Review

When the Brain Grows Old Too Soon: Aging and Senescence as a Driver of MS Progression

Sienna S. Drake,[1,2,3] **Aliyah Zaman,**[3] **and Alyson E. Fournier**[3]

[1]The Gene Lay Institute of Immunology and Inflammation, Brigham & Women's Hospital, Massachusetts General Hospital, and Harvard Medical School, Boston, Massachusetts 02115, [2]Ann Romney Center for Neurologic Diseases, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115, and [3]Department of Neurology and Neurosurgery, Montreal Neurological Institute, McGill University, Montreal, Quebec H3A 2B4, Canada

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease. While onset usually occurs in young adulthood, older age worsens MS prognosis with accelerated accumulation of disability and higher susceptibility to the progressive form of MS, characterized by continuous symptoms without periods of remission. Treatment responsiveness also declines with age, changing the landscape of available therapies for older patients. Recent work has begun to uncover an accelerated aging and senescence-like phenotype arising in patients with MS and its preclinical animal models. This review explores the current evidence for inflammatory injury driving age-related changes in brain cells in patients with MS and preclinical animal models, its interactions with sex and hormones, and the possible future for anti-aging therapeutic strategies to address this evolving neurodegenerative phenotype of MS during aging.

Key words: **aging; multiple sclerosis; neurodegeneration; neuroimmunology; neuroinflammation; senescence**

Introduction

Aging and multiple sclerosis: a conversation between inflammation and neurodegeneration

Multiple sclerosis (MS) is an autoimmune inflammatory neurodegenerative disorder, affecting ∼2 million people worldwide (Filippi et al., 2018). Aging is the primary risk factor in the development of neurodegenerative diseases, suggesting that the brain is particularly impacted by aging (Khan et al., 2017). Increased age is associated with a decrease in the regenerative capacity of various tissues, an increase in chronic tissue inflammation, and a decline in immune system function. These factors impact brain function through decreased repair and regeneration, increased chronic and local tissue inflammation, and decreased capacity to appropriately respond to and resolve infections and injury (Khan et al., 2017). Although many studies have investigated the correlation between chronological age and MS disease severity and progression, fewer studies have been able to characterize what specific mechanisms may be driving this relationship and how they may affect the brain (Kuhlmann et al., 2023). Additionally, studies are now finding that chronic inflammation and injury, like seen in patients with MS, exacerbate phenotypes associated with biological aging, acting at both the organ macroscale and cellular level in a phenomenon described as "accelerated aging." As such, it is imperative to understand the relationships between aging, inflammation, and MS and their effects on the brain to develop new lifetime-effective therapeutics that promote CNS resilience and slow or even stop the continuous development of neurological deficits. Therefore, this review summarizes what is currently known about the interactions between aging and MS; how sex and hormones modify these interactions; how, at a cellular level, aging alters the normal functioning of various brain cells and their relevance to MS disease progression; and finally how new discoveries in this domain may affect the development of future disease-modifying therapies for patients with MS.

Age-related changes in the clinical features of people with MS

When patients with MS first present in the clinic with MS symptoms, they usually receive a diagnosis of relapsing-remitting MS (RRMS), which is characterized by periods of new or worsening symptoms that eventually resolve, corresponding with new or evolving CNS lesions visualized by MRI (Filippi et al., 2018). However, starting around the fifth decade of life, most patients with MS will begin to transition from RRMS to a secondary progressive disease course (SPMS), defined by gradual worsening of symptoms without remission, while the development of new inflammatory lesions wanes (Coerver et al., 2024). Some patients are diagnosed with progressive MS at symptom onset (primary progressive MS; PPMS); however, these patients are typically of older age at diagnosis, suggesting a relationship between increased age and a more neurodegenerative disease course (Coerver et al., 2024). In fact, a study comparing patients with MS between the ages of 50 and 75, diagnosed either with adult-onset MS (<50 years of age at diagnosis) or late-onset

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Correspondence should be addressed to Sienna S. Drake at ssdrake@ualberta.ca, sienna.drake@mail.mcgill.ca or Alyson E. Fournier at alyson.fournier@mcgill.ca.

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MS (>50 years of age at diagnosis), found that rates of progressive disease were similar, supporting the fact that progressive disease is a function of age, not disease duration. Rates of cognitive impairment were also similar between these two groups, suggesting that while age and MS diagnosis affect cognition, it is independent of disease duration (Soares-Dos-Reis et al., 2025).

The primary pathological hallmark of MS is the presence of inflammatory demyelinated lesions, visualized by magnetic resonance imaging (MRI), disseminated throughout the central nervous system (Filippi et al., 2018). Different lesion types prevail at different disease stages, with active lesions, characterized by new CNS immune cell infiltrates, dominating in RRMS, and inactive and chronic active lesions characteristic in older people with MS and people with progressive disease (Filippi et al., 2018). Chronic active lesions constitute compartmentalized CNS inflammation, with an expanding inflammatory rim of microglia and macrophages that result in a slowly expanding demyelinating and neurodegenerative pathology (Bagnato et al., 2024). While demyelinated lesions may spontaneously remyelinate after resolution of inflammation, this outcome is more common in younger people with MS and is less frequently observed in older people, reflecting an age-related decline in tissue regenerative capacity (Goyne et al., 2024). Similarly, older age is associated with lessened recovery from relapses, and histologically with a higher and more diffuse burden of pathology, with substantial gliosis and axonal injury presenting throughout the normal-appearing gray and white matter, not only at lesion sites, and widespread brain volume loss, indicative of broader neurodegeneration (Conway et al., 2019; Chitnis et al., 2020; Goyne et al., 2024).

