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Multiple Sclerosis and Aging: The Dynamics of Demyelination and Remyelination

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Abstract

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) leading to demyelination and neurodegeneration. Life expectancy and age of onset in MS patients have been rising over the last decades, and previous studies have shown that age affects disease progression. Therefore, age appears as one of the most important factors in accumulating disability in MS patients. Indeed, the degeneration of oligodendrocytes (OGDs) and OGD precursors (OPCs) increases with age, in association with increased inflammatory activity of astrocytes and microglia. Similarly, age-related neuronal changes such as mitochondrial alterations, an increase in oxidative stress, and disrupted paranodal junctions can impact myelin integrity. Conversely, once myelination is complete, the long-term integrity of axons depends on OGD supply of energy. These alterations determine pathological myelin changes consisting of myelin outfolding, splitting, and accumulation of multilamellar fragments. Overall, these data demonstrate that old mature OGDs lose their ability to produce and maintain healthy myelin over time, to induce *de novo* myelination, and to remodel pre-existing myelinated axons that contribute to neural plasticity in the CNS. Furthermore, as observed in other tissues, aging induces a general decline in regenerative processes and, not surprisingly, progressively hinders remyelination in MS. In this context, this review will provide an overview of the current knowledge of age-related changes occurring in cells of the oligodendroglial lineage and how they impact myelin synthesis, axonal degeneration, and remyelination efficiency.

Keywords

NEURO glia, oligodendrocytes, myelin, aging, multiple sclerosis, NEURO degeneration, demyelination, NEURO repair, remyelination

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) leading to demyelination and neurodegeneration. Although its pathogenesis is not yet fully understood, several lines of evidence indicate that autoimmunity plays a major role in disease susceptibility and development (Thompson et al., 2018). The course of the disease is highly variable; approximately 85% of individuals initially present a relapsing-remitting course (RRMS) characterized by recurrent episodes of neurological dysfunction followed by full or partial recovery. After 10–15 years, up to 50% of untreated patients develop a more progressive course called secondary progressive MS (SPMS), characterized by increasing disability with fewer relapses. In about 15% of MS patients, however, disease progression is relentless as from onset, a subtype known as primary progressive MS (PPMS; Lublin et al., 2014). Like most autoimmune disorders, MS is more prevalent in women, and its onset peaks at around 20–40 years of age. Nevertheless, the disease can appear in children as well as in subjects over 50, which may constitute a diagnostic challenge (Krupp et al., 2013; Polliack et al., 2001; Sanai et al., 2016)

Over the last two decades, different studies have revealed that life expectancy and age of onset in people with MS are rising, in line with aging in the general population (Marrie et al., 2010; Simpson et al., 2011; Solaro et al., 2015; Rotstein et al., 2018). Notably, this increase in the age of affected patients significantly influences the course of the disease. Indeed, as different from young adults, people with late MS onset are more likely to have a progressive course

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(Minden et al., 2004; Scalfari et al., 2011; Tutuncu et al., 2013).

The degeneration of oligodendrocytes (OGDs) and OGD precursor cells (OPCs) increases with age (Phillips et al., 2019; Schmitt et al., 2015; Sugiyama et al., 2002). As a consequence, an increase in myelin breakdown is observed (Peters, 2002; Safaiyan et al., 2016) which contributes to neurodegeneration in the progressive phase of the disease. White matter aging is also associated with higher inflammatory activity of microglial cells and astrocytes (Safaiyan et al., 2021; Salminen et al., 2011), mitochondrial dysfunction (Correia-Melo et al., 2014), and iron deposition in the CNS resulting in oxidative injury (Bergsland et al., 2017; Pertusa et al., 2007). Moreover, aging is accompanied by a chronic, systemic low-grade inflammation process known as inflammaging (Fulop et al., 2021), brought about by a continuous antigenic load that mainly stimulates the innate immune system to produce pro-inflammatory cytokines (Franceschi et al., 2000). Additionally, as in many reparative processes, the efficiency of remyelination declines with age (Shields et al., 1999). In experimental models, aged rodents have shown slower differentiation of OPCs toward mature myelinating OGDs, which determines a less effective remyelination process as compared to young animals (Shen et al., 2008b). Similarly, in humans, the ensheathment capacity of OGD lineage cells is significantly higher in pediatric cells than in adult cells. These findings have been associated with higher expression of progenitor cell signatures and enrichment in cell proliferation pathways (Luo et al., 2022). Taken together, these data may provide a better understanding of age-related changes underlying white matter degeneration and remyelination failure, which drive the transition from the RRMS to the SPMS phenotype.

