLR family pyrin domain containing 3; NO, nitric oxide; OPC, oligodendrocyte precursor cell; p16INK4A, cyclin-dependent kinase inhibitor 2A; p21WAF1/CIP1, cyclin-dependent kinase inhibitor 1; p53, tumor protein p53; PGRN, progranulin; PRRs, pattern recognition receptors; RNA, ribonucleic acid; ROS, reactive oxygen species; SAHF, senescence-associated heterochromatin foci; SASP, senescence-associated secretory phenotype; SA-β-gal, senescence-associated beta-galactosidase; SR-B1, scavenger receptor B1; STAT, signal transducers and activators of transcription; TauO, tau oligomers; TGF-β1, transforming growth factor beta 1; TLRs, toll-like receptors; TNF-α, tumor necrosis factor alpha; WHO, World Health Organization; γH2AX, gamma-H2A histone family member X.

The first two authors contributed equally to this article.

Senescent cells have been shown to accumulate in the body with time (Al-Azab et al. 2022; Going et al. 2002; Hudgins et al. 2018). They are characterized by a loss of proliferation/regenerative capacity, alteration of metabolic functions, and resistance to apoptosis. Senescent cells have been shown to present altered lipid metabolism, which likely occurs as a consequence of increased energy demand (Wiley and Campisi 2021). Moreover, they undergo widespread changes in lipid composition, which result in membrane remodeling and consequent morphological changes (Millner and Atilla-Gokcumen 2020). Senescent cells have also been shown to accumulate transition metals, such as iron, and iron accumulation has been associated with aging and age-related diseases (Wiley and Campisi 2021; Tian et al. 2022; Crescenzi et al. 2023). Overall, metabolic alterations result in shifted energy metabolism, increased oxidative stress, and disrupted cellular homeostasis, thus contributing to general tissue dysfunction.

During aging, proliferating cells exhibit progressive telomere shortening, which triggers replicative senescence and plays a crucial role in the aging process (Roger et al. 2021; Satyanarayana et al. 2003). Additionally, cellular senescence can be triggered by DNA damage, which can occur as a consequence of several replication-dependent and independent mechanisms such as telomere erosion, replicative stress, oxidative stress, and extrinsic factors such as exposure to radiation and genotoxic chemicals (Satyanarayana et al. 2003). The activation of the DNA damage response (DDR) promotes cell-cycle arrest through the activation of p53, which in turn activates the cyclin-dependent kinases (CDK) inhibitor p21.$^{WAF1/CIP1}$. Alternatively, cell-cycle arrest is mediated by the upregulation of the CDK inhibitor p16^{INK4A} (d'Adda di Fagagna 2008). When DNA damage becomes too severe, persistent, or irreparable, the DDR remains chronically active, enforcing the cell to undergo a permanent cell-cycle arrest and become senescent (Roger et al. 2021; d'Adda di Fagagna 2008). Accordingly, increased expression of p16^{INK4A}, p21,$^{WAF1/CIP1}$ and p53 with age has been reported in several tissues, and their removal has been shown to rescue aging-related phenotypes in mice (Chin et al. 1999; Baker et al. 2008; Janzen et al. 2006; Sato et al. 2015). Despite senescence having traditionally been associated with a permanent growth arrest in proliferating cells, recent evidence suggests that post-mitotic cells might also enter a senescence-like state, possibly as a defense mechanism against stress-induced tissue degeneration (Sapieha and Mallette 2018).

Senescent cells exhibit DNA damage, marked by the accumulation of γH2AX foci (Siddiqui et al. 2015), and chromatin remodeling, which occurs due to the loss of the nuclear lamina protein Lamin B1 (Freund et al. 2012) and the DNA chaperone protein high-mobility group box 1 (HMGB1) (Lopez-Otin et al. 2023; Sofiadis et al. 2021). Additionally, HMGB1 is released into the extracellular microenvironment, where it has been shown to promote inflammation, further amplifying age-related dysfunction (Gaikwad et al. 2024; Davalos et al. 2013). Finally, senescent cells release a mix of interleukins, chemokines, growth factors, and proteases, known as the senescence-associated secretory phenotype (SASP), which propagates senescence and contributes to the chronic inflammation seen in advanced age, ultimately leading to tissue damage (Schafer et al. 2020). The accumulation of senescent cells is associated with several age-related pathological conditions, such as atherosclerosis, cataracts, glaucoma, diabetes, and osteoarthritis (Holdt et al. 2011; Jeon et al. 2017; Childs et al. 2016). Recent evidence suggests that senescence also aggravates neurodegenerative conditions, including Alzheimer's disease (AD) (Baker and Petersen 2018).

1.1 | Cellular Senescence in Alzheimer's Disease

Alzheimer's disease is responsible for 60%–70% of cases of dementia worldwide, affecting an estimated 33–38 million individuals in 2023, according to the (World Health Organization (WHO) n.d.). Neuropathologically, AD is characterized by the presence of amyloid plaques, primarily composed of amyloid β (Aβ), and neurofibrillary tangles (NFTs), composed of the

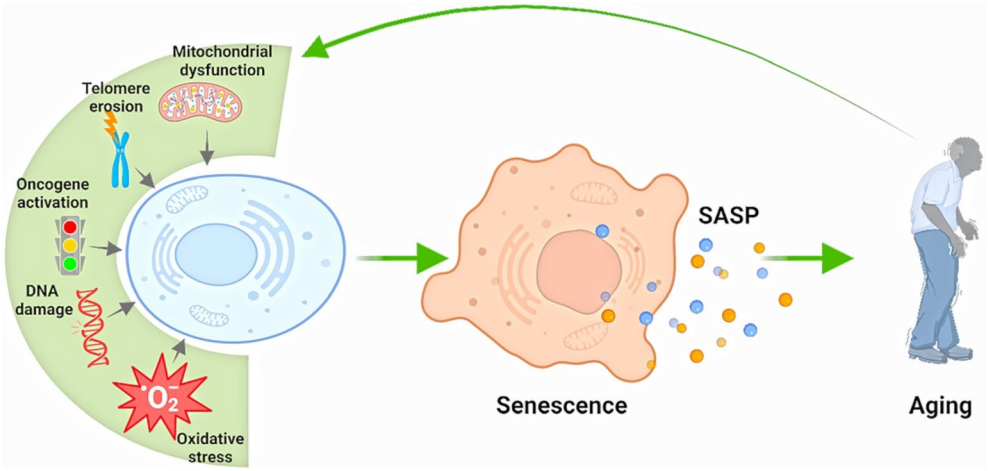

FIGURE 1 | Potential causes and consequences of cellular senescence. Cellular senescence is triggered by various factors, including mitochondrial dysfunction, telomere shortening, oncogene activation, DNA damage, and oxidative stress. These stressors lead to a state of permanent growth arrest, accompanied by metabolic changes, altered apoptosis sensitivity, and the secretion of pro-inflammatory molecules known as the senescence-associated secretory phenotype (SASP). SASP not only drives chronic inflammation and tissue dysfunction but also enhances aging processes and serves as a significant contributor to neurodegenerative diseases, including Alzheimer's disease (AD).

microtubule-associated protein tau (Trejo-Lopez et al. 2022). Extensive neuroinflammation, neurodegeneration, and brain atrophy, specifically affecting the hippocampus, entorhinal cortex, and neocortex, are also present (Leng and Edison 2021; Pini et al. 2016). Age is the major risk factor for AD, with 1 in 10 people aged over 65 years being at risk of developing the disease (Hou et al. 2019). Nevertheless, the process driving the increased vulnerability to AD associated with aging remains unclear. Senescent cells have been reported in the post-mortem brain tissues of AD patients, as well as in mouse models of the same disease (McShea et al. 1997; Bhat et al. 2012; Bussian et al. 2018; Wei et al. 2016; Zhang et al. 2019; Musi et al. 2018), suggesting that senescence plays a pivotal role in AD pathogenesis and progression. Several cellular changes typical of senescence are found in AD. DNA damage, in the form of telomeric alterations and DNA double-strand breaks, is widely present in AD and increases with disease progression (de la Monte et al. 1997; Frost et al. 2014; Frost et al. 2016; Panossian et al. 2003). AD patients exhibit shorter telomeres in their T lymphocytes, cortical microglia, and hippocampal neurons compared to healthy controls of the same age (Panossian et al. 2003; Thomas et al. 2008; Franco et al. 2006; Flanary et al. 2007; Forero et al. 2016).

Hightened expression of $p16^{INK4A}$ has been observed in tau tangle-bearing neurons and neuritic plaques within the cortices of AD patients, suggesting that senescence may be occurring in post-mitotic neurons affected by AD (McShea et al. 1997; Arendt et al. 1996; Arendt et al. 1998). Lamin B1 depletion has been observed in neurons of AD brains (Frost et al. 2016; Islam et al. 2022). Additionally, neurons from human AD brains and tauopathy mouse models display a loss of heterochromatin (Islam et al. 2022). Increased levels of $p16^{INK4A}$ and the DNA damage marker γH2AX have been observed in cortical astrocytes of AD patients (Bhat et al. 2012; Gaikwad et al. 2021), and elevated levels of HMGB1 in astrocytes have been associated with the presence of tau oligomers (Gaikwad et al. 2021). Levels of $p21^{WAF1/CIP1}$ and p53 are increased in AD (Bussian et al. 2018; Zhang et al. 2019; de la Monte et al. 1997; Luth et al. 2000; Ohyagi et al. 2005; Welch et al. 2022). Several SASP factors, including IL-1α, IL-1β, IL-6, MMP-1, MMP-3, TNF-α, and TGF-β, have been identified in AD brains (Bussian et al. 2018; Musi et al. 2018; Bjerke et al. 2011; Dursun et al. 2015; Horstmann et al. 2010; Lai et al. 2017; Gezen-Ak et al. 2013; Swardfager et al. 2010), and increased senescence-associated beta-galactosidase (SA-β-gal) activity has been observed in both neuronal and non-neuronal cells in AD mouse models (Bussian et al. 2018; Zhang et al. 2019; Hu et al. 2021; He et al. 2013).

The hallmarks of AD pathology, amyloid plaques and neurofibrillary tangles (NFTs), have been linked to increased expression of the cell cycle repressors $p16^{INK4A}$ and $p21^{WAF1/CIP1}$ and of the SASP genes. Aβ oligomers have been found to induce $p16^{INK4A}$ expression and SA-β-gal activity in neural stem/progenitor cells by activating the ROS-MAPK signaling pathway (He et al. 2013). Additionally, Aβ oligomers have been shown to trigger $p16^{INK4A}$ expression in mouse hippocampal neurons (Wei et al. 2016). In the APP/PS1 mouse model of Alzheimer's disease, senescent oligodendrocyte precursor cells (OPCs) marked by $p16^{INK4A}$ and $p21^{WAP1/CIP1}$ have been found near Aβ plaques. Senolytic treatment in these mice effectively removed senescent OPCs, reduced Aβ accumulation, and enhanced cognitive performance (Zhang et al. 2019). Additionally, pharmacological intervention to prevent microglial senescence has been shown to alleviate Aβ-related pathology in APP/PS1 mice (Hu et al. 2021). Pathological tau has been found to induce $p16^{INK4A}$ expression and secretion of SASP factors, including IL-1β and CXCL-1 (Bussian et al. 2018; Musi et al. 2018; Gaikwad et al. 2021). Senescent astrocytes and microglia expressing SA-β-gal, $p16^{INK4A}$, and SASP factors have been detected in a tauopathy mouse model, and clearance of $p16^{INK4A}$-positive senescent glial cells in these mice reduced tau phosphorylation, NFT formation, cortical and hippocampal neurodegeneration, and ameliorated memory and cognitive decline (Bussian et al. 2018). These findings highlight the significant role of cellular senescence in neurodegeneration associated with Aβ and tau. Nonetheless, the specific mechanisms by which senescence affects different brain cell types including neurons, astrocytes, microglia, neural stem/progenitor cells, and oligodendrocyte precursor cells in the context of Alzheimer's disease pathogenesis are not yet fully understood and warrant further investigation.

1.2 | Glial Cells Senescence

Glial cells constitute approximately 50% of the brain's cellular population (von Bartheld et al. 2016) and are crucial in maintaining brain homeostasis, both under healthy conditions and in disease. They include astrocytes, which maintain the blood–brain barrier and chemical balance; oligodendrocytes, which produce myelin to insulate neurons; and microglia, which act as immune cells by clearing debris and responding to injury (Salas et al. 2020; Sikora et al. 2021). These cells perform essential roles, including supplying neurons with nutrients, activating immune responses, and regulating synaptic transmission and plasticity (Salas et al. 2020; Sikora et al. 2021). Unlike neurons, glial cells retain the ability to proliferate in the adult brain (Lee et al. 2000), playing a crucial role in neuronal maintenance and repair. Their proliferation has been shown to significantly increase after injury (Ardaya et al. 2020; Joya and Martin 2021), contributing to tissue repair and neuronal survival. Astrocytes have the lowest proliferation rate in the healthy human brain (~0.3%–0.5% at a given time) but can rapidly expand after injury and form a glial scar, a physical and chemical barrier around the injury site that prevents the spreading of inflammation and supports tissue remodeling (Faulkner et al. 2004; Colodner et al. 2005). Microglia proliferation can reach up to 2% at a given time and can further increase after injury to clear debris and modulate neuroinflammation (Askew et al. 2017; Rodriguez et al. 2022; Sierra et al. 2007). Oligodendrocyte precursor cells (OPCs), which possess the highest proliferation rate amongst glial cells, generate new oligodendrocytes to restore myelin in demyelinated areas (Bradl and Lassmann 2010; Wang et al. 2020; Young et al. 2013).

However, excessive proliferation, particularly with aging or chronic injury, increases susceptibility to cellular senescence, leading to chronic inflammation, impaired regeneration, and a decline in neural function. Notably, a transcriptional analysis of age-related gene expression changes across various human brain regions, conducted on 480 individuals aged 16–106 years, revealed that most age-related gene expression differences were observed in glial cells rather than neurons (Soreq et al. 2017).