Although there are numerous disease-modifying therapies available to patients with MS, these therapies are most effective at mitigating disease relapses in young people with RRMS (Goyne et al., 2024). Some DMTs are approved for use in people with progressive MS, but they are mostly efficacious where there is evidence of new inflammatory lesion activity, suggesting that the DMTs are still functioning to reduce inflammation without altering neurodegenerative processes or promoting remyelination or tissue regeneration to a measurable extent (Goyne et al., 2024). As people with MS age, DMT side effects tend to worsen, and the benefits of staying on DMTs, especially for people with minimal new inflammatory activity, are unclear. Currently available immunomodulatory therapies also appear to have little impact on the compartmentalized CNS inflammation, demyelination, and neurodegeneration that underlies symptom worsening and disease progression particularly in older people with MS. Together, increased age correlates with an increased level of disability (even when controlling for duration of disease), accelerates disease progression, decreases DMT efficacy, and increases DMT side effects (Soares-Dos-Reis et al., 2025; van der Walt et al., 2025). Although some people with MS may benefit from remaining on DMTs depending on their individual level of disease activity, a meta-analysis of 13 immunomodulatory drugs found no measurable benefit in the average person with MS over 53 years of age, supporting the fact that age-related changes in disease activity result in differential responsivity to currently available DMTs (Weideman et al., 2017). Part of this is mediated by the lack of sensitive measures of DMT efficacy in cases with a more neurodegenerative, progressive disease course, and where the formation of new gadolinium enhancing lesions (the standard metric for measuring DMT efficacy) is rarer, and the expanded disability status scale (EDSS) is higher in general, resulting in greater variability of rating, and also may be abnormal even in healthy patients during aging, making it a less sensitive tool for monitoring disease progression (van der Walt et al., 2025). Additional biomarkers in development for monitoring MS progression, such as neurofilament light chain or glial fibrillary acid protein in CSF and serum, also increase during aging, requiring further investigation to use when differentiating between MS-driven increases versus aging (van der Walt et al., 2025). In fact, people greater than 55 years of age are often excluded from clinical trials for this reason, so the continued efficacy of first-line MS DMTs in this population is not well studied (van der Walt et al., 2025). Altogether, as people with MS age, there are considerable changes to the type of lesions they develop, the relative benefits of available therapeutic interventions, and a lack of sensitive methods or biomarkers for monitoring further disease progression.

Sex, hormones, and aging in people with MS

There are notable sex-based differences in MS prevalence and progression. Women develop RRMS at a higher rate than men, in a ratio ~3:1, whereas PPMS is diagnosed at a similar rate in men and women, and male patients with MS typically experience faster disability accrual and a more severe disease course overall, with more gray matter and cerebellar involvement (Filippi et al., 2018). Thus, biological sex is an important modifier of MS disease activity, and sex-related changes in hormone levels during aging further alter MS disease activity. Pregnancy is strongly protective against MS disease and protects against worsening, particularly in the third trimester of pregnancy, which is attributed to the anti-inflammatory shift in immune cells, epigenetic adaptations, and production of high levels of estrogens and other sex hormones (R. Voskuhl et al., 2016; Campagna et al., 2023; Zenere et al., 2023). A placebo-controlled clinical trial providing estriol to people with MS who were already receiving glatiramer acetate found a decreased annual relapse rate; however, the maximum age of people included in the study was 50 and limited to those diagnosed with RRMS, so older patients, more likely to be postmenopausal with decreased circulating hormone levels, and those with progressive disease were not evaluated (R. R. Voskuhl et al., 2016). MS disease severity develops more rapidly postmenopause, although the contribution of decreasing levels of female sex hormones, including estrogens and progesterone, versus other nonreproductive aging-related changes, to the acceleration of disease activity is not well delineated. Although decreased inflammatory relapse rates and increased gray matter atrophy are commonly observed postmenopause in people with MS, a large cohort study suggested that it is unlikely menopause itself is causal and these changes may be more attributable to somatic aging (Baroncini et al., 2019; Lorefice et al., 2023; Bridge et al., 2025). Yet, ovarian reserve, measured by levels of anti-Mullerian hormone, is associated with gray matter atrophy and level of disability, invoking the idea that reproductive aging may be associated with neurodegenerative processes and complicating interpretation (Graves et al., 2018). The exacerbation of numerous symptoms, including vasomotor and urinary symptoms, fatigue, and cognitive changes, is associated with menopause in people with MS and requires careful management by clinicians in determining whether these should be treated as symptoms of MS or of menopause (McConville and Bove, 2026). Overall, the paucity of studies on people with MS through menopause and on hormone-replacement therapy (HRT) limits the disentanglement of aging, menopause, and hormone levels on the MS disease course. More research is needed in this field to

better treat and manage both MS and menopause symptoms in people as they age (McConville and Bove, 2026). A small clinical trial on HRT in people with MS undergoing menopause found increased satisfaction and fewer missed doses in people receiving HRT, suggesting that HRT is effective at least in managing negative symptoms of menopause in this cohort, but larger studies are needed to evaluate the effect on MS-related symptoms and disability accrual (Bove et al., 2022).

Similarly, men with MS experience disease acceleration with decreasing levels of sex hormones. Men with hypogonadism and lower levels of testosterone experience higher MS disease severity (Ysrraelit and Correale, 2021; Bove et al., 2026). One study found that older men on androgen modulation therapy (AMT), a testosterone-lowering therapy to treat certain prostate cancers and hair loss, experienced higher relapse rates and inflammatory disease activity, further supporting the protective role testosterone may play in the MS disease course (Zeydan et al., 2025). Especially as men age, AMT becomes more commonly prescribed and therefore requires careful consideration and management in men with MS who may be at risk of disease worsening (Zeydan et al., 2025). Gender-diverse and transgender patients with MS are also likely to be recipients of hormone therapy and would likewise benefit from a better understanding of the role hormones play in the MS disease course. So far, some small studies exist reassuring that gender-affirming hormone therapy may not impact overall disease development, but continued research and clinical follow-up is necessary to ensure long-term patient safety and inform clinical management (Balshi et al., 2025; Neyal et al., 2025).

At a cellular level, preclinical evidence exists to support neuroprotective roles for sex hormones in models of neuroinflammatory injury. Both estrogen and testosterone promote oligodendrocyte differentiation, resulting in increasing myelin production (Taylor et al., 2010; Collongues et al., 2018; Ghoumari et al., 2020; Bardy-Lagarde et al., 2025). They tend to have anti-inflammatory effects in the CNS as well, including decreasing microglia reactivity, and may likewise have neuroprotective effects, particularly testosterone which was shown to maintain hippocampal synapses in a mouse model of MS (Kipp et al., 2012; Spence and Voskuhl, 2012; Wisdom et al., 2013; Collongues et al., 2018; Yang et al., 2020). Their decreasing levels with age therefore may very well have cellular level effects on neuronal resilience, myelin repair, and inflammation in the CNS of people with MS. Overall, a protective effect of sex hormones on the brain and on immune system function in people with MS is supported by clinical and preclinical research, and changes in these hormone levels during aging should not be excluded as a contributor to heightened disease activity (Ysrraelit and Correale, 2019). Further research on the interaction between aging and sex hormones in people with MS will inform care of MS symptoms and disease progression and the clinical management of sex- and hormone-related syndromes in aging people with MS.