In this review, we will provide an overview of the current knowledge of age-related changes occurring in cells of the OGD lineage, including intrinsic factors such as cellular senescence and extrinsic influences such as interactions with neighboring cells and the extracellular environment. We will highlight how these changes impact white matter damage and axonal degeneration and further discuss what aging-associated changes lead to a decline in remyelination efficiency.

Influence of Age on MS

Age is one of the most important factors associated with accumulating disability in MS. Previous studies have shown that age affects disease progression regardless of the number of previous relapses, disease duration, or gender (Scalfari et al., 2011) In fact, the transition from RRMS to SPMS often takes place in the fifth decade, with a mean age of 45 $\pm$ 10 years and independently of previous disease activity and duration (Koch et al., 2007; Tutuncu et al., 2013). Patients with PPMS and those undergoing 1 to over 4 relapses in the RRMS phase start progressing at a similar age (Scalfari, 2019).

Age is also a key contributor to MS phenotypes. Patients with childhood-onset of disease very rarely present PPMS, are more likely to be female (Renoux et al., 2007), to have more relapses, and to show evidence of more active MS lesions on magnetic resonance imaging (MRI) (Dahlke et al., 2021). Moreover, the estimated median time to conversion to SPMS is approximately 10 years longer in patients with childhood onset than in patients with adult onset (Renoux et al., 2007). Conversely, older-age onset is associated with a higher risk of entering the progressive phase, shorter duration of the relapsing-remitting phase, and a lower number of relapses. In fact, the annualized relapse rate decreases approximately 2% per year, evidencing an age-dependent decline in focal inflammatory activity (Scalfari et al., 2016). However, relapse recovery also linearly declines with age (Conway et al., 2019), and radiologically isolated syndrome moves on to PPMS more commonly at older ages when compared to clinically isolated syndrome or MS, regardless of follow-up duration (Kantarci et al., 2016).

Late-onset MS (LOMS) is defined as symptoms initiating after the age of 50 and represents approximately 5–10% of MS patients (Naseri et al., 2021). In a recent meta-analysis, 49.8% of LOMS patients showed a RRMS course. A comparison of this number and the 85% proportion of RRMS in all MS cases (Correia-Melo et al., 2014) is indicative of a higher chance of acquiring a progressive phenotype for LOMS patients. In the same line, patients of the London Ontario database who presented their first demyelinating event at 50 years of age were 3 times more likely to develop progressive disease than those presenting their first event at 20 years of age (Scalfari et al., 2011). LOMS is also more prevalent in women, although the proportion of male LOMS increases with age (Cossburn et al., 2012). Interestingly, the transition period from RRMS to a progressive disease phase overlaps with the expected median age of natural menopause, which suggests a role of sex hormones in MS progression (Gubbels Bupp, 2015)

Another important issue in elderly MS patients is the age-dependent efficacy of disease modifying therapies (DMTs). Of note, clinical trials for these compounds were not designed to assess efficacy in aging patients, and patients above the age of 55 are thus rarely involved in these studies. Nevertheless, a meta-analysis from 2017 suggested that older age may be associated with lower efficacy of DMTs, particularly for high efficacy drugs whose beneficial effects on disability progression may be lost beyond the age of 40 (Weideman et al., 2017). These findings may be explained by the fact that current MS treatments are primarily designed to attack inflammatory activity and only have a modest effect on the neurodegenerative process and, hence, on the progression of disability. The treatment of elderly patients also raises concerns regarding the frequency of adverse events, including risk of infections and cancer (Schweitzer et al., 2019).