Dysregulation of astrocyte- and microglia-specific genes appeared to be the best predictor of aging, with the hippocampus and substantia nigra being the most affected brain regions (Soreq et al. 2017). Hippocampal and nigral neurons have higher energy demands and are more vulnerable to glucose deprivation, hypoxia, and oxidative stress (Wang and Michaelis 2010; Flores-Ponce and Velasco 2024), potentially explaining their heightened susceptibility to aging and neurodegenerative diseases. Notably, even within these regions, selective subfield vulnerability exists. In the hippocampus, for instance, CA1 pyramidal neurons experience extensive cell death following hypoxia-ischemia and oxidative stress, while morphologically similar pyramidal neurons in the neighboring CA3 regions remain largely intact (Wang and Michaelis 2010; Kreisman et al. 2000). Accordingly, only CA1 neurons exhibited an age-dependent volumetric decline, whereas other hippocampal subfields did not show an age effect (Mueller et al. 2007). This is especially significant given that CA1 neurons are affected early in AD pathology (Scheff et al. 2007; West et al. 2004). Therefore, their selective vulnerability, potentially exacerbated by glial dysfunction in this region, may play a key role in the development of age-related neurodegenerative disorders.

Neuronal pathology in AD is accompanied by elevated glial activation and chronic neuroinflammation, which disturb cellular homeostasis and contribute to cell death (Leng and Edison 2021). Several AD risk factors, such as APOE, TREM2, PGRN, and NLRP3, are specifically associated with glial cells and are responsible for the altered phagocytosis of Aβ and the instauration of a pro-inflammatory state (Raulin et al. 2022; Mendsaikhan et al. 2019; Li et al. 2023; Heneka et al. 2013). The release of inflammatory factors by senescent cells additionally contributes to chronic inflammation, exacerbates tissue dysfunction, and might further glial cell activation (Schafer et al. 2020), possibly creating a feedback loop that sustains neuroinflammation. In fact, senolytic therapy in mouse models has been shown to decrease neuroinflammation (Bussian et al. 2018; Drake et al. 2024; Wang et al. 2023; Yao et al. 2024), raising the potential of modulating senescence as a therapeutical approach for slowing down disease progression (Hickson et al. 2019).

1.2.1 | Astrocyte Senescence

Astrocytes make up approximately 20% of brain cells (Verkhratsky and Nedergaard 2018) and are vital for brain physiology and neuronal function. Among other functions, astrocytes provide nutrients to neurons, regulate synaptic cleft composition, maintain extracellular ion balance (e.g., by redistributing potassium ions from areas of high to low neuronal activity), regulate cerebral blood flow, preserve the integrity of the blood–brain barrier, and are involved in the repair of neural tissue (e.g., following traumatic brain injury) (Verkhratsky and Nedergaard 2018; Hussaini and Jang 2018). As components of the tripartite synapse, astrocytes control glutamate concentration and glutamatergic transmission and release their own glial transmitters (Perea et al. 2009). Additionally, they play a key role in post-injury recovery by reducing excitotoxicity from wounds, limiting damage, contributing to scar formation, and later aiding in tissue regeneration (Faulkner et al. 2004; Tanaka et al. 1997). Astrocytes also perform various immune functions, including expressing pattern-recognition receptors and secreting cytokines and chemokines (Ahmad et al. 2019; Farina et al. 2007).

Following acute injury, the number of reactive astrocytes increases, undergoing changes such as swelling, hypertrophy, proliferation, and elevated expression of the cytoskeletal glial fibrillary acidic protein (GFAP), a primary intermediate filament protein and key astrocyte marker (Verkhratsky et al. 2010). With aging, astrocytes exhibit notable increases in the expression of GFAP, which is one of the most common changes seen in these cells (Kawano et al. 2012; Salminen et al. 2011; Porchet et al. 2003). Vimentin, another intermediate filament once thought to be exclusive to immature astrocytes, also rises with age (Salminen et al. 2011; Porchet et al. 2003). Age-related transcriptomic analysis has identified dysregulated genes involved in cytoskeletal structure, proliferation, immune response, apoptosis, protein trafficking, and ubiquitin-mediated proteolysis (Simard et al. 2003; Simpson et al. 2011; Lee et al. 2022). Additionally, aging astrocytes often lose the ability to regulate synaptic glutamate levels and glutamate-glutamine homeostasis due to altered astrocyte-specific glutamate transporter expression (Kawano et al. 2012; Matias et al. 2023; Limbad et al. 2020). Several studies have shown that these functional changes weaken neuronal support and reduce synaptic interactions, leading to impaired synaptic function and plasticity, increased oxidative and proteolytic stress, and mitochondrial dysfunction in in vitro and in vivo models of normal aging (Lee et al. 2022; Chen et al. 2020; Gildea and Liddelow 2025; Pertusa et al. 2007). In the aging brain, astrocytic impairments are significantly correlated with hippocampal deterioration and defects in memory retrieval and consolidation (Ojo et al. 2015).

Astrocytes have been shown to undergo senescence similarly to other proliferation-competent cells. Murine and human senescent astrocytes exhibit reduced proliferation and increased expression of several established senescence markers, such as elevated SA-β-gal activity, increased expression of SASP components, and increased levels of $^{WAF1}p21^{CIP1}$, p53, and $p16^{INK4A}$ proteins in response to oxidative stress or proteasome inhibitors (Pertusa et al. 2007; Bitto et al. 2010; Evans et al. 2003). The transcription factor GATA4 was also identified as a mediator of senescence in astrocytes, oligodendrocytes, and pyramidal neurons (Kang et al. 2015). GATA4 was shown to accumulate in the prefrontal cortex of aged versus young human brains, and its expression spatially correlated with that of $p16^{INK4A}$. GATA4 regulated the expression of NF-κB as well as several SASP components, including IL6, IL1-A, and Cxcl1. Interestingly, GATA4 was activated in response to the DDR regulators ataxia telangiectasia and Rad3–related (ATR) and ataxia telangiectasia mutated (ATM) but independently from p53 and $p16^{INK4A}$ signaling (Kang et al. 2015).

Senescent astrocytes also display elevated levels of the DNA damage markers, senescence-associated heterochromatin foci (SAHF), γH2AX foci, and loss of lamin B1 (Gaikwad et al. 2021; Bitto et al. 2010; Matias et al. 2022). Lamin B1 reduction was associated with nuclear deformation in vitro and in vivo in the mouse and human hippocampus, with the granular layer of the dentate gyrus being the most affected area (Matias et al. 2022). Notably, Evans et al. (2003) demonstrated that human astrocytes undergo a form of senescence that is independent of telomere

erosion but dependent on p53. Their research also revealed elevated $p16^{INK4A}$ levels in the frontal cortex of older individuals and those with AD compared to younger subjects.

In vitro studies indicate that astrocytes can experience both replicative senescence and senescence induced by various external stressors (Pertusa et al. 2007; Cohen and Torres 2019; Dai et al. 2020; Yu et al. 2017). For example, ammonia induces senescence in cultured astrocytes through mechanisms dependent on glutamine synthesis and oxidative stress, driven by p53-mediated transcription of cell cycle regulatory genes, including $p21^{WAF1/CIP1}$ and GADD45a (Dai et al. 2020). Increased expression of $p21^{WAF1/CIP1}$, p53, and GADD45a mRNA was also noted in postmortem brain samples from patients with liver cirrhosis and hepatic encephalopathy (Yu et al. 2017). In long-term rat astrocyte cultures, enhanced generation of reactive oxygen species and decreased mitochondrial activity were observed, alongside an increase in proteins staining positively for nitro-tyrosine (Pertusa et al. 2007). Aged astrocytes in vitro also exhibited elevated expression of Cu/Zn superoxide dismutase (SOD-1), heme oxygenase-1 (HO-1), and inducible nitric oxide synthase (iNOS) as well as increased glutamate uptake. By day 90 in vitro, these cells were SA-β-gal positive and showed heightened GFAP expression (Pertusa et al. 2007). Ovarian estradiol has been shown to induce senescence in hypothalamic astrocytes, with these senescent cells affecting the regulation of progesterone synthesis and GnRH secretion, potentially influencing age-related declines in female reproductive function (Dai et al. 2020). Additionally, both HIV and methamphetamine have been implicated in inducing astrocyte senescence in vitro and in various animal models (Yu et al. 2017).

In co-cultures with hippocampal neurons, senescent astrocytes reduced the pool of synaptic vesicles (Kawano et al. 2012) and exerted neurotoxicity through increased release of pro-inflammatory factors and decreased release of neurotrophic growth factors (Turnquist et al. 2016). Additionally, senescent astrocytes have been shown to induce glutamate excitotoxicity, thus further contributing to neuronal dysfunction and cell death (Limbad et al. 2020). Following X-irradiation, human astrocytes exhibited a downregulation of genes encoding glutamate and potassium transporters, which resulted in impaired neurotransmitter reuptake and led to neuronal cell death in co-culture assays (Limbad et al. 2020). Taken together, these results highlight the critical role of cellular senescence in astrocyte-mediated neurotoxicity, which may significantly contribute to neurodegeneration and cognitive decline in age-related neurological diseases including AD.

In the context of AD, astrocytes are observed in the surrounding area of Aβ plaques and are thought to participate in Aβ clearance and degradation (Frost and Li 2017). Recent studies have shown that genetic variants linked to late-onset AD and genetic diversity modulate the astrocytic response in the 5xFAD mouse model, influencing resistance to AD development (Soni et al. 2024; Garcia-Agudo et al. 2024). Aged astrocytes present a reduced expression of the receptors responsible for Aβ uptake, the low-density lipoprotein receptor-related protein 1 (LRP1) and the scavenger receptor B1 (SR-B1), suggesting that senescent astrocytes may have a reduced capacity to degrade Aβ (Iram et al. 2016). Furthermore, astrocytes can become senescent when exposed to Aβ or tau. Aβ has been shown to trigger senescence in astrocytes by activating SA-β-gal and promoting the expression of $p16^{INK4A}$ and a secretory phenotype associated with p38 MAP kinase (Bhat et al. 2012). Primary human astrocytes treated with oligomeric Aβ presented increased expression of p53, $p21^{WAF1}$, and $p16^{INK4A}$, increased SA-β-gal activity, and decreased expression of the cell proliferation marker Ki-67 (Ungerleider et al. 2022). Furthermore, they exhibited increased secretion of IL-6, a member of the SASP, and reduced expression of the neurotrophic factors IGF-1 and NGF. DNA damage, as identified by the increase of γH2AX- and 53BP1-positive foci, was also present (Ungerleider et al. 2022). Additionally, reactive astrocytes present increased levels of β- and γ-secretase (Frost and Li 2017; Zhao et al. 2011), the enzymes responsible for Aβ production, raising the possibility that astrocytes might contribute to the total amyloid load.

In a study utilizing triple-label immunostaining of the frontal cortex tissue, it was found that more than 75% of GFAP-positive astrocytes in AD exhibited reactivity to both tau oligomers (TauO) and $p16^{INK4A}$, while significantly fewer TauO- and $p16^{INK4A}$-positive astrocytes were identified in age-matched non-demented controls. Additionally, the study reported elevated levels of HMGB1, indicative of the SASP, and increased γH2AX foci in TauO-associated astrocytes within AD brains (Gaikwad et al. 2021). Ablation of senescent astrocytes and microglia significantly reduced tau hyperphosphorylation and NFT formation in a tauopathy mouse model, indicating that senescent astrocytes might directly contribute to tau aggregation and deposition (Bussian et al. 2018).

Overall, evidence indicates that astrocyte senescence might contribute to AD pathophysiology by directly causing impaired neurotransmission and neuronal dysfunction, by exacerbating tau and Aβ aggregation, and by promoting a sustained state of neuroinflammation. Furthermore, senescent astrocytes have also been described in other neurodegenerative conditions, such as Parkinson's disease and amyotrophic lateral sclerosis (Turnquist et al. 2016; Chinta et al. 2018), suggesting that astrocyte senescence represents a common feature of neurodegeneration.

1.2.2 | Microglia Senescence

Microglia make up 5%–10% of cells in the brain on average, with significantly higher percentages found in the white matter in human brains (Mittelbronn et al. 2001). They are commonly referred to as the resident macrophages of the central nervous system, where they represent the main active immune defense. Microglia express a wide range of pattern-recognition receptors (PRRs) responsible for the detection of pathogens as well as tissue damage, including Toll-like receptors TLR1/2 and TLR4 and NOD-like receptors such as the NLRP3 inflammasome (Rodriguez et al. 2022). Microglia are responsible for the removal of infectious agents as well as damaged or unnecessary neurons and synapses, which they uptake through phagocytic and endocytic processes (Rodriguez et al. 2022; Sierra et al. 2014). Along with their implications in response to injury, microglia are thought to play a critical role in synaptic maturation during development (Pont-Lezica et al. 2014; Zhan et al. 2014) and synaptic surveillance in the adult brain (Nimmerjahn et al. 2005).

Aged microglia from non-demented individuals present a dystrophic appearance, characterized by loss of fine branches, short tortuous processes, and cytoplasmic fragmentation (Streit et al. 2004). In the retina of aged mice, the number of microglial cells has been shown to increase with age, and by 18 months, microglia had lost their characteristic ramified morphology and presented shortened dendrites and decreased branching (Sierra et al. 2007; Stojiljkovic et al. 2019; Xu et al. 2008; Damani et al. 2011). Additionally, aged microglia accumulated lipofuscin (Sierra et al. 2007; Xu et al. 2008), a polymorphous mixture of oxidized proteins and lipid waste material, likely resulted from decreased efficiency of degradation processes with age. Aged microglia exhibited reduced phagocytic activity (Ritzel et al. 2015) and significantly lower process motility and migratory velocity when compared to microglia from young mice (Damani et al. 2011). In another study, microglial senescence was investigated in the spinal cord of aged mice. Here, microglia presented increased mitochondrial activity and consequent elevated oxidative stress (Ritzel et al. 2015), characteristic of activated microglia.

In long-term cultures and in vivo, aged microglia displayed increased SA-β-gal activity and $p16^{INK4A}$ protein levels, while $p21^{WAF1/CIP1}$ and p53 were upregulated in vitro but not ex vivo (Stojiljkovic et al. 2019). Single-cell transcriptome analysis of different mouse models revealed that microglia undergo cellular senescence in the brain and the spinal cord during aging (Matsudaira et al. 2023). Specifically, old but not young mice presented elevated expression of $p16^{INK4A}$ mRNA and protein in the white matter, mainly in microglial cells. Overexpression of $p16^{INK4A}$ was accompanied by increased expression of SASP genes, such as *Il1b* and *Cxcl10*, and increased γH2AX levels, indicative of senescence-associated DNA damage. Interestingly, transcriptomic analyses revealed that $p16^{INK4A}$ expression was enriched in disease-associated microglia (DAM), and the DAM-related microglia cluster was only identified in old mice, indicating that aging is associated with increased DAM and that the majority of DAM are senescent (Matsudaira et al. 2023).