Accelerated aging in people with MS

People with MS exhibit signs of accelerated aging, suggesting that inflammatory disease activity may drive age-related changes throughout the body that result in increased disability over time. Biological aging is typically measured using aging- and longevity-associated metrics including telomere length, DNA methylation as a measure of epigenetic aging, and composite biomarker scoring strategies such as the US National Health and Nutrition Survey Biological Age Index (NHANES BAI; Mulero et al., 2025). Other biomarkers, including decreased immune cell function, thymic involution, chronic low-grade inflammation, and levels of serum proteins including neurofilament light chain (Nf-L) and IL-6, are altered with aging (Iribarren-López et al., 2025). These factors are also modulated by MS, lending to investigations of accelerated aging in people with MS (Iribarren-López et al., 2025).

In both children and adults with MS, epigenetic age as measured by DNA methylation is higher than age-matched healthy controls, with another study similarly observing an increased aging signal in whole blood that was strongly associated with B-cells (Maltby et al., 2023; Goyne et al., 2025). Premature thymic involution has been observed in people with MS, as well as premature aging in CD8+ T-cells in young people with MS (Thewissen et al., 2005; Eschborn et al., 2021; Iribarren-López et al., 2025). Even in pediatric MS, increased proportions of T-cells associated with aging are found, mirroring the premature thymic involution phenotype (Balint et al., 2013). Additionally, a metabolic age prediction model based on plasma and serum metabolites found that people with MS aged 1.19 years per year of chronological age (Siavoshi et al., 2026). Similarly, people with MS also score higher on the NHANES BAI compared with their chronological age. In this cohort, a higher BAI was also associated with faster disability progression (Miner et al., 2023). Telomere length in peripheral blood cells is often shorter in people with MS, including in pediatric MS, compared with age-matched healthy controls, although not all studies have replicated this association (Guan et al., 2015; Habib et al., 2020; Bühring et al., 2021; Iribarren-López et al., 2025; Mulero et al., 2025; Jacques et al., 2026). Within individuals with MS, one study found that shorter telomere lengths were associated with higher disability and lower brain volume independent of chronological age (Krysko et al., 2019). Overall, a preponderance of evidence supports accelerated aging in peripheral blood and cells of people with MS that tends to correlate with disability and progression, suggesting that biological aging may be at least a useful prognostic metric, and possibly a biological mechanism related to disease worsening.

Predicted brain age based on MRI scans also appears older than chronological age in people with MS, with some studies predicting brain ages ranging from ∼4 to ∼10 years older than their chronological age (Cole et al., 2020; Brier et al., 2023; Pontillo et al., 2024; La Rosa et al., 2025). Disease duration can also be predicted using MRI scans and machine learning, further informing characterization of the relative level of disease-associated neurodegeneration. Both the brain age gap and brain disease duration are predictive of clinical disability and disease progression, correlating with measures of physical disability and cognitive impairment (Brier et al., 2023; Pontillo et al., 2024; Romme et al., 2024; Bos et al., 2026). Equally, ventricle expansion and brain volume reduction occur more rapidly in people with MS over time (Romme et al., 2024; Bos et al., 2026). Periventricular gradients, MRI abnormalities associated with inflammation and microstructural changes to the white matter, increase with aging and are more pronounced in people with MS (Zhuo et al., 2025). Overall, people with MS exhibit numerous indicators of accelerated aging, particularly impacting the brain and immune system, which may underlie decreased regenerative potential, decreased acute inflammatory activity, increased neurodegenerative processes, and increased disability and disease progression in midlife. Although it is not fully determined how aging occurs in organisms, evidence suggests a strong link between cellular senescence and organismal aging as, with age, senescent cells

accumulate in organs, and animal models demonstrating increased cellular senescence also exhibit signs of accelerated aging, while models eliminating senescent cells result in longer lifespans and health spans (Beck et al., 2020; López-Otín et al., 2023). Thus, to understand what might be underlying accelerated aging in people with MS, it is important to understand how neuroinflammatory injury might drive cellular senescence, and likewise how cellular senescence might exacerbate or drive neuroinflammation.

Cellular Senescence in the Brain during Neuroinflammation and Demyelination

As mentioned, the predominant hallmark of aging across tissues is an increase in cellular senescence and age-associated cellular dysfunction (López-Otín et al., 2023). Cellular senescence is typically defined by a combination of features including cell cycle exit, dysregulation of metabolic activity, accumulation of DNA damage, epigenetic modifications, resistance to apoptosis through upregulation of BCL-family proteins, increased expression of an age-associated gene expression signature, and acquisition of a senescence-associated secretory phenotype (SASP; Saul et al., 2022; López-Otín et al., 2023). A study of SASP components in the CSF of people with MS found significant increases in numerous factors including IL-6, IL-10, CXCL2, CCL7, CCL3, CCL25, TNF-α, and MIF compared with age-matched healthy controls, so broad dysregulation of the SASP may be occurring in people with MS. Notably, some of these markers were further correlated with increased numbers of senescent brain cells by histopathology suggesting that these factors are promoting cellular senescence in the brain (Papadopoulos et al., 2025). Other specific protein markers frequently used to implicate cellular aging and senescence include expression of specific cell cycle proteins such as p16 and p16ink4a, p21, and p53; DNA damage markers including pRb, TP53BP1, and yH2AX; alteration or loss of LAMINB1 indicating deficits with the nuclear lamina; and increased beta-galactosidase activity (López-Otín et al., 2023). Meanwhile, transcriptional analysis often relies upon pathway-level analysis implicating senescence-related pathways. Recently, a collection of genes upregulated with aging and senescence across numerous tissue lines and organs in both humans and mice was described, and enrichment for this gene set is frequently used to measure cellular senescence in RNA-sequencing datasets (Saul et al., 2022).