Overall, given that the ages of real-world patients differ from those in clinical trials, the benefit/risk balance could change in the elderly population and may impact neurologists' decisions to start, switch, or stop DMTs.

A parallel can be drawn between these clinical observations and some of the biological mechanisms governed by age. Different studies have led to the hypothesis that the progressive course of the disease occurs when a threshold of neuronal and axonal loss is reached and the compensatory mechanisms of the CNS are inadequate to maintain neurologic function (Trapp et al., 1999). For instance, studies using MRI have documented brain atrophy in the earliest stages of MS (Calabrese et al., 2011; Pérez-Miralles et al., 2013), and magnetic resonance spectroscopy suggests that axonal loss caused by chronic demyelination begins at the onset of the disease (Filippi et al., 2003; Ranjeva et al., 2003). It should be noted that brain atrophy increases during these early stages without concurrent disability progression. In the same line, functional MRI (fMRI) provides evidence of altered recruitment of additional cortical areas that contribute to limiting the clinical consequences of MS-related structural damage (Rocca & Filippi, 2007; Rocca et al., 2003). In addition, increased activation of motor regions located in the contralateral hemisphere has been reported in nondisabled patients during the performance of different motor tasks (Rocca et al., 2002). These functional changes might represent a first step in cortical reorganization, with the potential to maintain normal brain function. This process is thought to continue as patients age until CNS plasticity is overwhelmed, after which MS patients develop progressive neurologic disability (Criste et al., 2014; Tuohy et al., 1997). Structural CNS reserve and natural compensatory repair processes decrease with aging and contribute to the dynamic nature of white matter pathology in MS. Active plaques are the most frequent during exacerbations and predominate in RRMS, while slowly expanding latent plaques (also called smoldering plaques) are found almost exclusively in progressive forms of MS and contribute to disease progression (Frischer et al., 2015). Notably, smoldering plaques—which typically show an inactive center with few or no macrophages surrounded by a rim of activated microglia—peak around the age of 50, correlating with the age of onset of progressive disease.

Considering the neurodegenerative process in progressive MS as solely dependent on age may certainly be an oversimplification, particularly given the inter-individual variability in patients' evolution (Scalfari et al., 2016). However, evidence strongly suggests that progression in MS is robustly influenced by age-related pathological processes.

Aging Mechanisms Associated with Demyelination and Remyelination

Alterations in OGD Characteristics with Age

In the CNS, myelin is synthesized by fully differentiated cells of the oligodendroglial lineage, i.e., mature OGDs. Most myelin forming OGDs are originated in the early post-natal period by differentiation of proliferative, migratory OPCs. In contrast to the classical notion of myelin as a passive insulator for axons, recent studies have revealed that OGD development and myelination are highly dynamic processes. Myelination in the human brain is most intense over the first two years of life but can continue for decades and is influenced by neuronal activity (Mukherjee et al., 2002; Schneider et al., 2004). Also, in some regions of the adult brain, mature OGDs may myelinate previously unmyelinated axons, thus contributing to synaptic remodeling and neural plasticity in response to diverse physiological demands (Bergles & Richardson, 2015; Yeung et al., 2019; Zatorre et al., 2012). Alternatively, mature OGDs may be needed to compensate for OGD turnover, either replacing dying OGDs or remodeling myelin sheaths in the absence of cell death. These two possibilities are certainly not mutually exclusive (Young et al., 2013), and the age at which myelinating OGDs are generated conditions internode number and length. Indeed, the length of newly formed internodes progressively decreases with the time of appearance of mature OGDs. In rodents and primates, internode lengths significantly decrease while paranode frequency increases with age (Lasiene et al., 2009; Peters et al., 2008). These features demonstrate ongoing oligodendrogenesis and myelinogenesis as a function of age.