Upon immune challenge or brain injury, microglia shift from a homeostatic to an activated stage, become highly ramified, and adopt a pro-inflammatory profile. Compared to young microglia, microglia from aged mice presented increased basal expression of the pro-inflammatory cytokines TNFα, IL-1β, and IL-6 and of the anti-inflammatory cytokine TGFβ1 (Sierra et al. 2007; Ritzel et al. 2015). Moreover, following LPS administration, microglia from aged mice exhibited an exaggerated neuroinflammatory response compared to young microglia, with increased expression of both pro-inflammatory and anti-inflammatory cytokines (Sierra et al. 2007; Henry et al. 2009). It is possible to speculate that over time the sustained production of pro-inflammatory cytokines in older individuals might contribute to the increased neuroinflammation observed in aged brains and ultimately lead to cognitive deficits.

In a recent comprehensive analysis of senescent cells in AD, post-mortem cortical tissue from AD patients showed significantly higher numbers of senescent microglia, characterized by increased expression of $p16^{INK4A}$, $p21^{WAF1/CIP1}$, γH2AX, and GLB1 (encoding for β-galactosidase), when compared to age-matched non-demented control individuals (Fancy et al. 2024). Additionally, single-nuclei RNA sequencing showed upregulation of genes involved in DNA damage response and cellular senescence and downregulation of phagocytosis-related genes in AD (Fancy et al. 2024). Consistent with neuropathological observations that found senescent microglia to be mostly localized in proximity to Aβ plaques (Hu et al. 2021), senescence markers and transcripts for genes associated with DNA damage and mitochondrial stress were expressed at significantly higher levels in plaque-associated microglia (PAM) compared to microglia localized far from plaques (Fancy et al. 2024), suggesting that microglia senescence is dependent on the Aβ load. In a recent study, the selective targeting of PAMs in the 5xFAD mouse model of amyloidosis was shown to reduce Aβ burden and neuroinflammation and to improve behavioral deficits (Henningfield et al. 2024), indicating that targeting PAMs could represent a therapeutic strategy for AD.

In response to the abnormal protein misfolding and aggregation characteristic of neurodegenerative diseases, microglia adopt an activated state, which promotes neuroinflammation and the reactivation of proliferative programs (Leng and Edison 2021). Rapid microglia proliferation is often observed in AD neuropathology (Olmos-Alonso et al. 2016), where it is thought to lead to replicative senescence. In APP/PS1 mice, microglia were shown to rapidly expand after the appearance of Aβ plaques (Hu et al. 2021; Olmos-Alonso et al. 2016). Following this rapid expansion, microglia associated with Aβ plaques expressed markers of DAM and exhibited characteristics of senescent cells, including increased SA-β-gal activity, progressive telomere shortening, and the expression of senescence signature genes (Hu et al. 2021), supporting the hypothesis that microglia undergo replicative senescence subsequent to pathology-driven excessive proliferation. In this model, the pharmacological inhibition of microglia proliferation prevented the appearance of DAM, reduced microglial senescence likely by avoiding the onset of replicative senescence, mitigated Aβ-dependent synaptic damage, and improved cognitive deficits (Hu et al. 2021; Olmos-Alonso et al. 2016). These findings support the hypothesis that replicative senescence in microglia exacerbates amyloid pathology and contributes to cognitive decline.

Similarly to Aβ, exposure to tau has also been shown to promote microglia senescence. In primary microglia, exposure to recombinant human tau increased the levels of $p16^{INK4A}$ and $p21^{WAF1/CIP1}$ proteins and induced secretion of the SASP factors, including IL-1β, IL-6, and TNF-α (Karabag et al. 2023). Additionally, tau-treated microglia presented decreased levels of lamin B1 and accumulated γH2AX foci, indicating the presence of DNA damage, and exhibited cytoskeletal alterations and reduced migration towards the site of insult following an in vitro scratch wound assay. The uptake of tau was also decreased in these cells, suggesting a correlation between microglia senescence and tau clearance capability (Karabag et al. 2023). In PS19 mice, the overexpression of P301S mutant tau causes increased microglial expression of $p16^{INK4A}$, indicative of senescence as well as an increase in CD68- and CD11c-positive cells, indicative of DAM (Bussian et al. 2018; Yao et al. 2024). In this mouse model, the treatment with dasatinib + quercetin, a well-characterized senolytic therapy, reduced the number of $p16^{INK4A}$-positive microglia cells. Additionally, senolytic therapy promoted a reduction in DAM and a concomitant increase in

homeostatic microglia, which resulted in improved cognitive function (Yao et al. 2024).

Altogether, Aβ and tau pathology have been shown to promote microglia senescence, and senescent microglia have been shown to display reduced phagocytosis of tau and Aβ (Ritzel et al. 2015; Karabag et al. 2023; Hellwig et al. 2015). The inability of microglia to clear Aβ plaques and NFTs is thought to contribute to microglia's prolonged activation, which results in chronic neuroinflammation. Furthermore, constant microglia activation is thought to promote a sustained proliferation already at the early stages of the disease, which amplifies the inflammatory response, intensifies microglia senescence, and exacerbates neuropathology (Hu et al. 2021; Olmos-Alonso et al. 2016).

1.2.3 | Oligodendrocyte Senescence

Oligodendrocytes are specialized glial cells of the central nervous system, whose major function is to provide support and insulation to axons by encapsulating them in myelin sheaths (Bradl and Lassmann 2010). Myelin contributes to axon integrity and is essential for saltatory nerve conduction. Myelination defects disrupt neuronal excitability and synaptic transmission (Sutor et al. 2000), and neurons with altered myelin sheaths display impaired axonal transport and microtubule stability and have a dystrophic appearance (Haines et al. 2011; Kirkpatrick et al. 2001; Edgar et al. 2004). In mice, myelination appeared to be promoted by memory formation and to be essential for memory maintenance (Pan et al. 2020; Steadman et al. 2020). Furthermore, myelin content has been shown to decrease with age in mice and humans (Wang et al. 2020; Luan et al. 2021), suggesting that myelin loss might be responsible for age-dependent cognitive decline. In a recent study that investigated myelin formation and stability over time in mice, the age-dependent loss of myelin only partially resulted from myelin degradation and was mostly dependent on the loss of proliferation and differentiation capacity of OPCs (Wang et al. 2020). Additionally, preventing OPC differentiation was sufficient to induce spatial memory deficits in young mice, while promoting OPC differentiation in old mice was able to rescue synaptic loss and improve memory function (Wang et al. 2020). OPCs from aged mouse brains appear enlarged and flattened, present increased γH2AX foci and DNA damage, and have been shown to withdraw from the cell cycle (Kujuro et al. 2010; Gomez et al. 2024; Neumann et al. 2019; Ogrodnik et al. 2021; Windener et al. 2024). They have reduced differentiation potential and are characterized by a senescent profile including elevated expression of $p16^{INK4A}$, upregulation of senescence-related pathways, and increased SA-β-gal activity (Kujuro et al. 2010; Gomez et al. 2024; Neumann et al. 2019; Ogrodnik et al. 2021; Windener et al. 2024).

Besides OPCs, mature oligodendrocytes have also been shown to become senescent. Single-cell RNA sequencing of old versus young mouse brains revealed downregulation of genes related to myelin production and differentiation, suggesting a correlation between brain aging and myelin degeneration (Luan et al. 2021). Oligodendrocytes from aged brains presented increased expression of $p16^{INK4A}$ and $p21^{WAF1/CIP1}$ as well as other senescence- and aging-related genes (Luan et al. 2021; Ogrodnik et al. 2021). Additionally, oligodendrocytes from old but not young brains were shown to accumulate the transcriptional factor GATA4, which acts as a senescence and SASP inducer (Kang et al. 2015). Oligodendrocytes differentiated from fibroblasts of aged human donors presented increased $p16^{INK4A}$ and $p21^{WAF1/CIP1}$ expression and downregulation of lamin B1 (Windener et al. 2024). Oligodendrocytes associated with white matter lesions have been shown to upregulate γH2AX, $p16^{INK4A}$, and SA-β-gal activity in response to oxidative stress (Al-Mashhadi et al. 2015). Furthermore, inflammatory molecules released by microglia have been shown to prevent OPC differentiation and induce senescence markers in young oligodendrocytes (Luan et al. 2021; Windener et al. 2024). In mature oligodendrocytes, chronic NF-κB activation, which mimics the chronic inflammation observed in aged brains, induced SASP factors, increased expression of $p16^{INK4A}$, $p21^{WAF1/CIP1}$, and p53, and elevated SA-β-gal activity (Schlett et al. 2023).

As mature oligodendrocytes are post-mitotic cells, the acquisition of a senescent phenotype in these cells has to be based on mechanisms independent of cell division. Increased production of ROS, resulting from oligodendrocytes' elevated metabolic demands for myelin production and maintenance (Tepavcevic 2021), as well as increased susceptibility to oxidative stress, due to oligodendrocytes' limited antioxidant defenses (Thorburne and Juurlink 1996) can induce DNA damage and trigger cellular senescence. Moreover, the aging brain is often characterized by chronic inflammation. Therefore, senescence-related changes can be induced in mature oligodendrocytes by exposure to pro-inflammatory cytokines and extracellular matrix remodeling factors released by surrounding cells.

White matter deficits, caused by oligodendrocyte dysfunction and consequent axon demyelination, have been reported in several neurodegenerative diseases, including Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and AD (Nasrabady et al. 2018; Huang et al. 2024; Kolind et al. 2013; Dean 3rd et al. 2016; Bourbon-Teles et al. 2019). In AD patients, changes in myelin density in the left temporoparietal cortex have been correlated with disease duration (Ota et al. 2019). In another study, white matter hyperintensities, indicative of white matter lesions, have been shown to correlate with tau pathology (McAleese et al. 2015). In APP/PS1 mice, the shrinkage of the corpus callosum and the decrease in myelin content with age have been observed (Dong et al. 2018). Triple transgenic AD mice present myelin alterations, including granulations in the myelin lamina and lower myelin density, at 8 months (Qiu et al. 2023). Myelin dysfunction has been shown to increase APP cleavage and promote plaque formation (Depp et al. 2023). Conversely, Aβ has been shown to induce demyelination of the corpus callosum and a reduction of mature oligodendrocytes in rats (Jantaratnotai et al. 2003).

Exposure to Aβ has been shown to trigger SA-β-gal activity in OPCs in vitro (Zhang et al. 2019). OPCs associated with amyloid plaques exhibit increased levels of $p16^{INK4A}$ and $p21^{WAF1/CIP1}$ in both human AD and APP/PS1 mice. Additionally, APP/PS1 brains display an age-dependent increase in SA-β-gal activity, which colocalizes with OPC markers (Zhang et al. 2019). In the same model, pharmacologically preventing senescence of OPCs ameliorated myelination and reduced Aβ load (Xie et al. 2021). Although direct evidence of senescence in mature

oligodendrocytes has not yet been reported in AD and other neurodegenerative conditions, the presence of myelin defects and the knowledge that oligodendrocytes can acquire a senescent phenotype suggest that this possibility should not be ruled out. Given the increasing recognition of oligodendrocyte involvement in neurodegeneration, more targeted studies are needed to investigate whether mature oligodendrocytes undergo senescence and how oligodendrocyte senescence contributes to disease progression. Whether it is triggered by aging, amyloid pathology, or neuroinflammation, OPCs and possibly mature oligodendrocyte senescence can directly impair myelin repair and may significantly contribute to AD disease progression and cognitive decline.

A summary of the most common senescence markers in normal aging and Alzheimer's Disease can be found in Tables 1 and 2, respectively. The overall mechanisms through which glial cell senescence might contribute to neurodegeneration and AD pathology are summarized in Figure 2.

1.3 | Therapeutic Approaches Targeting Glial Cell Senescence in AD

Therapeutic strategies aimed at targeting glial cell senescence are emerging as a promising approach to slowing down neurodegeneration and ameliorating its associated symptoms. The use of senolytics, small molecules designed to selectively eliminate senescent cells and induce apoptosis, has already shown promising results in preclinical models. The senolytic agents dasatinib and quercetin (D + Q) have been shown to reduce the burden of senescent cells and alleviate neuroinflammation in animal models of neurodegenerative conditions. In a TBI model, intermittent administration of D + Q reduced $p16^{INK4A}$- and $p21^{CIP1/WAF1}$-positive cells, decreased levels of the pro-inflammatory cytokines IL-1 β and IL-6, attenuated neurodegeneration, and improved spatial and recognition memory (Wang et al. 2023). In APP/PS1 mice, weekly treatment with D + Q for 11 weeks reduced Aβ-plaque load and plaque-associated SA-β-Gal activity, and decreased the levels of pro-inflammatory cytokines IL-1β and TNF-α in the hippocampus (Zhang et al. 2019). Furthermore, senolytic treatment enhanced memory performance in the Y-maze and water maze tests, suggesting that improved cognition results from suppression of senescence-associated neuroinflammation and neurotoxicity. In the PS19 tauopathy model, D + Q reduced $p16^{INK4A}$-positive microglia cells, decreased tau hyperphosphorylation, rescued cerebral oxygen hypometabolism, preserved blood–brain barrier (BBB) integrity, and improved cognitive performance (Yao et al. 2024). In very old tauopathy mice, intermittent D + Q senolytic treatment reduced NFTs, improved cerebral blood flow, and decreased ventricular pathology and brain atrophy, overall exhibiting protective effects against neurodegeneration (Musi et al. 2018). In a phase I clinical trial, oral administration of D + Q decreased SA-β-Gal activity, reduced $p16^{INK4A}$ expression, and decreased levels of the circulating SASP factor MMP-12 (Hickson et al. 2019). In older adults presenting symptomatic early AD, D + Q oral administration decreased the level of several cytokines and chemokines associated with the SASP, including IL-17, IL-21, IL-10, IL-6, and MMPs-9 (Gonzales et al. 2023). Both dasatinib and quercetin were increased in the plasma of patients post-treatment, while only dasatinib was detected in the cerebrospinal fluid, indicating crossing of the blood–brain barrier. Although the treatment did not exhibit effects on cognition nor structural MRI measures, it is remarkable that senescence biomarkers were affected in both plasma and CSF in the short study period (Gonzales et al. 2023; Longo and Massa 2023).