Some caution is warranted when interpreting these phenotypes as the diversity of markers associated with aging and senescence are not each individually indicative of aging or senescence themselves and may instead reflect other alterations in cellular function. Additionally, these often serve as observational, phenotypic markers, with little functional follow-up. Finally, many markers associated with cellular senescence are secreted inflammatory factors, which already overlap with commonly dysregulated cytokines in people with MS (e.g., TNF-α, IL-6, and beta-2-microglobulin), so their increase may be incidental to the dysregulated immune system and increased inflammation and not a true sign of senescence. Further studies are needed to differentiate the relative influence of MS diagnosis and aging on their circulating levels. Nonetheless, within the brain of people with MS, numerous studies have described senescent phenotypes in various cell types, and animal models of neuroinflammation and demyelination have likewise shed light on the functional role that aging-associated phenotypes and cellular senescence may play in the disease pathogenesis. While cellular senescence may self-propagate through the SASP, meaning that peripheral inflammation and senescence may be contributing to brain cell senescence and vice versa, this section focuses on recent evidence of senescence specifically in the brain of patients with MS and its potential functional consequences drawing on evidence from animal models in order to understand how senescence of brain cells may be a therapeutically targetable phenotype to slow or prevent neurodegeneration, or promote repair in patients with MS. Here, results from studies focusing on senescence-associated phenotypes in oligodendrocytes and oligodendrocyte progenitor cells (OPCs), astrocytes and blood–brain barrier (BBB) cells, microglia, and neurons are described in detail (Fig. 1).

Oligodendrocytes and OPCs

Oligodendrocytes produce the myelin sheath that is the primary target for injury in MS. Evidence for the presence of senescent OPCs in MS arises from single-nucleus sequencing studies of MS lesions, demonstrating their transcriptional enrichment at the periplaque and lesion core (Absinta et al., 2021). At the protein level, histopathological assessment of MS lesions found that acute active lesions contain the highest rates of cellular senescence, as evidenced by positive p16 and 53BP1 staining, although chronic active lesions also demonstrated high levels of cellular senescence (Papadopoulos et al., 2025). Another study specifically assessing postmortem brain tissue from people with progressive MS found SOX2+ oligodendrocyte progenitor cells frequently express p16ink4a throughout normal-appearing white matter as well as in demyelinated lesions (Nicaise et al., 2019).

Experimental models have also provided mechanistic insight into OPC and oligodendrocyte changes in aging and in neuroinflammatory and demyelinating injury. OPCs isolated from aged animals have decreased differentiation potential compared with young OPCs and increased expression of numerous markers of senescence, including higher gene expression of *Cdkn2a*, increased mTOR activity, increased DNA damage, and reduced cellular respiration (Neumann et al., 2019). Metformin, a drug that modulates mTOR signaling and cellular energetics, could restore aged OPC differentiation potential (Neumann et al., 2019). Similarly, NPCs produced from progressive MS iPSC lines exhibited higher expression of senescence-associated beta-galactosidase activity and higher mRNA expression of both p16ink4a and p53; rapamycin, another mTOR modulator, reversed the presence of these markers (Nicaise et al., 2019). Nicaise et al. further pinpointed HMGB1, a senescence-associated protein, as a secreted factor that could induce NPC senescence and inhibit their differentiation into oligodendrocytes (Nicaise et al., 2019). Application of recombinant HMGB1 in an in vivo model of acute demyelination halted OPC differentiation and prevented remyelination (Rouillard et al., 2022). Together, these results suggest that OPCs from patients with MS, like naturally aged OPCs, have reduced potential for differentiation into oligodendrocytes, limiting their capacity to promote recovery following demyelinating injury.

While natural aging results in OPC senescence, reduces differentiation into myelinating oligodendrocytes, and results in shorter new myelin sheaths, chronic demyelination by cuprizone treatment was able to induce a similar phenotype in OPCs in young animals as well, linking demyelination to OPC senescence (Parandavar et al., 2024; Looprasertkul et al., 2025). Direct conversion of human oligodendrocytes from young and old donors found that oligodendrocytes from old donors exhibit markers of cellular senescence and are inefficient at producing new myelin, and conditioned media from pro-inflammatory microglia was