The multi-stage process of OGDs development is tightly regulated, to ensure proper lineage progression of OPCs to myelinating OGDs. Extensive studies have identified individual and/or synergistic roles of specific growth factors regulating different stages of OGDs development, which promote endogenous recovery following demyelination (Adams et al., 2021; Dubois-Dalcq & Murray, 2000). Several growth factors and intracellular pathways can either promote or inhibit OPC differentiation. Thus, in experimental models and in MS lesions, insulin-like growth factor 1 (IGF-1; Goddard et al., 1999; Gveric et al., 1999; Jiang et al., 2001; Min et al., 2012), brain-derived neurotrophic factor (BDNF; Geraghty et al., 2019; Tsiperson et al., 2015; van't Veer et al., 2009), and platelet-derived growth factor (PDGF; Calver et al., 1998; Fruttiger et al., 1999) have been shown to promote OPC proliferation and enhance differentiation. In contrast, transforming growth factor β1 (TGF-β1), associated to activation of the Jagged1–Notch1–Hes5 pathway, inhibits mitogen-induced proliferation of OPCs (McKinnon et al., 1993) blocking OGDs maturation (John et al., 2002). Likewise, the interaction of the canonical Wnt and bone morphogenic proteins (BMPs) has been shown to exert inhibitory effects on OPC differentiation in animal models of demyelinating disease and in MS lesions (Fancy et al., 2009; Gao et al., 2022). In addition, OGDs and their precursors are highly influenced by fibroblast growth factors (FGF), particularly FGF-2, which drive proliferation of OPCs, but block their terminal differentiation (Bansal & Pfeiffer, 1997; Bryant et al., 2009; Fortin et al., 2005). All of these complex interactions mediated by growth factors after myelin injury in aged mice versus young mice, remain

only partially understood and will require future study. Of note, in the context of age-related changes during remyelination of lysolecithin-induced demyelination, mRNA expression of two growth factors associated with OPCs differentiation, IGF-1 and TGF-β1, showed delayed and lower peaks of expression in old rats compared to young animals. Parallel although there was an initial delay in PDGF-AA mRNA expression in old rats, values returned to normal after 5 days. Based on this observation, a hypothesis was proposed in which PDGF-AA might be involved in the initial phase of OPC recruitment, while IGF-1 and TGF-β1 may trigger differentiation of OGDs to a myelinating phenotype (Hinks & Franklin, 2000; Sim et al., 2002). However, earlier expression of IGF-1 in old animals is not enough to improve OPC differentiation (O'Leary et al., 2002), which suggests involvement of other growth factors. Moreover, differences in chronological age and initial state of OPC differentiation can impact response to different growth factors. For example, while the combination of PDGF-AA/basic fibroblast growth factor (bFGF) is mitogenic for fetal OPCs, it stimulates differentiation of adult OPCs (Cui et al., 2010).

Mechanisms of OGD Damage that Increase with Age

Other than producing myelin sheaths and being passive targets of an immune system attack in the context of MS, OGDs and OPCs can acquire a disease-specific state characterized by the expression of immune-related genes (Falcão et al., 2018). Aging can induce immunological properties in OGDs. For instance, aged mice show higher expression of MHC-I genes (*B2m, H2-D1*, and *H2-K1*), *C4b* gene, and genes involved in antigen processing and presentation in OPCs and OGDs as compared to young counterparts (Dulken et al., 2019; Spitzer et al., 2019). Furthermore, aged subventricular zone OGDs and OPCs exhibit increased expression of genes involved in IFN-γ and IFN-α response, as well as IL6/JAK/STAT3 signaling (Dulken et al., 2019; Kirby & Castelo-Branco, 2021). Worth pointing out, the acquisition of this alternative functionality by OGDs and OPCs may be induced by different stimuli including: (i) a large array of environmental cues, (ii) inflammatory molecules from peripheral T cells that penetrate the CNS, or (iii) local inflammation in the early stages of the disease driven by dead OGDs or viral infections (Falcão et al., 2018).