Another senolytic agent, AP20187, which induces apoptosis of highly $p16^{INK4A}$-expressing cells, was shown to reduce microglia activation, alleviate SASP cytokine expression, and improve cognitive function in aged INK-ATTAC mice (Ogrodnik et al. 2021). In INK-ATTAC mice crossed with PS19 transgenic mice, AP20187 cleared $p16^{INK4A}$-, $p19^{Arf}$-, and $p21^{CIP1/WAF1}$-positive cells in the cortex and hippocampus, reduced IL-6 and IL-1β levels, decreased tau hyperphosphorylation in both the soluble and insoluble fractions, and alleviated NFT deposition in the dentate gyrus (Bussian et al. 2018). Inhibitors of the anti-apoptotic proteins BCL-2 and BCL-xL have been shown to induce selective apoptosis of senescent cells, including glial cells. Repeated treatment with Navitoclax (ABT-263) prevented the upregulation of the senescence-associated genes p16, p19, p21, IL-6, and IL-1 β and reduced tau hyperphosphorylation in the cortex and hippocampus of PS19 mice (Bussian et al. 2018). Fisetin, a naturally occurring flavonoid found in fruits and vegetables, has been shown to reduce $p16^{INK4A}$, $p21^{CIP1/WAF1}$, and SASP markers in several tissues, reduce age-related pathology, and improve lifespan in aged mice (Yousefzadeh et al. 2018).

Senomorphics are small molecules that inhibit the activation of signaling pathways responsible for SASP expression, such as p38MAPK, mTOR, and JAK/STAT, or target transcription factors, such as NF-κB and STAT3, which are responsible for the maintenance of the senescent phenotype. The mTOR kinase inhibitor rapamycin was shown to reduce amyloid plaques and improve vascular and cognitive function in the J20 (PDGF-APPSw,Ind) AD mouse model (Van Skike et al. 2021; Lin et al. 2013). Rapamycin long-term treatment starting from a young age prevented tau pathological hyperphosphorylation and aggregation in the cerebral cortex of P301S mice, while treatment with PQR530, which exhibits improved pharmacokinetic properties, reduced tau pathology even at later time points (Morawe et al. 2022). The polyphenol resveratrol exhibits anti-inflammatory properties by inhibiting NF-κB. Resveratrol treatment was shown to prevent the secretion of IL-6 and TNF-α in microglial cells exposed to fibrillar Aβ and to reduce Aβ deposition and microglial activation in APP/PS1 mice (Capiralla et al. 2012). A recent meta-analysis of randomized clinical trials provided preliminary evidence for the potential effect of resveratrol in reducing Aβ load, inflammation, and oxidative stress and delaying cognitive impairment in AD patients (Tosatti et al. 2022). The polyphenol apigenin was shown to downregulate NO and pro-inflammatory cytokines in microglial cell lines and primary microglia. In iPSC-derived neurons from familial AD exposed to activated microglia-conditioned media, apigenin exhibited protective effects against inflammation-induced neuronal cell death and neurite shortening (Balez et al. 2016). Additionally, in Wistar rats stereotaxically injected with Aβ, apigenin ameliorated spatial working memory and protected against hippocampal neuronal loss.

TABLE 1 | Markers of age-related senescence.

	Astrocytes	Microglia	OPCs	Oligodendrocytes
Morphology		Dystrophic appearance (Streit et al. 2004)		
Metabolism	↑ Oxidative stress (Pertusa et al. 2007) ↑ SA-β-gal (Pertusa et al. 2007; Bitto et al. 2010)	↑ Oxidative stress (Ritzel et al. 2015) ↑ SA-β-gal (Stojiljkovic et al. 2019) ↓ phagocytosis (Ritzel et al. 2015) ↑ lipofuscin (Sierra et al. 2007; Streit et al. 2004; Safaiyan et al. 2016)	↑ SA-β-gal (Kujuro et al. 2010)	↑ SA-β-gal (Kujuro et al. 2010)
Cell-cycle arrest	↑ $p16^{INK4A}$ (Bitto et al. 2010; Evans et al. 2003) ↑ $p21^{WAF1/CIP1}$ (Bitto et al. 2010; Ogrodnik et al. 2021) ↑ p53 (Bhat et al. 2012; Bitto et al. 2010; Evans et al. 2003)	↑ $p16^{INK4A}$ (Stojiljkovic et al. 2019; Matsudaira et al. 2023; Ogrodnik et al. 2021) ↑ $p21^{WAF1/CIP1}$ (Stojiljkovic et al. 2019; Ogrodnik et al. 2021) ↑ p53 (Stojiljkovic et al. 2019)	↑ $p16^{INK4A}$ (Gomez et al. 2024; Neumann et al. 2019; Ogrodnik et al. 2021) ↑ $p21^{WAF1/CIP1}$ (Ogrodnik et al. 2021)	↑ $p16^{INK4A}$ (Gomez et al. 2024; Neumann et al. 2019; Ogrodnik et al. 2021) ↑ $p21^{WAF1/CIP1}$ (Ogrodnik et al. 2021)
DNA damage	↑ γH2AX (Gaikwad et al. 2021) ↑ SAHF (Bitto et al. 2010) ↓ Lamin B1 (Matias et al. 2022)	↑ γH2AX (Matsudaira et al. 2023)	↑ DNA strand breaks (Neumann et al. 2019)	↑ γH2AX (Al-Mashhadi et al. 2015) ↓ Lamin B1 (Windener et al. 2024)
Inflammation	↑ SASP (Turnquist et al. 2016) ↑ GATA4 (Kang et al. 2015)	↑ SASP (Sierra et al. 2007; Ritzel et al. 2015; Henry et al. 2009; Ogrodnik et al. 2021)		↑ GATA4 (Kang et al. 2015)

TABLE 2 | Markers of pathology-induced senescence.

	Astrocytes	Microglia	OPCs
Morphology		Dystrophic appearance (Streit et al. 2009)	
Metabolism	↑ SA-β-gal (Bhat et al. 2012; Ungerleider et al. 2022) ↓ Aβ endocytosis (Iram et al. 2016)	↑ SA-β-gal (Hu et al. 2021; Fancy et al. 2024) ↓ phagocytosis (Fancy et al. 2024; Karabag et al. 2023; Hellwig et al. 2015)	↑ SA-β-gal (Zhang et al. 2019; Xie et al. 2021)
Cell-cycle arrest	↑ $p16^{INK4A}$ (Bhat et al. 2012; Bussian et al. 2018; Gaikwad et al. 2021; Ungerleider et al. 2022) ↑ $p21^{WAF1/CIP1}$ (Ungerleider et al. 2022) ↑ p53 (Ungerleider et al. 2022) ↓ Ki67 (Ungerleider et al. 2022)	↑ $p16^{INK4A}$ (Bussian et al. 2018; Yao et al. 2024; Fancy et al. 2024; Karabag et al. 2023) ↑ $p21^{WAF1/CIP1}$ (Fancy et al. 2024; Karabag et al. 2023)	↑ $p16^{INK4A}$ (Zhang et al. 2019) ↑ $p21^{WAF1/CIP1}$ (Zhang et al. 2019; Xie et al. 2021)
DNA damage	↑ γH2AX (Gaikwad et al. 2021; Ungerleider et al. 2022) ↑ 53BP1 (Ungerleider et al. 2022)	↑ γH2AX (Fancy et al. 2024; Karabag et al. 2023) ↓ Lamin B1 (Karabag et al. 2023)	
Inflammation	↑ SASP (Gaikwad et al. 2021; Ungerleider et al. 2022) ↑ HMGB1 (Gaikwad et al. 2021)	↑ SASP (Karabag et al. 2023)	

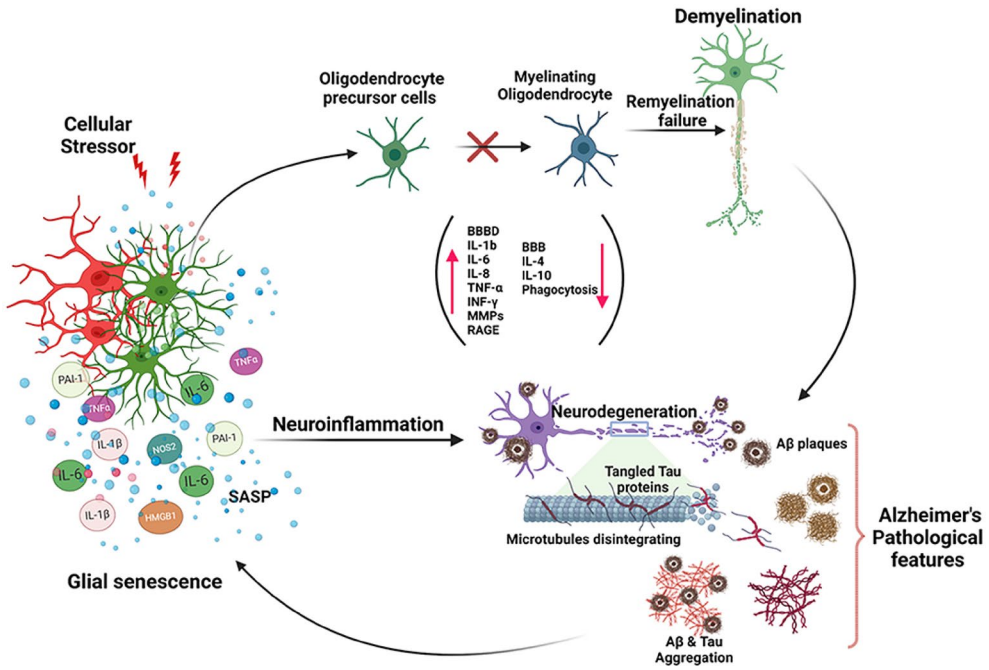

FIGURE 2 | Potential mechanisms underlying brain glial senescence contributing to or enhancing Alzheimer's disease (AD). Glial cell senescence plays a pivotal role in the pathophysiology of Alzheimer's Disease (AD), with astrocytes, microglia, and oligodendrocytes in the AD brain or AD model mice undergoing senescence in response to stressors such as mitochondrial dysfunction, telomere shortening, oncogene activation, DNA damage, and oxidative stress. These stressors induce permanent growth arrest in glial cells. Senescent glial cells secrete pro-inflammatory cytokines and molecules, collectively known as the senescence-associated secretory phenotype (SASP), which promotes a neuroinflammatory environment that exacerbates neurodegenerative processes in AD. Specifically, the SASP impairs the function of oligodendrocyte precursor cells (OPCs), hindering their differentiation into myelinating oligodendrocytes and leading to remyelination failure. Additionally, the accumulation of hyperphosphorylated tau and amyloid-β (Aβ) oligomers accelerates neurodegeneration and further drives the progression of brain cell senescence, reinforcing the senescent state through positive feedback loops. These processes contribute to cognitive decline and neuronal loss, hallmarks of AD. BBBD, blood–brain barrier dysfunction; HMGB1, high mobility group box 1; IL-10, interleukin-10; IL-1β, interleukin-1 beta; IL-4, interleukin-4; IL-6, interleukin-6; IL-8, interleukin-8; INF-γ, interferon gamma; MMPs, matrix metalloproteinases; NOS2, nitric oxide synthase 2 (inducible NOS); PAI-1, plasminogen activator inhibitor-1; RAGE, receptor for advanced glycation end products; TNF-α, tumor necrosis factor alpha.

The monoclonal antibody adalimumab, which specifically targets TNF-α, was shown to attenuate neuroinflammation by preventing astrocyte and microglia activation in mice injected with $A\beta_{1\text{-}40}$. Additionally, adalimumab treatment prevented hippocampal neuronal loss, reduced amyloidosis, and rescued memory impairments (Park et al. 2019). Ginsenoside F1 suppresses the NF-κB signaling pathway and exhibits strong antioxidant and anti-inflammatory properties. The Ginsenoside F1-enhanced mixture (SGB121) was shown to mitigate oxidative stress, reduce $p16^{INK4A}$ levels and SA-β-gal activity, and rescue telomere shortening in the brain of mice fed a high-fat diet. Furthermore, SGB121 reduced the secretion of several pro-inflammatory cytokines and chemokines, including IL-6, TNF-α, CXCL-11, and MMP-2, prevented astrocyte and microglia activation, and reduced tau hyperphosphorylation (Hou et al. 2022). Overall, senotherapeutics offer a variety of mechanisms to target senescence, including glial cell senescence and open up new therapeutic possibilities for Alzheimer's disease by reducing neuroinflammation and preserving brain function. It must be noted that when it comes to senomorphics, different from senolytics that eliminate senescent cells, continuous treatment is needed to maintain the suppression of the SASP and/or the inflammatory processes driven by senescent cells.

Senolytic therapy has been shown to extend lifespan and ameliorate several age-related conditions in mice (Yousefzadeh et al. 2018; Xu et al. 2018; Mikawa et al. 2024). While promising, senotherapeutics face significant limitations, particularly in their efficacy and potency across different models. Given the diverse triggers of cellular senescence, the effects of senotherapeutics are not universal and might be more effective in certain cell types than in others. For example, outside the context of neurodegeneration, dasatinib selectively eliminated senescent preadipocytes but not human endothelial cells, whereas quercetin exhibited the opposite effect (Zhu et al. 2015). Additionally, the cellular microenvironment plays a crucial role, with factors such as oxygen levels, circulating SASP components, and nutrient availability influencing senescence (Wiley and Campisi 2021; Schafer et al. 2020). Notably, metabolic alterations are closely linked to cellular senescence (Wiley and Campisi 2021), and caloric restriction has shown protective effects against age-related dysfunctions (Mikawa et al. 2024; Dorling et al. 2020). These findings suggest that dietary factors could significantly modulate the efficacy of senotherapeutics, a consideration that must be integrated into clinical trial designs.