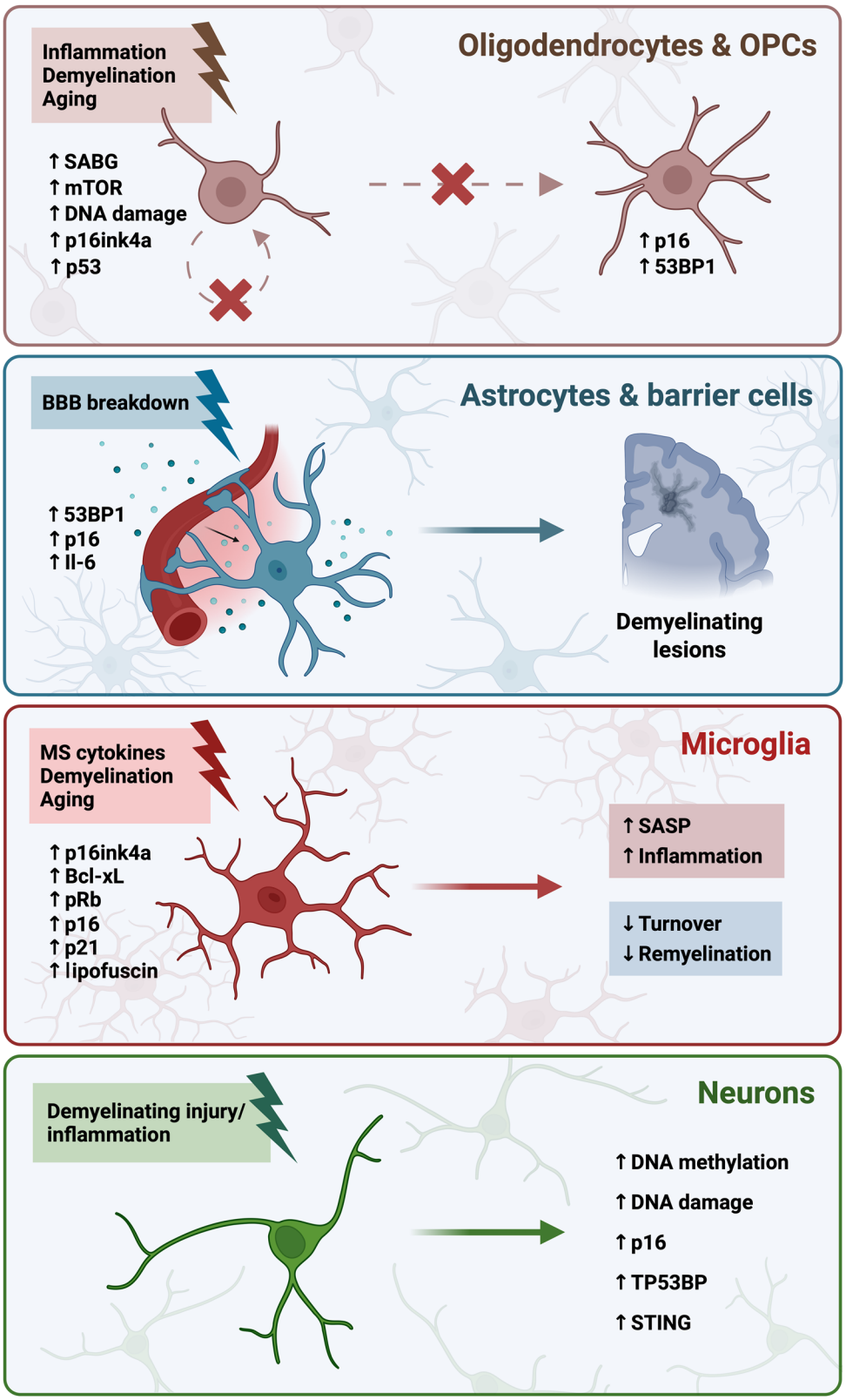

Figure 1. Summary of senescent markers identified in OPCs and oligodendrocytes, astrocytes and barrier cells, microglia, and neurons resulting from demyelinating injury, aging, and inflammation.

sufficient to induce a similar phenotype in oligodendrocytes from young donors, suggesting that secreted inflammatory factors may promote oligodendrocyte senescence and diminish remyelinating potential (Windener et al., 2024). This suggests that both demyelination and inflammation can produce environments that promote and maintain OPC and oligodendrocyte senescence, decreasing their capacity for remyelination. It is likely then that increased senescence of OPCs and oligodendrocytes

and MS lesions are key mediators of progressive disease as they acquire a nonregenerative and pro-inflammatory phenotype with increasing age and injury. Injury and inflammation both can promote senescence in these cells; likewise, senescence further drives inflammatory signaling and decreased regenerative capacity, thus acting as a positive feedback loop to inhibit resolution of inflammation and tissue repair over time as senescent cells accumulate. Thus, targeting OPC and oligodendrocyte senescence is an important consideration in addressing progressive disease in MS.

Astrocytes and barrier cells

Astrocytes and barrier cells, including ependymal cells, pericytes, and vascular cells, are in close contact with the blood and CSF and are therefore the first cells exposed to immune cells and noxious inflammatory stimuli in MS, presumably resulting in the gradient-in pathology observed on MRI, radiating from periventricular and perivascular edges inward into the brain (Magliozzi et al., 2022; Zhuo et al., 2025). Within MS lesions, p16+ senescent astrocytes are commonly present (Preininger et al., 2023; Papadopoulos et al., 2025). Single-nucleus RNA sequencing of different lesion types found that senescent astrocytes are particularly enriched in chronic active lesions, and both endothelial cells and astrocytes were highly vulnerable to cellular senescence in MS (Fagiani et al., 2025).

In a model of BBB dysfunction, exposure to blood-borne albumin induced premature senescence in astrocytes, through TGFβ signaling, a component of the SASP (Preininger et al., 2023). Senescent astrocytes secrete higher levels of cytokines associated with sustained inflammatory responses such as IL-6, which could promote chronic neuroinflammation, preventing resolution of neuroinflammatory injury and repair (Preininger and Kaufer, 2022; Preininger et al., 2023). IL-6 is also a known SASP factor and can induce senescence in other cells through paracrine signaling (López-Otín et al., 2023). CSF IL-6 levels are increased in patients with MS and are correlated with senescent cell density in MS normal-appearing gray matter (Papadopoulos et al., 2025). Histopathology for senescence-associated protein markers in postmortem tissue similarly identified an ependymal-in gradient of 53BP1+ cells, a marker for DNA damage and cellular senescence, and p16 also strongly labeled the ependyma in MS patients (Papadopoulos et al., 2025). Senescent astrocytes and ependymal cells also strongly correlated with the formation of new demyelinating lesions in a primate model of MS, suggesting that cellular senescence in astrocytes and ependymal cells is related to the development of subsequent demyelinating lesions (Lin et al., 2025).

Since BBB dysfunction is associated with aging, and pericyte senescence causes increased BBB permeability, aging may further exacerbate senescence phenotypes caused by loss of barrier integrity in a positive feedback loop as peripheral SASP components penetrate the leaky BBB and induce senescence in the brain (Iwao et al., 2023). This may be further exacerbated by premature thickening of the choroid plexus in people with MS, an MRI phenotype also seen during natural aging, which leads to changes in albumin concentration in the CSF, reduced CSF waste clearance and flow, and altered immune cell infiltration patterns in the choroid plexus and ventricles (Fleischer et al., 2021; Klistorner et al., 2025; Watanabe et al., 2026). Choroid plexus thickening likewise correlates with relapse-free progression and neurodegeneration, supporting its association with progressive neurodegenerative disease (Bergsland et al., 2024; Fleischer et al., 2026). Impaired CSF flow may contribute to reduced clearance of SASP components from the CSF and drive paracrine senescence in the choroid plexus and ventricles (Fleischer et al., 2021). Overall, loss of BBB integrity and exposure to paracrine inflammatory signals seem to be a driver of perivascular and periventricular lesions, exacerbated by local cellular senescence in astrocytes, ependymal cells, and other barrier cells, and bidirectionally influenced by the same senescent cells releasing SASP factors that further drive CSF inflammation and paracrine senescence. Therapeutically targeting senescence of barrier cells and astrocytes may help prevent the BBB dysfunction that underlies lesion formation, demyelination, and neurodegeneration.

Microglia

Microglia are brain-resident innate immune cells essential for myelin repair in numerous models of myelin injury as they phagocytose myelin debris, clearing the area of inhibitory myelin proteins to enable remyelination. However, they exhibit significant dysfunction in MS, adopting pro-inflammatory, lipid-laden, and senescent phenotypes that may contribute to sustained tissue injury and an inability to engage adequate tissue repair (Fagiani et al., 2025). Single-nucleus sequencing of MS lesions found that lipid-laden microglia commonly exhibit a transcriptional signature of cellular senescence, and senescent microglia are strongly associated with chronic active lesions in multiple single-nucleus sequencing studies of MS patient lesions (Fagiani et al., 2025). Microglia in MS chronic active lesions have been shown to equally express protein markers of senescence including p16ink4a (Absinta et al., 2021; Fagiani et al., 2025), pRB (Drake et al., 2024), BCL-xL (Drake et al., 2024), and lipofuscin accumulation (Fagiani et al., 2025). In glia-enriched brain organoids, CSF treatment from patients with MS significantly increased markers of cellular senescence, with specific MS-specific cytokine combinations particularly inducing senescence in microglia, although a trend toward increased senescence was also seen in astrocytes and neurons in this model (Fagiani et al., 2025). Thus, it is evident that pro-inflammatory cytokine activity in MS CSF is sufficient to induce senescence in microglia.

This phenotype is mirrored in murine models of neuroinflammation and demyelination. In young murine experimental autoimmune encephalomyelitis (EAE), a model that induces BBB breakdown, peripheral immune cell trafficking to the CNS, myelin injury, gliosis, and neurodegeneration, microglia exhibit senescence-associated beta-galactosidase activity (Drake et al., 2024), express p16 and p21(Manavi et al., 2025), and by RNA sequencing are enriched for pathways related to cellular senescence, dysregulation of apoptosis, DNA damage, and cell cycle regulation (Drake et al., 2024). Similarly, lysolecithin-induced acute demyelination corresponded with rapid accumulation of p16+ senescent microglia in the lesion area, but these cells decreased over time in young and middle-aged mice as the lesion underwent remyelination (Gross et al., 2025). However, in aged mice, senescent microglia persisted over time and were associated with impaired remyelination and decreased numbers of mature oligodendrocytes, confirming that natural aging also promotes a dysfunctional senescent phenotype that inhibits remyelination (Gross et al., 2025). This strongly correlated with increased and sustained presence of a SASP in these demyelinated lesions which may promote maintenance of cellular senescence in other cell types in the demyelinated lesions (Gross et al., 2025). Genetic depletion of p16ink4a+ senescent microglia in these aged mice was unable to improve remyelination, indeed suggesting that other factors are involved in impaired remyelination capacity in this model, including

oligodendrocyte senescence (Gross et al., 2025). On a similar vein, aged mice undergoing EAE exhibit stronger microglial activation corresponding with a more severe disease course, suggesting that natural aging and senescence may further exacerbate inflammatory demyelinating disease (Atkinson et al., 2022). So, while inflammatory demyelination appears to induce senescent microglia, aging also alters their function and response to neuroinflammation, typically resulting in more severe disease and impaired recovery. Given microglial involvement in chronic active lesion pathology, senescent microglia driving chronic tissue inflammation are likely to be a key component of disease progression, and rejuvenation of microglia or elimination of senescent microglia may be promising therapeutic avenues to consider to resolve chronic inflammatory activity and promote a lesion microenvironment more conducive to myelin repair. Altogether, microglia are susceptible to aging and senescent phenotypes during autoimmune neuroinflammation that may be detrimental to myelin repair processes.

Neurons

Neurons are considered bystanders in MS pathogenesis, undergoing neurodegeneration in response to the inflammatory, demyelinating context driven by the disease. As such, few studies have investigated cellular senescence and aging in neurons in the context of MS and neuroinflammatory disease and how they may alter neuronal injury and resilience. Nonetheless, some evidence exists.

First, in MS patient lesions, neurons exhibit markers of senescence including p16, TP53BP, and lipofuscin expression (Papadopoulos et al., 2025). Somatic DNA mutations arise faster in neurons from people with MS, suggesting that neuroinflammatory injury is mutagenic to neurons, which may contribute to DNA damage-induced cellular senescence (Motyer et al., 2025). Similarly, neurons in patients with MS exhibit higher levels of DNA damage based on yH2AX immunofluorescence and exhibit expression of genes and pathways relevant to cellular aging (Drake et al., 2025). A recent study found that L2/3 cortical neurons are particularly susceptible to DNA damage-induced death, exhibiting high expression of yH2AX and 53BP1 (Morcom et al., 2026). DNA methylation marks associated with epigenetic aging also trend higher in neurons in PMS (Kular et al., 2022).

In experimental models, high levels of DNA damage are similarly observed in spinal cord and retinal neurons in murine EAE, alongside markers of oxidative stress in retinal neurons, increased senescence-associated beta-galactosidase expression in the brain and spinal cord neurons, and increased histone methylation marks associated with aging (Duarte et al., 2024; Drake et al., 2025; Garton et al., 2025; Mace et al., 2026). Interestingly, the DNA damage phenotype is exacerbated by asymptomatic viral infection in the EAE model; viral DNA expression has also previously been shown to induce neurons to a senescent-like phenotype, and viral infection is strongly implicated in MS as a causative factor, potentially linking viral infection, neuronal injury and senescence, and MS (Duarte et al., 2024). Other models of demyelination and neuroinflammation similarly induce DNA damage responses in neurons, driving neuronal cell death particularly within cortical layers 2–4 (Morcom et al., 2026). It is therefore possible that DNA damage-induced cellular senescence is a component of the neuronal response to neuroinflammatory injury. Gene expression analysis further revealed that, in murine EAE, neurons exhibit a gene program akin to naturally aged neurons, suggesting that neuroinflammatory injury and aging may both result in similar phenotypic changes in gene expression (Drake et al., 2025). The neuronal inflammatory stress response is also driven by STING, a canonical inflammation-sensing pathway protein, responding to glutamate and calcium stores driving neuronal cell death via ferroptosis. Here, neurons were demonstrated to exclusively express STING in response to inflammatory challenge. Subsequently, glutamate excitotoxicity increased autophagy and ROS production, ultimately driving neuronal cell death through ferroptosis (Woo et al., 2024a). STING signaling and autophagy are both processes that are activated in senescent cells, although not necessarily indicative of cellular senescence (López-Otín et al., 2023). Neuronal injury and death are further promoted by inflammation-induced alterations to glycolytic pathways and neuronal metabolism, pathological protein accumulation, and proteasomal dysfunction (Schattling et al., 2019; Woo et al., 2024b, 2025). Altogether, these features are common to senescent cells, but further research into neuronal senescence in MS and its animal models is needed to properly characterize its role in inflammation-mediated neurodegeneration.