Senescence is a systemic process, occurring throughout the body rather than being confined to the brain (Al-Azab et al. 2022; Going et al. 2002; Hudgins et al. 2018). Given that local administration of senolytics for neurodegenerative conditions is impractical, systemic effects of such treatments are unavoidable. In aged individuals, several biological processes that act as triggers for senescence, such as mitochondrial function and protein degradation, are often already compromised in cells that are not yet senescent (Lopez-Otin et al. 2023; Wiley and Campisi 2021), raising concerns that senolytic therapy could disrupt homeostasis and exert more generalized cytotoxic effects. Additionally, senescence is involved in essential beneficial responses such as facilitating wound healing and suppressing tumorigenesis (de Magalhaes 2024). Thus, the indiscriminate elimination of senescent cells may lead to unforeseen harmful consequences. Finally, the long-term efficacy of senolytic treatments remains largely unexplored. Intermittent administration of senolytic agents, employing a "hit-and-run" strategy, has been proposed to minimize off-target effects, but further research is required to determine its efficacy. Furthermore, as senescent cells accumulate in the aging brain, it is unclear whether their large-scale removal could per se have detrimental effects.

2 | Conclusions

Glial cell senescence is increasingly recognized as a significant contributor to Alzheimer's disease pathology. Glial cells, including microglia, astrocytes, and oligodendrocytes, play critical roles in maintaining homeostasis in the central nervous system (Salas et al. 2020; Sikora et al. 2021). When they become senescent, glial cells lose their supportive and neuroprotective functions, promote neuroinflammation, exacerbate synaptic dysfunction, and drive neurodegeneration (Sierra et al. 2007; Wang et al. 2020; Kawano et al. 2012; Limbad et al. 2020; Turnquist et al. 2016; Ritzel et al. 2015; Henry et al. 2009; Luan et al. 2021) (Figure 2). The failure of cell repair mechanisms was observed with aging results in autophagy and mitochondria dysfunction, both associated with several neurodegenerative diseases (Lopez-Otin et al. 2023). Impaired proteostasis and defective autophagy contribute to the accumulation of misfolded proteins within neurons (Cozachenco et al. 2023; Barmaki et al. 2023), while impaired phagocytosis and disruption of lysosomal degradation pathways halt Aβ and tau aggregates' clearance by glial cells (Kreher et al. 2021; Tajbakhsh et al. 2021; Wang et al. 2009). Mitochondrial dysfunction is responsible for the increased production of reactive oxygen species, promoting oxidative stress and causing damage to DNA, proteins, and lipids (Bhatti et al. 2017; Miwa et al. 2022). Persistent DNA damage activates p53 and $p16^{INK4A}$ pathways, triggering senescence (d'Adda di Fagagna 2008). In turn, several senescence-related mechanisms can impair mitochondrial function (Miwa et al. 2022), creating a feedback loop that drives tissue dysfunction. The increased oxidative stress and the release of pro-inflammatory molecules by senescent cells as part of the SASP contribute to the instauration of a chronic, low-grade inflammation, often referred to as inflammaging (Schafer et al. 2020). Chronic neuroinflammation promotes senescence in neighboring cells (Schafer et al. 2020), creating a feedback loop that perpetuates glial senescence and worsens neuronal injury.

In AD, Aβ and tau have been shown to directly induce senescence of glial cells. Tau pathology has been associated with the senescence of astrocytes, microglia, neurons, and endothelial cells in AD patients and animal models (Bussian et al. 2018; Musi et al. 2018; Gaikwad et al. 2021; Karabag et al. 2023; Hussong et al. 2023). Exposure to Aβ induced senescence in hippocampal neural stem and progenitor cells (NSPCs), astrocytes, and oligodendrocyte progenitor cells (OPCs) (Zhang et al. 2019; He et al. 2013; Ungerleider et al. 2022; Xie et al. 2021; Li et al. 2024). Senescent microglia and astrocytes exhibit a decline in their phagocytic capacity, resulting in impaired clearance of cellular debris and protein aggregates (Iram et al. 2016; Fancy et al. 2024; Karabag et al. 2023; Hellwig et al. 2015). Furthermore, senescent microglia and astrocytes have been involved in Aβ seeding (Frost and Li 2017; Parhizkar et al. 2019), contributing to

amyloid plaque formation and accelerating disease progression. The release of pro-inflammatory cytokines by senescent microglia and astrocytes promotes the senescence of oligodendrocytes and OPCs (Luan et al. 2021; Windener et al. 2024). Additionally, senescent astrocytes have been shown to release HMGB1 (Gaikwad et al. 2021), which further fosters OPC senescence (Rouillard et al. 2022). Oligodendrocyte senescence leads to demyelination and synaptic deficits, contributing to cognitive decline (Sutor et al. 2000; Steadman et al. 2020; Luan et al. 2021).

Given the role of senescence in protein pathology and disease progression, specifically targeting senescent cells has emerged as a promising therapeutic approach in AD. The targeted removal of senescent cells through the use of senolytic drugs has been shown to alleviate both Aβ and tau pathologies while also improving cognitive function in mouse models of AD (Bussian et al. 2018; Zhang et al. 2019; Musi et al. 2018). In humans, the D + Q clinical trial was shown to reduce SASP factors while being well tolerated, supporting the potential of senolytic therapy in AD (Hickson et al. 2019; Gonzales et al. 2023). Given the heterogeneity of senescence triggers, cell types, and extracellular environments, developing senolytic therapies specific to particular cellular subpopulations remains a great challenge. Therefore, further research is needed to elucidate the mechanisms underlying senescent cell heterogeneity and to identify common molecular targets across pathological models. Additionally, personalized combinations of senolytic and senomorphic treatments may be required for optimal therapeutic outcomes. Building upon early-phase clinical findings, future large, randomized, controlled trials are essential to establish the safety, efficacy, and target engagement of senotherapeutics. Additionally, if proven safe and effective in patients with advanced diseases, senolytics and senomorphics could potentially be explored as preventive interventions for age-related dysfunction in older individuals.

The key factors that drive the transition from normal to pathological brain aging are still unknown, making it essential to investigate the progression of senescence in health and disease. It is possible that AD pathology exacerbates the senescence processes that are already occurring in the aging brain, accelerating cellular dysfunction and inflammation. Senescence is a complex and heterogeneous process, and the expression of traditional markers can vary significantly depending on the cell type, brain region, and pathological context. For instance, while characteristic markers such as SA-β-gal, $p16^{INK4A}$, and $p21^{WAF1/CIP1}$ are widely observed across glial cell types, other markers such as HMGB1 have been linked to a single cell type so far. Furthermore, different expression levels of senescence markers have been reported between cell types. For instance, mouse models showed higher expression of the cell-cycle regulators $p16^{INK4A}$ and $p21^{WAF1/CIP1}$ in microglia and OPCs compared to astrocytes (Ogrodnik et al. 2021). While these markers have been widely used to identify senescent cells, their non-universal expression across different cell types highlights the need for a more nuanced understanding of senescence. Furthermore, commonly used senescent markers are often aspecific or present low sensitivity, and senescent cells are hard to discriminate from quiescent or terminally differentiated cells in tissues, making the investigation of senescence still a challenge. The variability in senescence markers underscores the importance of developing more precise and context-specific markers to fully capture the diversity of senescent cell phenotypes and their roles in aging and disease. To better understand senescence's impact on clinical outcomes and develop targeted therapeutic interventions, it will be crucial to develop more sensitive markers, unravel the pathogenetic mechanisms driving increased senescence, and identify the cellular identity and spatial distribution of senescent cells during the progression of diseases like Alzheimer's disease.

Author Contributions

Fadhl Alshaebi: conceptualization, writing – original draft. **Alessia Sciortino:** writing – original draft. **Rakez Kayed:** funding acquisition, writing – review and editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article because no new data were created or analyzed in this study.

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References

Ahmad, M. H., M. Fatima, and A. C. Mondal. 2019. "Influence of Microglia and Astrocyte Activation in the Neuroinflammatory Pathogenesis of Alzheimer's Disease: Rational Insights for the Therapeutic Approaches." *Journal of Clinical Neuroscience* 59: 6–11.

Al-Azab, M., M. Safi, E. Idiiatullina, F. Al-Shaebi, and M. Y. Zaky. 2022. "Aging of Mesenchymal Stem Cell: Machinery, Markers, and Strategies of Fighting." *Cellular & Molecular Biology Letters* 27, no. 1: 69.

Al-Mashhadi, S., J. E. Simpson, P. R. Heath, et al. 2015. "Oxidative Glial Cell Damage Associated With White Matter Lesions in the Aging Human Brain." *Brain Pathology* 25, no. 5: 565–574.

Ardaya, M., A. Joya, D. Padro, et al. 2020. "In Vivo PET Imaging of Gliogenesis After Cerebral Ischemia in Rats." *Frontiers in Neuroscience* 14: 793.

Arendt, T., M. Holzer, and U. Gartner. 1998. "Neuronal Expression of Cycline Dependent Kinase Inhibitors of the INK4 Family in Alzheimer's Disease." *Journal of Neural Transmission (Vienna)* 105, no. 8–9: 949–960.

Arendt, T., L. Rödel, U. Gärtner, and M. Holzer. 1996. "Expression of the Cyclin-Dependent Kinase Inhibitor p16 in Alzheimer's Disease." *Neuroreport* 7, no. 18: 3047–3049.

Askew, K., K. Li, A. Olmos-Alonso, et al. 2017. "Coupled Proliferation and Apoptosis Maintain the Rapid Turnover of Microglia in the Adult Brain." *Cell Reports* 18, no. 2: 391–405.

Baker, D. J., C. Perez-Terzic, F. Jin, et al. 2008. "Opposing Roles for p16Ink4a and p19Arf in Senescence and Ageing Caused by BubR1 Insufficiency." *Nature Cell Biology* 10, no. 7: 825–836.

Baker, D. J., and R. C. Petersen. 2018. "Cellular Senescence in Brain Aging and Neurodegenerative Diseases: Evidence and Perspectives." *Journal of Clinical Investigation* 128, no. 4: 1208–1216.

Balez, R., N. Steiner, M. Engel, et al. 2016. "Neuroprotective Effects of Apigenin Against Inflammation, Neuronal Excitability and Apoptosis in an Induced Pluripotent Stem Cell Model of Alzheimer's Disease." *Scientific Reports* 6: 31450.

Barmaki, H., A. Nourazarian, and F. Khaki-Khatibi. 2023. "Proteostasis and Neurodegeneration: A Closer Look at Autophagy in Alzheimer's Disease." *Frontiers in Aging Neuroscience* 15: 1281338.

Bhat, R., E. P. Crowe, A. Bitto, et al. 2012. "Astrocyte Senescence as a Component of Alzheimer's Disease." *PLoS One* 7, no. 9: e45069.

Bhatti, J. S., G. K. Bhatti, and P. H. Reddy. 2017. "Mitochondrial Dysfunction and Oxidative Stress in Metabolic Disorders—A Step Towards Mitochondria Based Therapeutic Strategies." *Biochimica et Biophysica Acta, Molecular Basis of Disease* 1863, no. 5: 1066–1077.

Bitto, A., C. Sell, E. Crowe, et al. 2010. "Stress-Induced Senescence in Human and Rodent Astrocytes." *Experimental Cell Research* 316, no. 17: 2961–2968.

Bjerke, M., H. Zetterberg, Å. Edman, K. Blennow, A. Wallin, and U. Andreasson. 2011. "Cerebrospinal Fluid Matrix Metalloproteinases and Tissue Inhibitor of Metalloproteinases in Combination With Subcortical and Cortical Biomarkers in Vascular Dementia and Alzheimer's Disease." *Journal of Alzheimer's Disease* 27, no. 3: 665–676.

Bourbon-Teles, J., S. Bells, D. K. Jones, E. Coulthard, A. Rosser, and C. Metzler-Baddeley. 2019. "Myelin Breakdown in Human Huntington's Disease: Multi-Modal Evidence From Diffusion MRI and Quantitative Magnetization Transfer." *Neuroscience* 403: 79–92.

Bradl, M., and H. Lassmann. 2010. "Oligodendrocytes: Biology and Pathology." *Acta Neuropathologica* 119, no. 1: 37–53.

Bussian, T. J., A. Aziz, C. F. Meyer, B. L. Swenson, J. M. van Deursen, and D. J. Baker. 2018. "Clearance of Senescent Glial Cells Prevents Tau-Dependent Pathology and Cognitive Decline." *Nature* 562, no. 7728: 578–582.

Capiralla, H., V. Vingtdeux, H. Zhao, et al. 2012. "Resveratrol Mitigates Lipopolysaccharide- and Aβ-Mediated Microglial Inflammation by Inhibiting the TLR4/NF-κB/STAT Signaling Cascade." *Journal of Neurochemistry* 120, no. 3: 461–472.

Chen, Y., C. Qin, J. Huang, et al. 2020. "The Role of Astrocytes in Oxidative Stress of Central Nervous System: A Mixed Blessing." *Cell Proliferation* 53, no. 3: e12781.

Childs, B. G., D. J. Baker, T. Wijshake, C. A. Conover, J. Campisi, and J. M. van Deursen. 2016. "Senescent Intimal Foam Cells Are Deleterious at all Stages of Atherosclerosis." *Science* 354, no. 6311: 472–477.

Chin, L., S. E. Artandi, Q. Shen, et al. 1999. "p53 Deficiency Rescues the Adverse Effects of Telomere Loss and Cooperates With Telomere Dysfunction to Accelerate Carcinogenesis." *Cell* 97, no. 4: 527–538.

Chinta, S. J., G. Woods, M. Demaria, et al. 2018. "Cellular Senescence Is Induced by the Environmental Neurotoxin Paraquat and Contributes to Neuropathology Linked to Parkinson's Disease." *Cell Reports* 22, no. 4: 930–940.

Cohen, J., and C. Torres. 2019. "Astrocyte senescence: Evidence and significance." *Aging Cell* 18, no. 3: e12937.

Colodner, K. J., R. A. Montana, D. C. Anthony, R. D. Folkerth, U. de Girolami, and M. B. Feany. 2005. "Proliferative Potential of Human Astrocytes." *Journal of Neuropathology and Experimental Neurology* 64, no. 2: 163–169.

Cozachenco, D., F. C. Ribeiro, and S. T. Ferreira. 2023. "Defective Proteostasis in Alzheimer's Disease." *Ageing Research Reviews* 85: 101862.

Crescenzi, E., A. Leonardi, and F. Pacifico. 2023. "Iron Metabolism in Cancer and Senescence: A Cellular Perspective." *Biology (Basel)* 12, no. 7: 989.

d'Adda di Fagagna, F. 2008. "Living on a Break: Cellular Senescence as a DNA-Damage Response." *Nature Reviews. Cancer* 8, no. 7: 512–522.