Therapeutically Targeting Senescence to Attenuate Neuroinflammation and Promote Remyelination

The accumulation of senescent cells during neuroinflammatory injury in the brain is a new focus for therapeutic intervention, with two major drug classes targeting the senescent phenotype. Senolytics are a class of drugs that typically induce cell death in senescent cells; senomorphics are a class of drugs that reverse or counteract cellular senescence phenotypes without inducing cell death. Common senolytics include the combination therapy dasatinib and quercetin (D + Q) and BCL2 inhibitors such as ABT-263, whereas metformin and rapamycin are representative senomorphic molecules (Li et al., 2021). Some of these have been explored in preclinical research and even clinical trials to modulate, deplete, or rejuvenate senescent cells in the CNS in models of MS, to varying levels of success. So far, the main approaches have been promoting rejuvenation of OPCs and oligodendrocytes using senomorphics, to achieve remyelination and repair of previously demyelinated lesions, while also promoting resilience and preventing extensive demyelination in new areas. Senolytics have been more commonly used to deplete dysfunctional senescent immune cells, predominantly targeting macrophages and microglia, to resolve chronic neuroinflammation and promote a lesion microenvironment more conducive to repair, which may be particularly relevant in the context of chronic active lesions which are strongly associated with progressive disease.

Senomorphic rejuvenation of OPCs and oligodendrocytes

There is a strong focus on rejuvenating OPCs and oligodendrocytes to promote remyelination, as this would directly address the main pathological feature of MS. Clemastine is a molecule that promotes substantial differentiation of OPCs into myelinating oligodendrocytes, generating new myelin in vitro and in vivo (Mei et al., 2014; Li et al., 2015). One clinical trial in RRMS found promising results in shortening latency delay on visual evoked potentials, an indicator of improved optic nerve function (Green et al., 2017). However, a recent report found that treatment with clemastine in an animal model of demyelinating injury induced OPC senescence, ultimately leading to depletion of the progenitor pool (Cooper et al., 2024). While immediate remyelination may therefore be enhanced, this effect may decrease over time as the pool of OPCs no longer produce new

oligodendrocytes. Incidentally, a small trial in PMS stopped treatment after significant worsening with clemastine, although this was attributed to metabolic dysfunction and some measures of pyroptosis (Kocot et al., 2025).

Metformin equally has shown promise for improving remyelination, as it is able to rejuvenate aged OPCs in vitro (Neumann et al., 2019). However, it has demonstrated limited potential so far in in vivo animal models. When treatment is provided daily starting prior to disease induction, it reduces disease severity, but when given post-onset as an intervention, it has no measurable effect, suggesting that OPC responsiveness to metformin-mediated rejuvenation may be dependent upon an initially healthy CNS environment (Gilbert et al., 2024). Additionally, obesity and metabolic syndrome are known to increase risk and severity of MS, so any effects on cellular senescence are difficult to disentangle from its concurrent function regulating metabolic energy expenditure and treatment of metabolic syndromes (Negrotto et al., 2016). Nonetheless, it is a promising treatment for promoting remyelination and preventing neurodegeneration currently being explored in numerous clinical trials (Cunniffe et al., 2021; De Keersmaecker et al., 2024; Riboni-Verri et al., 2025).

Meanwhile, specific protein targets have also been explored to promote remyelination and OPC differentiation. HMGB1 is a senescence-associated protein dysregulated in OPCs that inhibits OPC differentiation into myelinating oligodendrocytes and is overexpressed in neural precursor cells in PMS (Nicaise et al., 2019; Rouillard et al., 2022). Inhibiting HMGB1 promoted remyelination in demyelinating animal models (Rouillard et al., 2022). Small molecule-mediated rejuvenation by ESI1 also enhanced myelin production and OPC differentiation in animal models of demyelination—it functions by altering aging-associated epigenetic marks, restoring the epigenome to a more youthful state (Liu et al., 2024). Another approach taken to rejuvenate OPCs relies on diabetes and obesity-related (DOR) gene activation, which alters cellular metabolism through alpha-ketoglutarate signaling, ultimately promoting myelin production (Huang et al., 2024). Altogether, these preclinical data suggest there are multiple routes to rejuvenating OPCs and oligodendrocytes that may help promote remyelination, but these remain to be robustly tested and translated into promising clinical approaches.

Senolytic targeting to deplete senescent microglia

Similarly, targeting senescent microglia through senotherapeutic or senolytic agents has been attempted in preclinical models, with mixed results. One study described accumulation of a senescent-like population of *Bcl2l1*+ microglia in murine EAE (Drake et al., 2024). Treatment with a BCL-2 inhibitor, ABT-263, depleted spinal cord microglia, decreased microgliosis in the white matter, promoted myelin maintenance, and prevented neuronal death, strongly implicating this senescent microglial population in EAE disease activity (Drake et al., 2024). However, another study published soon after found the drug combination of dasatinib and quercetin (D + Q), a commonly used senolytic therapy, depleted senescent microglia but did not alter disease course or overall pathology (Manavi et al., 2025). They also described involvement of other senescent peripheral immune cells in the demyelinated lesions and CNS meninges, suggesting that senolytics may also target peripheral immune cell senescence (Manavi et al., 2025). Interestingly, a short study in middle-aged adoptive transfer EAE, which presents with a more progressive and severe clinical course, found that both D + Q and ABT-263 treatment reduced clinical disease and modulated microglial phenotypes in the CNS (Atkinson et al., 2025). Together, these findings emphasize the importance of the age of the animals and the specific senolytic administration in delineating effects of senescent cell depletion in inflammatory and demyelinating disease models. Notably, in the lysolecithin-induced demyelinating lesions model, depletion of senescent microglia only promoted remyelination in young and middle-aged mice, while aged mice were unable to remyelinate even following senescent cell depletion (Gross et al., 2025). CCL11, a specific SASP factor, was enriched in aged lesions and inhibited oligodendrocyte maturation in vitro (Gross et al., 2025). Neutralization of CCL11 following LPC-mediated demyelination promoted oligodendrocyte maturation and myelin formation (Gross et al., 2025). Thus, targeting both intrinsic senescent cellular phenotypes and secreted factors may be needed to address the inhibitory effect of senescent microglia during neuroinflammatory demyelination and promote remyelination and recovery. One of the main limitations that will remain to be addressed is the BBB permeability of these molecules, as well as whether they have any consequences in the peripheral immune system, as BCL-2 inhibitors like ABT-263 are already known to cause decreased platelet counts (Negi and Voisin-Chiret, 2022).