Dai, X., L. Hong, H. Shen, et al. 2020. "Estradiol-Induced Senescence of Hypothalamic Astrocytes Contributes to Aging-Related Reproductive Function Declines in Female Mice." *Aging (Albany NY)* 12, no. 7: 6089–6108.

Damani, M. R., L. Zhao, A. M. Fontainhas, J. Amaral, R. N. Fariss, and W. T. Wong. 2011. "Age-Related Alterations in the Dynamic Behavior of Microglia." *Aging Cell* 10, no. 2: 263–276.

Davalos, A. R., M. Kawahara, G. K. Malhotra, et al. 2013. "p53-Dependent Release of Alarmin HMGB1 Is a Central Mediator of Senescent Phenotypes." *Journal of Cell Biology* 201, no. 4: 613–629.

de la Monte, S. M., Y. K. Sohn, and J. R. Wands. 1997. "Correlates of p53- and Fas (CD95)-mediated Apoptosis in Alzheimer's Disease." *Journal of the Neurological Sciences* 152, no. 1: 73–83.

de Magalhaes, J. P. 2024. "Cellular Senescence in Normal Physiology." *Science* 384, no. 6702: 1300–1301.

Dean, D. C., 3rd, J. Sojkova, S. Hurley, et al. 2016. "Alterations of Myelin Content in Parkinson's Disease: A Cross-Sectional Neuroimaging Study." *PLoS One* 11, no. 10: e0163774.

Depp, C., T. Sun, A. O. Sasmita, et al. 2023. "Myelin Dysfunction Drives Amyloid-beta Deposition in Models of Alzheimer's Disease." *Nature* 618, no. 7964: 349–357.

Dong, Y. X., H. Y. Zhang, H. Y. Li, P. H. Liu, Y. Sui, and X. H. Sun. 2018. "Association Between Alzheimer's Disease Pathogenesis and Early Demyelination and Oligodendrocyte Dysfunction." *Neural Regeneration Research* 13, no. 5: 908–914.

Dorling, J. L., C. K. Martin, and L. M. Redman. 2020. "Calorie Restriction for Enhanced Longevity: The Role of Novel Dietary Strategies in the Present Obesogenic Environment." *Ageing Research Reviews* 64: 101038.

Drake, S. S., A. Zaman, C. Gianfelice, et al. 2024. "Senolytic Treatment Diminishes Microglia and Decreases Severity of Experimental Autoimmune Encephalomyelitis." *Journal of Neuroinflammation* 21, no. 1: 283.

Dursun, E., D. Gezen-Ak, H. Hanağası, et al. 2015. "The Interleukin 1 Alpha, Interleukin 1 beta, Interleukin 6 and Alpha-2-Macroglobulin Serum Levels in Patients With Early or Late Onset Alzheimer's Disease, Mild Cognitive Impairment or Parkinson's Disease." *Journal of Neuroimmunology* 283: 50–57.

Edgar, J. M., M. McLaughlin, D. Yool, et al. 2004. "Oligodendroglial Modulation of Fast Axonal Transport in a Mouse Model of Hereditary Spastic Paraplegia." *Journal of Cell Biology* 166, no. 1: 121–131.

Evans, R. J., F. S. Wyllie, D. Wynford-Thomas, D. Kipling, and C. J. Jones. 2003. "A P53-Dependent, Telomere-Independent Proliferative Life Span Barrier in Human Astrocytes Consistent With the Molecular Genetics of Glioma Development." *Cancer Research* 63, no. 16: 4854–4861.

Fancy, N. N., A. M. Smith, A. Caramello, et al. 2024. "Characterisation of Premature Cell Senescence in Alzheimer's Disease Using Single Nuclear Transcriptomics." *Acta Neuropathologica* 147, no. 1: 78.

Farina, C., F. Aloisi, and E. Meinl. 2007. "Astrocytes Are Active Players in Cerebral Innate Immunity." *Trends in Immunology* 28, no. 3: 138–145.

Faulkner, J. R., J. E. Herrmann, M. J. Woo, K. E. Tansey, N. B. Doan, and M. V. Sofroniew. 2004. "Reactive Astrocytes Protect Tissue and Preserve Function After Spinal Cord Injury." *Journal of Neuroscience* 24, no. 9: 2143–2155.

Flanary, B. E., N. W. Sammons, C. Nguyen, D. Walker, and W. J. Streit. 2007. "Evidence That Aging and Amyloid Promote Microglial Cell Senescence." *Rejuvenation Research* 10, no. 1: 61–74.

Flores-Ponce, X., and I. Velasco. 2024. "Dopaminergic Neuron Metabolism: Relevance for Understanding Parkinson's Disease." *Metabolomics* 20, no. 6: 116.

Forero, D. A., Y. González-Giraldo, C. López-Quintero, L. J. Castro-Vega, G. E. Barreto, and G. Perry. 2016. "Meta-Analysis of Telomere Length in Alzheimer's Disease." *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences* 71, no. 8: 1069–1073.

Franco, S., M. A. Blasco, S. L. Siedlak, et al. 2006. "Telomeres and Telomerase in Alzheimer's Disease: Epiphenomena or a New Focus for Therapeutic Strategy?" *Alzheimers Dement* 2, no. 3: 164–168.

Freund, A., R. M. Laberge, M. Demaria, and J. Campisi. 2012. "Lamin B1 Loss Is a Senescence-Associated Biomarker." *Molecular Biology of the Cell* 23, no. 11: 2066–2075.

Frost, B., F. H. Bardai, and M. B. Feany. 2016. "Lamin Dysfunction Mediates Neurodegeneration in Tauopathies." *Current Biology* 26, no. 1: 129–136.

Frost, B., M. Hemberg, J. Lewis, and M. B. Feany. 2014. "Tau Promotes Neurodegeneration Through Global Chromatin Relaxation." *Nature Neuroscience* 17, no. 3: 357–366.

Frost, G. R., and Y. M. Li. 2017. "The Role of Astrocytes in Amyloid Production and Alzheimer's Disease." *Open Biology* 7, no. 12: 170228.

Gaikwad, S., N. Puangmalai, A. Bittar, et al. 2021. "Tau Oligomer Induced HMGB1 Release Contributes to Cellular Senescence and Neuropathology Linked to Alzheimer's Disease and Frontotemporal Dementia." *Cell Reports* 36, no. 3: 109419.

Gaikwad, S., S. Senapati, M. A. Haque, and R. Kayed. 2024. "Senescence, Brain Inflammation, and Oligomeric Tau Drive Cognitive Decline in Alzheimer's Disease: Evidence From Clinical and Preclinical Studies." *Alzheimers Dement* 20, no. 1: 709–727.

Garcia-Agudo, L. F., Z. Shi, I. F. Smith, et al. 2024. "BIN1(K358R) Suppresses Glial Response to Plaques in Mouse Model of Alzheimer's Disease." *Alzheimers Dement* 20, no. 4: 2922–2942.

Gezen-Ak, D., E. Dursun, H. Hanağası, et al. 2013. "BDNF, TNFalpha, HSP90, CFH, and IL-10 Serum Levels in Patients With Early or Late Onset Alzheimer's Disease or Mild Cognitive Impairment." *Journal of Alzheimer's Disease* 37, no. 1: 185–195.

Gildea, H. K., and S. A. Liddelow. 2025. "Mechanisms of Astrocyte Aging in Reactivity and Disease." *Molecular Neurodegeneration* 20, no. 1: 21.

Going, J. J., R. C. Stuart, M. Downie, A. J. Fletcher-Monaghan, and W. Nicol Keith. 2002. "'Senescence-associated' beta-Galactosidase Activity in the Upper Gastrointestinal Tract." *Journal of Pathology* 196, no. 4: 394–400.

Gomez, P. T., C. M. Carver, S. L. Rodriguez, L. Wang, X. Zhang, and M. J. Schafer. 2024. "Aging and Senescent Fates of Oligodendrocyte Precursor Cells in the Mouse Brain." *NPJ Aging* 10, no. 1: 47.

Gonzales, M. M., V. R. Garbarino, T. F. Kautz, et al. 2023. "Senolytic Therapy in Mild Alzheimer's Disease: A Phase 1 Feasibility Trial." *Nature Medicine* 29, no. 10: 2481–2488.

Haines, J. D., M. Inglese, and P. Casaccia. 2011. "Axonal damage in multiple sclerosis." *Mount Sinai Journal of Medicine* 78, no. 2: 231–243.

He, N., W. L. Jin, K. H. Lok, Y. Wang, M. Yin, and Z. J. Wang. 2013. "Amyloid-beta(1-42) Oligomer Accelerates Senescence in Adult Hippocampal Neural Stem/Progenitor Cells via Formylpeptide Receptor 2." *Cell Death & Disease* 4, no. 11: e924.

Hellwig, S., W. L. Jin, K. H. Lok, Y. Wang, M. Yin, and Z. J. Wang. 2015. "Forebrain Microglia From Wild-Type but Not Adult 5xFAD Mice Prevent Amyloid-beta Plaque Formation in Organotypic Hippocampal Slice Cultures." *Scientific Reports* 5: 14624.

Heneka, M. T., M. P. Kummer, A. Stutz, et al. 2013. "NLRP3 Is Activated in Alzheimer's Disease and Contributes to Pathology in APP/PS1 Mice." *Nature* 493, no. 7434: 674–678.

Henningfield, C. M., N. Soni, R. W. Lee, R. Sharma, J. L. Cleland, and K. N. Green. 2024. "Selective Targeting and Modulation of Plaque Associated Microglia via Systemic Hydroxyl Dendrimer Administration in an Alzheimer's Disease Mouse Model." *Alzheimer's Research & Therapy* 16, no. 1: 101.

Henry, C. J., Y. Huang, A. M. Wynne, and J. P. Godbout. 2009. "Peripheral Lipopolysaccharide (LPS) Challenge Promotes Microglial Hyperactivity in Aged Mice That Is Associated With Exaggerated Induction of Both Pro-Inflammatory IL-1beta and Anti-Inflammatory IL-10 Cytokines." *Brain, Behavior, and Immunity* 23, no. 3: 309–317.

Hickson, L. J., L. G. P. Langhi Prata, S. A. Bobart, et al. 2019. "Senolytics Decrease Senescent Cells in Humans: Preliminary Report From a Clinical Trial of Dasatinib Plus Quercetin in Individuals With Diabetic Kidney Disease." *eBioMedicine* 47: 446–456.

Holdt, L. M., K. Sass, G. Gäbel, H. Bergert, J. Thiery, and D. Teupser. 2011. "Expression of Chr9p21 Genes CDKN2B (p15(INK4b)), CDKN2A (p16(INK4a), p14(ARF)) and MTAP in Human Atherosclerotic Plaque." *Atherosclerosis* 214, no. 2: 264–270.

Horstmann, S., L. Budig, H. Gardner, et al. 2010. "Matrix Metalloproteinases in Peripheral Blood and Cerebrospinal Fluid in Patients With Alzheimer's Disease." *International Psychogeriatrics* 22, no. 6: 966–972.

Hou, J., B. Jeon, J. Baek, et al. 2022. "High Fat Diet-Induced Brain Damaging Effects Through Autophagy-Mediated Senescence, Inflammation and Apoptosis Mitigated by Ginsenoside F1-Enhanced Mixture." *Journal of Ginseng Research* 46, no. 1: 79–90.

Hou, Y., X. Dan, M. Babbar, et al. 2019. "Ageing as a Risk Factor for Neurodegenerative Disease." *Nature Reviews. Neurology* 15, no. 10: 565–581.

Hu, Y., G. L. Fryatt, M. Ghorbani, et al. 2021. "Replicative Senescence Dictates the Emergence of Disease-Associated Microglia and Contributes to Abeta Pathology." *Cell Reports* 35, no. 10: 109228.

Huang, Z., J. D. Jordan, and Q. Zhang. 2024. "Myelin Pathology in Alzheimer's Disease: Potential Therapeutic Opportunities." *Aging and Disease* 15, no. 2: 698–713.

Hudgins, A. D., C. Tazearslan, A. Tare, Y. Zhu, D. Huffman, and Y. Suh. 2018. "Age- and Tissue-Specific Expression of Senescence Biomarkers in Mice." *Frontiers in Genetics* 9: 59.

Hussaini, S. M. Q., and M. H. Jang. 2018. "New Roles for Old Glue: Astrocyte Function in Synaptic Plasticity and Neurological Disorders." *International Neurourology Journal* 22, no. Suppl 3: S106–S114.

Hussong, S. A., A. Q. Banh, C. E. van Skike, et al. 2023. "Soluble Pathogenic Tau Enters Brain Vascular Endothelial Cells and Drives Cellular Senescence and Brain Microvascular Dysfunction in a Mouse Model of Tauopathy." *Nature Communications* 14, no. 1: 2367.

Iram, T., D. Trudler, D. Kain, et al. 2016. "Astrocytes From Old Alzheimer's Disease Mice Are Impaired in Abeta Uptake and in Neuroprotection." *Neurobiology of Disease* 96: 84–94.

Islam, M. I., P. Nagakannan, T. Shcholok, et al. 2022. "Regulatory Role of Cathepsin L in Induction of Nuclear Laminopathy in Alzheimer's Disease." *Aging Cell* 21, no. 1: e13531.

Jantaratnotai, N., J. K. Ryu, S. U. Kim, and J. G. McLarnon. 2003. "Amyloid beta Peptide-Induced corpus Callosum Damage and Glial Activation In Vivo." *Neuroreport* 14, no. 11: 1429–1433.

Janzen, V., R. Forkert, H. E. Fleming, et al. 2006. "Stem-Cell Ageing Modified by the Cyclin-Dependent Kinase Inhibitor p16INK4a." *Nature* 443, no. 7110: 421–426.

Jeon, O. H., C. Kim, R. M. Laberge, et al. 2017. "Local Clearance of Senescent Cells Attenuates the Development of Post-Traumatic Osteoarthritis and Creates a Pro-Regenerative Environment." *Nature Medicine* 23, no. 6: 775–781.

Joya, A., and A. Martin. 2021. "Evaluation of Glial Cell Proliferation With Non-invasive Molecular Imaging Methods After Stroke." *Neural Regeneration Research* 16, no. 11: 2209–2210.