Partial reprogramming to rejuvenate neurons

Finally, partial reprogramming of neurons via AAV-OSK (*Oct4*, *Sox2*, and *Klf4*) resulted in improvements in neuronal function and survival in a murine model of EAE (Drake et al., 2025). This approach has equally been demonstrated to reduce aging-related neurological deficits and remarkably improve vision following glaucomatous injury in a murine model of glaucoma (Lu et al., 2020; Karg et al., 2023). Promoting neuronal resilience may prove to be effective, although it will likely depend on concurrent treatment of CNS inflammation. So, although most therapeutic approaches are being designed to promote remyelination or reduce harmful CNS inflammation by modulating microglial states, there is some evidence that interventions directly promoting neuronal resilience through rejuvenation may be effective in preventing neurodegeneration and preserving CNS function. Given the substantial evidence for DNA damage and DNA damage-induced senescence in neurons, novel approaches that specifically target this phenotype may be a promising future approach. Furthermore, barrier cells remain an underexplored target in these contexts, and as likely first responders to these interventions due to their positioning at the BBB, further research on their response to senolytics and senomorphics is of high interest.

Future Directions

Targeting cellular senescence and aging is a new approach in the potential treatment of age-related diseases, including neurodegenerative diseases. D + Q, a combination therapy with senolytic effects, has been in numerous small clinical trials so far, including for Alzheimer's disease, and has a high safety and tolerability profile (Garbarino et al., 2025). However, here there is a lack of obvious consensus on fluid biomarkers that are useful and appropriate for monitoring its efficacy (Garbarino et al., 2025). Thus, one of the main areas for development is in identifying useful, sensitive biomarkers for monitoring the effectiveness of senescence-based therapies. Specific targets with clear functional reasoning will need to be delineated particularly for clinical trials in patients with MS who already have elevated levels of certain senescence proteins due to the overlap between inflammatory and senescent phenotypes. IL-6, for example, may serve as a

biomarker of cellular senescence and MS disease activity, but whether it can be modulated by senescence therapies, and whether its potential reduction would equally reflect clinical improvement, remains to be seen. Some studies have used SASP panels to measure reductions in senescence peripherally, which is a more robust approach than single marker measures (Riessland et al., 2024). In general, current measures of biological aging, like telomere length, or DNA methylation, have not yet been clearly demonstrated to be modulated by senotherapeutics, so additional work in this area is needed to define sensitive and relevant measures of therapeutic efficacy in reducing cellular senescence and biological aging in humans. When it comes to MS, focusing on the progressive disease markers that are likewise associated with aging, such as progression independent of relapse activity (PIRA), may be a more appropriate approach for monitoring success of any senotherapeutics (Calabrese et al., 2024). Some promising biomarkers for monitoring disease progression in this context have been reviewed recently and include PET imaging of TSPO, which labels microglia in chronic active lesions, therefore providing a potential window into monitoring whether senolytics may impact chronic active lesion activity; serum levels of GFAP, NfL, PVALB, and CHI3L1, protein markers associated commonly with neurodegenerative processes in the CNS; CSF levels of Activin A, secreted by activated microglia and associated with cellular senescence; and other sensitive MRI-based measures of brain atrophy, neuronal degeneration, and slowly expanding lesions (Calabrese et al., 2024). Thickening of the choroid plexus may also be monitored by MRI and may provide insight into the relative success of any therapeutics in reducing inflammation in the CSF and BBB (Fleischer et al., 2021). These would additionally need to be matched with clinical measures to detect disease worsening or improvement. More in-depth research in preclinical models to better define the specific protein and gene targets associated with senescent and aging phenotypes in different cell types may help give rise to novel biomarkers for monitoring the development of cellular senescence and aging as well.

Additionally, as immunosenescence may be contributing to the decreased inflammatory disease activity in mid-life with MS patients, it will be important to monitor whether rejuvenation of the immune system is a side effect of senescence-based therapeutics and consider combining them with preexisting high efficacy therapies to prevent reigniting active inflammatory relapses in patients. In general, people with progressive MS undergoing clinical trials for senotherapeutics will need to be carefully monitored for side effects and drug efficacy (Sutter et al., 2022). In the meantime, certain anti-aging interventions are known to be impactful and effective in MS symptom management, including exercise and diet-related interventions (Ploughman et al., 2020; Learmonth and Motl, 2021; Siavoshi et al., 2025; Sun et al., 2025). Therefore, lifestyle changes associated with healthy aging should continue to be recommended to people with MS to help manage disease progression as they age (Ploughman et al., 2020). Finally, sex-specific interventions should be explored further, as biological and reproductive aging have systemic effects that may be contributing to disease progression in mid-life that could potentially be mitigated through appropriate hormone therapies, some of which are being currently tested in clinical trial (Metzger-Peter et al., 2020; Bove et al., 2022).

Overall, there is substantial evidence that aging and cellular senescence drive disease progression in people with MS, contributing to neurodegeneration and decreased capacity for repair and decreased resolution of inflammatory lesions, resulting in chronically expanding lesions, gray and white matter degeneration, and clinical disease progression. People with MS over the age of 50, often with progressive disease, currently have few therapeutic avenues that provide significant promise, due to the currently available market of therapeutics being predominantly anti-inflammatory, not taking into account how aging and senescence contribute to the progressive disease course seen in later life. Senotherapeutic strategies, especially those already being trialed for other neurodegenerative diseases, should therefore be high priority in the MS therapeutic pipeline and treat patient populations who are older with progressive disease. Treating MS as a disease driven by cellular senescence and aging is a promising new approach, and novel strategies combating processes involved in biological aging and cellular senescence present an exciting opportunity to improve the landscape of disease-modifying therapies available to people with MS.

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