Kang, C., Q. Xu, T. D. Martin, et al. 2015. "The DNA Damage Response Induces Inflammation and Senescence by Inhibiting Autophagy of GATA4." *Science* 349, no. 6255: aaa5612.

Karabag, D., H. Scheiblich, A. Griep, et al. 2023. "Characterizing Microglial Senescence: Tau as a Key Player." *Journal of Neurochemistry* 166, no. 3: 517–533.

Kawano, H., S. Katsurabayashi, Y. Kakazu, et al. 2012. "Long-Term Culture of Astrocytes Attenuates the Readily Releasable Pool of Synaptic Vesicles." *PLoS One* 7, no. 10: e48034.

Kirkpatrick, L. L., A. S. Witt, H. R. Payne, H. D. Shine, and S. T. Brady. 2001. "Changes in Microtubule Stability and Density in Myelin-Deficient Shiverer Mouse CNS Axons." *Journal of Neuroscience* 21, no. 7: 2288–2297.

Kolind, S., R. Sharma, S. Knight, H. Johansen-Berg, K. Talbot, and M. R. Turner. 2013. "Myelin Imaging in Amyotrophic and Primary Lateral Sclerosis." *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration* 14, no. 7–8: 562–573.

Kreher, C., J. Favret, M. Maulik, and D. Shin. 2021. "Lysosomal Functions in Glia Associated With Neurodegeneration." *Biomolecules* 11, no. 3: 400.

Kreisman, N. R., S. Soliman, and D. Gozal. 2000. "Regional Differences in Hypoxic Depolarization and Swelling in Hippocampal Slices." *Journal of Neurophysiology* 83, no. 2: 1031–1038.

Kujuro, Y., N. Suzuki, and T. Kondo. 2010. "Esophageal cancer-Related Gene 4 Is a Secreted Inducer of Cell Senescence Expressed by Aged CNS Precursor Cells." *Proceedings of the National Academy of Sciences of the United States of America* 107, no. 18: 8259–8264.

Lai, K. S. P., C. S. Liu, A. Rau, et al. 2017. "Peripheral Inflammatory Markers in Alzheimer's Disease: A Systematic Review and meta-Analysis of 175 Studies." *Journal of Neurology, Neurosurgery, and Psychiatry* 88, no. 10: 876–882.

Lee, E., Y. J. Jung, Y. R. Park, et al. 2022. "A Distinct Astrocyte Subtype in the Aging Mouse Brain Characterized by Impaired Protein Homeostasis." *Nature Aging* 2, no. 8: 726–741.

Lee, J. C., M. Mayer-Proschel, and M. S. Rao. 2000. "Gliogenesis in the Central Nervous System." *Glia* 30, no. 2: 105–121.

Leng, F., and P. Edison. 2021. "Neuroinflammation and Microglial Activation in Alzheimer Disease: Where Do We Go From here?" *Nature Reviews. Neurology* 17, no. 3: 157–172.

Li, R., Y. Li, H. Zuo, G. Pei, S. Huang, and Y. Hou. 2024. "Alzheimer's Amyloid-beta Accelerates Cell Senescence and Suppresses SIRT1 in Human Neural Stem Cells." *Biomolecules* 14, no. 2: 189.

Li, Y., H. Xu, H. Wang, K. Yang, J. Luan, and S. Wang. 2023. "TREM2: Potential Therapeutic Targeting of Microglia for Alzheimer's Disease." *Biomedicine & Pharmacotherapy* 165: 115218.

Limbad, C., T. R. Oron, F. Alimirah, et al. 2020. "Astrocyte Senescence Promotes Glutamate Toxicity in Cortical Neurons." *PLoS One* 15, no. 1: e0227887.

Lin, A. L., W. Zheng, J. J. Halloran, et al. 2013. "Chronic Rapamycin Restores Brain Vascular Integrity and Function Through NO Synthase Activation and Improves Memory in Symptomatic Mice Modeling Alzheimer's Disease." *Journal of Cerebral Blood Flow and Metabolism* 33, no. 9: 1412–1421.

Longo, F. M., and S. M. Massa. 2023. "Senolytic Therapy for Alzheimer's Disease." *Nature Medicine* 29, no. 10: 2409–2411.

Lopez-Otin, C., M. A. Blasco, L. Partridge, M. Serrano, and G. Kroemer. 2023. "Hallmarks of Aging: An Expanding Universe." *Cell* 186, no. 2: 243–278.

Luan, W., X. Qi, F. Liang, et al. 2021. "Microglia Impede Oligodendrocyte Generation in Aged Brain." *Journal of Inflammation Research* 14: 6813–6831. https://doi.org/10.2147/JIR.S338242.

Luth, H. J., M. Holzer, H. J. Gertz, and T. Arendt. 2000. "Aberrant Expression of nNOS in Pyramidal Neurons in Alzheimer's Disease Is Highly Co-Localized With p21ras and p16INK4a." *Brain Research* 852, no. 1: 45–55.

Matias, I., L. P. Diniz, A. P. B. Araujo, et al. 2023. "Age-Associated Upregulation of Glutamate Transporters and Glutamine Synthetase in Senescent Astrocytes in Vitro and in the Mouse and Human Hippocampus." *ASN Neuro* 15: 17590914231157974.

Matias, I., L. P. Diniz, I. V. Damico, et al. 2022. "Loss of Lamin-B1 and Defective Nuclear Morphology Are Hallmarks of Astrocyte Senescence In Vitro and in the Aging Human hippocampus." *Aging Cell* 21, no. 1: e13521.

Matsudaira, T., S. Nakano, Y. Konishi, et al. 2023. "Cellular Senescence in White Matter Microglia Is Induced During Ageing in Mice and Exacerbates the Neuroinflammatory Phenotype." *Communications Biology* 6, no. 1: 665.

McAleese, K. E., M. Firbank, M. Dey, et al. 2015. "Cortical Tau Load Is Associated With White Matter Hyperintensities." *Acta Neuropathologica Communications* 3: 60.

McHugh, D., and J. Gil. 2018. "Senescence and Aging: Causes, Consequences, and Therapeutic Avenues." *Journal of Cell Biology* 217, no. 1: 65–77.

McShea, A., P. L. Harris, K. R. Webster, A. F. Wahl, and M. A. Smith. 1997. "Abnormal Expression of the Cell Cycle Regulators P16 and CDK4 in Alzheimer's Disease." *American Journal of Pathology* 150, no. 6: 1933–1939.

Mendsaikhan, A., I. Tooyama, and D. G. Walker. 2019. "Microglial Progranulin: Involvement in Alzheimer's Disease and Neurodegenerative Diseases." *Cells* 8, no. 3: 230.

Mikawa, T., K. Yoshida, and H. Kondoh. 2024. "Senotherapy Preserves Resilience in Aging." *Geriatrics & Gerontology International* 24, no. 9: 845–849.

Millner, A., and G. E. Atilla-Gokcumen. 2020. "Lipid Players of Cellular Senescence." *Metabolites* 10, no. 9: 339. https://doi.org/10.3390/metabo10090339.

Mittelbronn, M., K. Dietz, H. J. Schluesener, and R. Meyermann. 2001. "Local Distribution of Microglia in the Normal Adult Human Central Nervous System Differs by up to One Order of Magnitude." *Acta Neuropathologica* 101, no. 3: 249–255.

Miwa, S., S. Kashyap, E. Chini, and T. von Zglinicki. 2022. "Mitochondrial Dysfunction in Cell Senescence and Aging." *Journal of Clinical Investigation* 132, no. 13: e158447.

Morawe, M. P., F. Liao, W. Amberg, et al. 2022. "Pharmacological mTOR-Inhibition Facilitates Clearance of AD-Related Tau Aggregates in the Mouse Brain." *European Journal of Pharmacology* 934: 175301.

Mueller, S. G., L. Stables, A. T. du, et al. 2007. "Measurement of Hippocampal Subfields and Age-Related Changes With High Resolution MRI at 4T." *Neurobiology of Aging* 28, no. 5: 719–726.

Musi, N., J. M. Valentine, K. R. Sickora, et al. 2018. "Tau Protein Aggregation Is Associated With Cellular Senescence in the Brain." *Aging Cell* 17, no. 6: e12840.

Nasrabady, S. E., B. Rizvi, J. E. Goldman, and A. M. Brickman. 2018. "White Matter Changes in Alzheimer's Disease: A Focus on Myelin and Oligodendrocytes." *Acta Neuropathologica Communications* 6, no. 1: 22.

Neumann, B., R. Baror, C. Zhao, et al. 2019. "Metformin Restores CNS Remyelination Capacity by Rejuvenating Aged Stem Cells." *Cell Stem Cell* 25, no. 4: 473–485.e8.

Nimmerjahn, A., F. Kirchhoff, and F. Helmchen. 2005. "Resting Microglial Cells Are Highly Dynamic Surveillants of Brain Parenchyma In Vivo." *Science* 308, no. 5726: 1314–1318.

Ogrodnik, M., S. A. Evans, E. Fielder, et al. 2021. "Whole-Body Senescent Cell Clearance Alleviates Age-Related Brain Inflammation and Cognitive Impairment in Mice." *Aging Cell* 20, no. 2: e13296.

Ohyagi, Y., H. Asahara, D. H. Chui, et al. 2005. "Intracellular Abeta42 Activates p53 Promoter: A Pathway to Neurodegeneration in Alzheimer's Disease." *FASEB Journal* 19, no. 2: 255–257.

Ojo, J. O., P. Rezaie, P. L. Gabbott, and M. G. Stewart. 2015. "Impact of Age-Related Neuroglial Cell Responses on Hippocampal Deterioration." *Frontiers in Aging Neuroscience* 7: 57.

Olmos-Alonso, A., S. T. Schetters, S. Sri, et al. 2016. "Pharmacological Targeting of CSF1R Inhibits Microglial Proliferation and Prevents the Progression of Alzheimer's-Like Pathology." *Brain* 139, no. Pt 3: 891–907. https://doi.org/10.1093/brain/awv379.

Ota, M., N. Sato, Y. Kimura, Y. Shigemoto, H. Kunugi, and H. Matsuda. 2019. "Changes of Myelin Organization in Patients With Alzheimer's Disease Shown by q-Space Myelin map Imaging." *Dementia and Geriatric Cognitive Disorders Extra* 9, no. 1: 24–33.

Pan, S., S. R. Mayoral, H. S. Choi, J. R. Chan, and M. A. Kheirbek. 2020. "Preservation of a Remote Fear Memory Requires New Myelin Formation." *Nature Neuroscience* 23, no. 4: 487–499.

Panossian, L. A., V. R. Porter, H. F. Valenzuela, et al. 2003. "Telomere Shortening in T Cells Correlates With Alzheimer's Disease Status." *Neurobiology of Aging* 24, no. 1: 77–84.

Parhizkar, S., T. Arzberger, M. Brendel, et al. 2019. "Loss of TREM2 Function Increases Amyloid Seeding but Reduces Plaque-Associated ApoE." *Nature Neuroscience* 22, no. 2: 191–204.

Park, J., S. Y. Lee, J. Shon, et al. 2019. "Adalimumab Improves Cognitive Impairment, Exerts Neuroprotective Effects and Attenuates Neuroinflammation in an Abeta(1-40)-injected Mouse Model of Alzheimer's Disease." *Cytotherapy* 21, no. 6: 671–682.

Perea, G., M. Navarrete, and A. Araque. 2009. "Tripartite Synapses: Astrocytes Process and Control Synaptic Information." *Trends in Neurosciences* 32, no. 8: 421–431.

Pertusa, M., S. García-Matas, E. Rodríguez-Farré, C. Sanfeliu, and R. Cristòfol. 2007. "Astrocytes Aged In Vitro Show a Decreased Neuroprotective Capacity." *Journal of Neurochemistry* 101, no. 3: 794–805.

Pini, L., M. Pievani, M. Bocchetta, et al. 2016. "Brain Atrophy in Alzheimer's Disease and Aging." *Ageing Research Reviews* 30: 25–48.

Pont-Lezica, L., W. Beumer, S. Colasse, H. Drexhage, M. Versnel, and A. Bessis. 2014. "Microglia Shape corpus Callosum Axon Tract Fasciculation: Functional Impact of Prenatal Inflammation." *European Journal of Neuroscience* 39, no. 10: 1551–1557.

Porchet, R., A. Probst, C. Bouras, E. Dráberová, P. Dráber, and B. M. Riederer. 2003. "Analysis of Glial Acidic Fibrillary Protein in the Human Entorhinal Cortex During Aging and in Alzheimer's Disease." *Proteomics* 3, no. 8: 1476–1485.

Qiu, D., S. Zhou, J. Donnelly, D. Xia, and L. Zhao. 2023. "Aerobic Exercise Attenuates Abnormal Myelination and Oligodendrocyte Differentiation in 3xTg-AD Mice." *Experimental Gerontology* 182: 112293.

Raulin, A. C., S. V. Doss, Z. A. Trottier, T. C. Ikezu, G. Bu, and C. C. Liu. 2022. "ApoE in Alzheimer's Disease: Pathophysiology and Therapeutic Strategies." *Molecular Neurodegeneration* 17, no. 1: 72.

Ritzel, R. M., A. R. Patel, S. Pan, et al. 2015. "Age- and Location-Related Changes in Microglial Function." *Neurobiology of Aging* 36, no. 6: 2153–2163.

Rodriguez, A. M., J. Rodriguez, and G. H. Giambartolomei. 2022. "Microglia at the Crossroads of Pathogen-Induced Neuroinflammation." *ASN Neuro* 14: 17590914221104566.

Roger, L., F. Tomas, and V. Gire. 2021. "Mechanisms and Regulation of Cellular Senescence." *International Journal of Molecular Sciences* 22, no. 23: 13173.

Rouillard, M. E., J. Hu, P. A. Sutter, H. W. Kim, J. K. Huang, and S. J. Crocker. 2022. "The Cellular Senescence Factor Extracellular HMGB1 Directly Inhibits Oligodendrocyte Progenitor Cell Differentiation and Impairs CNS Remyelination." *Frontiers in Cellular Neuroscience* 16: 833186.

Safaiyan, S., N. Kannaiyan, N. Snaidero, et al. 2016. "Age-Related Myelin Degradation Burdens the Clearance Function of Microglia During Aging." *Nature Neuroscience* 19, no. 8: 995–998.

Salas, I. H., J. Burgado, and N. J. Allen. 2020. "Glia: Victims or Villains of the Aging Brain?" *Neurobiology of Disease* 143: 105008.

Salminen, A., J. Ojala, K. Kaarniranta, A. Haapasalo, M. Hiltunen, and H. Soininen. 2011. "Astrocytes in the Aging Brain Express Characteristics of Senescence-Associated Secretory Phenotype." *European Journal of Neuroscience* 34, no. 1: 3–11.

Sapieha, P., and F. A. Mallette. 2018. "Cellular Senescence in Postmitotic Cells: Beyond Growth Arrest." *Trends in Cell Biology* 28, no. 8: 595–607.

Sato, S., Y. Kawamata, A. Takahashi, et al. 2015. "Ablation of the p16(INK4a) Tumour Suppressor Reverses Ageing Phenotypes of Klotho Mice." *Nature Communications* 6: 7035.

Satyanarayana, A., S. U. Wiemann, J. Buer, et al. 2003. "Telomere Shortening Impairs Organ Regeneration by Inhibiting Cell Cycle Re-Entry of a Subpopulation of Cells." *EMBO Journal* 22, no. 15: 4003–4013.

Schafer, M. J., X. Zhang, A. Kumar, et al. 2020. "The Senescence-Associated Secretome as an indicator of Age and Medical Risk." *JCI Insight* 5, no. 12: e133668. https://doi.org/10.1172/jci.insight.133668.

Scheff, S. W., D. A. Price, F. A. Schmitt, S. T. DeKosky, and E. J. Mufson. 2007. "Synaptic Alterations in CA1 in Mild Alzheimer Disease and Mild Cognitive Impairment." *Neurology* 68, no. 18: 1501–1508.

Schlett, J. S., M. Mettang, A. Skaf, et al. 2023. "NF-kappaB Is a Critical Mediator of Post-Mitotic Senescence in Oligodendrocytes and Subsequent White Matter Loss." *Molecular Neurodegeneration* 18, no. 1: 24.

Siddiqui, M. S., M. François, M. F. Fenech, and W. R. Leifert. 2015. "Persistent gammaH2AX: A Promising Molecular Marker of DNA Damage and Aging." *Mutation Research, Reviews in Mutation Research* 766: 1–19.

Sierra, A., S. Beccari, I. Diaz-Aparicio, J. M. Encinas, S. Comeau, and M. È. Tremblay. 2014. "Surveillance, Phagocytosis, and Inflammation: How Never-Resting Microglia Influence Adult Hippocampal Neurogenesis." *Neural Plasticity* 2014: 610343.

Sierra, A., A. C. Gottfried-Blackmore, B. S. McEwen, and K. Bulloch. 2007. "Microglia Derived From Aging Mice Exhibit an Altered Inflammatory Profile." *Glia* 55, no. 4: 412–424.

Sikora, E., A. Bielak-Zmijewska, M. Dudkowska, et al. 2021. "Cellular Senescence in Brain Aging." *Frontiers in Aging Neuroscience* 13: 646924.

Simard, M., G. Arcuino, T. Takano, Q. S. Liu, and M. Nedergaard. 2003. "Signaling at the Gliovascular Interface." *Journal of Neuroscience* 23, no. 27: 9254–9262.

Simpson, J. E., P. G. Ince, P. J. Shaw, et al. 2011. "Microarray Analysis of the Astrocyte Transcriptome in the Aging Brain: Relationship to Alzheimer's Pathology and APOE Genotype." *Neurobiology of Aging* 32, no. 10: 1795–1807.

Sofiadis, K., N. Josipovic, M. Nikolic, et al. 2021. "HMGB1 Coordinates SASP-Related Chromatin Folding and RNA Homeostasis on the Path to Senescence." *Molecular Systems Biology* 17, no. 6: e9760.

Soni, N., L. A. Hohsfield, K. M. Tran, et al. 2024. "Genetic Diversity Promotes Resilience in a Mouse Model of Alzheimer's Disease." *Alzheimers Dement* 20, no. 4: 2794–2816.

Soreq, L., UK Brain Expression Consortium, North American Brain Expression Consortium, et al. 2017. "Major Shifts in Glial Regional Identity Are a Transcriptional Hallmark of Human Brain Aging." *Cell Reports* 18, no. 2: 557–570.

Steadman, P. E., F. Xia, M. Ahmed, et al. 2020. "Disruption of Oligodendrogenesis Impairs Memory Consolidation in Adult Mice." *Neuron* 105, no. 1: 150–164.e6.

Stojiljkovic, M. R., Q. Ain, T. Bondeva, R. Heller, C. Schmeer, and O. W. Witte. 2019. "Phenotypic and Functional Differences Between Senescent and Aged Murine Microglia." *Neurobiology of Aging* 74: 56–69.

Streit, W. J., H. Braak, Q. S. Xue, and I. Bechmann. 2009. "Dystrophic (Senescent) Rather Than Activated Microglial Cells Are Associated With Tau Pathology and Likely Precede Neurodegeneration in Alzheimer's Disease." *Acta Neuropathologica* 118, no. 4: 475–485.

Streit, W. J., N. W. Sammons, A. J. Kuhns, and D. L. Sparks. 2004. "Dystrophic Microglia in the Aging Human Brain." *Glia* 45, no. 2: 208–212.

Sutor, B., C. Schmolke, B. Teubner, C. Schirmer, and K. Willecke. 2000. "Myelination Defects and Neuronal Hyperexcitability in the Neocortex of Connexin 32-Deficient Mice." *Cerebral Cortex* 10, no. 7: 684–697.

Swardfager, W., K. Lanctôt, L. Rothenburg, A. Wong, J. Cappell, and N. Herrmann. 2010. "A meta-Analysis of Cytokines in Alzheimer's Disease." *Biological Psychiatry* 68, no. 10: 930–941.

Tajbakhsh, A., M. Read, G. E. Barreto, M. Ávila-Rodriguez, S. M. Gheibi-Hayat, and A. Sahebkar. 2021. "Apoptotic Neurons and Amyloid-beta Clearance by Phagocytosis in Alzheimer's Disease: Pathological Mechanisms and Therapeutic Outlooks." *European Journal of Pharmacology* 895: 173873.

Tanaka, K., K. Watase, T. Manabe, et al. 1997. "Epilepsy and Exacerbation of Brain Injury in Mice Lacking the Glutamate Transporter GLT-1." *Science* 276, no. 5319: 1699–1702.

Tepavcevic, V. 2021. "Oligodendroglial Energy Metabolism and (Re)myelination." *Life (Basel)* 11, no. 3: 238.

Thomas, P., O. C. NJ, and M. Fenech. 2008. "Telomere Length in White Blood Cells, Buccal Cells and Brain Tissue and Its Variation With Ageing and Alzheimer's Disease." *Mechanisms of Ageing and Development* 129, no. 4: 183–190.

Thorburne, S. K., and B. H. Juurlink. 1996. "Low Glutathione and High iron Govern the Susceptibility of Oligodendroglial Precursors to Oxidative Stress." *Journal of Neurochemistry* 67, no. 3: 1014–1022.

Tian, Y., Y. Tian, Z. Yuan, et al. 2022. "Iron Metabolism in Aging and Age-Related Diseases." *International Journal of Molecular Sciences* 23, no. 7: 3612.

Tosatti, J. A. G., A. F. S. Fontes, P. Caramelli, and K. B. Gomes. 2022. "Effects of Resveratrol Supplementation on the Cognitive Function of Patients With Alzheimer's Disease: A Systematic Review of Randomized Controlled Trials." *Drugs & Aging* 39, no. 4: 285–295.

Trejo-Lopez, J. A., A. T. Yachnis, and S. Prokop. 2022. "Neuropathology of Alzheimer's Disease." *Neurotherapeutics* 19, no. 1: 173–185.

Turnquist, C., I. Horikawa, E. Foran, et al. 2016. "p53 Isoforms Regulate Astrocyte-Mediated Neuroprotection and Neurodegeneration." *Cell Death and Differentiation* 23, no. 9: 1515–1528.

Ungerleider, K., J. A. Beck, D. Lissa, S. Joruiz, I. Horikawa, and C. C. Harris. 2022. "Delta133p53alpha Protects Human Astrocytes From Amyloid-beta Induced Senescence and Neurotoxicity." *Neuroscience* 498: 190–202.

Van Skike, C. E., S. A. Hussong, S. F. Hernandez, A. Q. Banh, N. DeRosa, and V. Galvan. 2021. "mTOR Attenuation With Rapamycin Reverses Neurovascular Uncoupling and Memory Deficits in Mice Modeling Alzheimer's Disease." *Journal of Neuroscience* 41, no. 19: 4305–4320.

Verkhratsky, A., and M. Nedergaard. 2018. "Physiology of Astroglia." *Physiological Reviews* 98, no. 1: 239–389.

Verkhratsky, A., M. Olabarria, H. N. Noristani, C. Y. Yeh, and J. J. Rodriguez. 2010. "Astrocytes in Alzheimer's Disease." *Neurotherapeutics* 7, no. 4: 399–412.

von Bartheld, C. S., J. Bahney, and S. Herculano-Houzel. 2016. "The Search for True Numbers of Neurons and Glial Cells in the Human Brain: A Review of 150 Years of Cell Counting." *Journal of Comparative Neurology* 524, no. 18: 3865–3895.

Wang, F., S. Y. Ren, J. F. Chen, et al. 2020. "Myelin Degeneration and Diminished Myelin Renewal Contribute to Age-Related Deficits in Memory." *Nature Neuroscience* 23, no. 4: 481–486.

Wang, J., Y. Lu, C. Carr, K. M. Dhandapani, and D. W. Brann. 2023. "Senolytic Therapy Is Neuroprotective and Improves Functional Outcome Long-Term After Traumatic Brain Injury in Mice." *Frontiers in Neuroscience* 17: 1227705.

Wang, X., and E. K. Michaelis. 2010. "Selective Neuronal Vulnerability to Oxidative Stress in the Brain." *Frontiers in Aging Neuroscience* 2: 12.

Wang, Y., M. Martinez-Vicente, U. Krüger, et al. 2009. "Tau Fragmentation, Aggregation and Clearance: The Dual Role of Lysosomal Processing." *Human Molecular Genetics* 18, no. 21: 4153–4170.

Wei, Z., X. C. Chen, Y. Song, et al. 2016. "Amyloid beta Protein Aggravates Neuronal Senescence and Cognitive Deficits in 5XFAD Mouse Model of Alzheimer's Disease." *Chinese Medical Journal* 129, no. 15: 1835–1844.

Welch, G. M., C. A. Boix, E. Schmauch, et al. 2022. "Neurons Burdened by DNA Double-Strand Breaks Incite Microglia Activation Through Antiviral-Like Signaling in Neurodegeneration." *Science Advances* 8, no. 39: eabo4662.

West, M. J., C. H. Kawas, W. F. Stewart, G. L. Rudow, and J. C. Troncoso. 2004. "Hippocampal Neurons in Pre-Clinical Alzheimer's Disease." *Neurobiology of Aging* 25, no. 9: 1205–1212.

Wiley, C. D., and J. Campisi. 2021. "The Metabolic Roots of Senescence: Mechanisms and Opportunities for Intervention." *Nature Metabolism* 3, no. 10: 1290–1301.

Windener, F., L. Grewing, C. Thomas, et al. 2024. "Physiological Aging and Inflammation-Induced Cellular Senescence May Contribute to Oligodendroglial Dysfunction in MS." *Acta Neuropathologica* 147, no. 1: 82.

World Health Organization (WHO). n.d. "Dementia 2023." https://www.who.int/news-room/fact-sheets/detail/dementia.

Xie, Y. Y., T. T. Pan, D. E. Xu, et al. 2021. "Clemastine Ameliorates Myelin Deficits via Preventing Senescence of Oligodendrocytes Precursor Cells in Alzheimer's Disease Model Mouse." *Frontiers in Cell and Development Biology* 9: 733945.

Xu, H., M. Chen, A. Manivannan, N. Lois, and J. V. Forrester. 2008. "Age-Dependent Accumulation of Lipofuscin in Perivascular and Subretinal Microglia in Experimental Mice." *Aging Cell* 7, no. 1: 58–68.

Xu, M., T. Pirtskhalava, J. N. Farr, et al. 2018. "Senolytics Improve Physical Function and Increase Lifespan in Old Age." *Nature Medicine* 24, no. 8: 1246–1256.

Yao, M., Z. Wei, J. S. Nielsen, et al. 2024. "Senolytic Therapy Preserves Blood-Brain Barrier Integrity and Promotes Microglia Homeostasis in a Tauopathy Model." *Neurobiology of Disease* 202: 106711.

Young, K. M., K. Psachoulia, R. B. Tripathi, et al. 2013. "Oligodendrocyte Dynamics in the Healthy Adult CNS: Evidence for Myelin Remodeling." *Neuron* 77, no. 5: 873–885.

Yousefzadeh, M. J., Y. Zhu, S. J. McGowan, et al. 2018. "Fisetin Is a Senotherapeutic That Extends Health and Lifespan." *eBioMedicine* 36: 18–28.

Yu, C., S. D. Narasipura, M. H. Richards, X. T. Hu, B. Yamamoto, and L. Al-Harthi. 2017. "HIV and Drug Abuse Mediate Astrocyte Senescence in a beta-Catenin-Dependent Manner Leading to Neuronal Toxicity." *Aging Cell* 16, no. 5: 956–965.

Zhan, Y., R. C. Paolicelli, F. Sforazzini, et al. 2014. "Deficient Neuron-Microglia Signaling Results in Impaired Functional Brain Connectivity and Social Behavior." *Nature Neuroscience* 17, no. 3: 400–406.

Zhang, P., Y. Kishimoto, I. Grammatikakis, et al. 2019. "Senolytic Therapy Alleviates Abeta-Associated Oligodendrocyte Progenitor Cell Senescence and Cognitive Deficits in an Alzheimer's Disease Model." *Nature Neuroscience* 22, no. 5: 719–728.

Zhao, J., T. O'Connor, and R. Vassar. 2011. "The Contribution of Activated Astrocytes to Abeta Production: Implications for Alzheimer's Disease Pathogenesis." *Journal of Neuroinflammation* 8: 150.

Zhu, Y., T. Tchkonia, T. Pirtskhalava, et al. 2015. "The Achilles' Heel of Senescent Cells: From Transcriptome to Senolytic Drugs." *Aging Cell* 14, no. 4: 644–658.