MRI studies of both human (Guttmann et al., 1998) and non-human primate (Wisco et al., 2008) brains have shown a loss of white matter from 50 years of age onwards—more evident in the optic nerve, the anterior commissure of the fornix and the splenium of the corpus callosum—, which suggests increased myelin breakdown with age (Feldman & Peters, 1998; Sandell & Peters, 2001, 2003). Regarding major age-related changes in myelin, electron microscopy studies in non-human primates have shown splitting at the major dense line leading to the accumulation of dense cytoplasm with vesicular inclusions, inter-period line alterations causing the myelin sheaths to bulge out, and multilamellar myelin fragments representing myelin outfolding or fragments engulfed by microglia (Feldman & Peters, 1998; Hill et al., 2018).

Biochemical analysis in myelin from aging primates and humans has revealed total protein content of white matter per gram of wet tissue comparable to that of young animals (Sloane et al., 2003). Western blot analyzes have shown that only myelin associated glycoprotein (MAG) decreases with age. By contrast, the levels of oligodendrocyte proteins 2′-3′-cyclic nucleotide 3′-phosphodiesterase (CNPase) and myelin/oligodendrocyte-specific protein (MOSP) are significantly higher in aged animals, with no differences in proteolipid protein (PLP), DM20 or the major 18-kDa isoform of myelin basic protein (MBP). This selective decrease in MAG could be associated with its preferential location on the periaxonal myelin membrane, while MOSP and CNPase overexpression could regulate membrane growth and the extension of OGD processes as a compensatory mechanism in response to myelin degradation (Gravel et al., 1996, Yin et al., 1997). In addition, lipid analyzes of human myelin samples from young adults (below 50 years of age) and old autopsy cases (over 70 years of age) revealed an age-dependent decrease in the total lipid-to-protein ratio accounted for by cholesterol, omega-3 fatty acids, ceramide, sphingomyelin, phosphatidylserine and cerebrosides (Stommel et al., 1989). Furthermore, lipid metabolism changes during aging (Chappus-McCendie et al., 2019), as the susceptibility of lipids to peroxidation increases with age. Indeed, a decline in omega-3 fatty acids—which have antioxidant properties—increases lipid peroxidation and may accelerate neuronal degeneration (Chen et al., 2017; Yehuda et al., 2002).

Overall, these data demonstrate that old OGDs lose their ability to produce and maintain healthy myelin over time, to induce *de novo* myelination, and to remodel pre-existing myelinated axons contributing to neural plasticity in the CNS, alterations which aged OPCs fail to compensate. These features are likely conditioned by interaction with senescent neighboring cells (see below), as well as by intrinsic age-related alterations in both OGDs and OPCs (Sams, 2021).

Intrinsic Age-related Alterations in OGDs and OPCs

DNA damage is one of the most consistent age-related cellular anomalies in the oligodendrocyte lineage as a result of their high metabolic needs (Bartzokis, 2004). Demyelinating lesions are characterized by a significant reduction in the number of OGDs, while surviving OGDs enter a senescent state in response to genomic stress. Senescent cells are characterized by the activation of p53-p21-retinoblastoma protein (RB) and $p16^{INK4A}$-RB pathways, which lead to a permanent growth arrest (Herbig et al., 2003; van Deursen, 2014). In addition, OGDs remain metabolically active, resisting apoptotic death for different periods of time, and *in vitro*

express the lysosomal enzyme hydrolase senescence-associated β-galactosidase (SA-β-GAL) as a biomarker (Al-Mashhadi et al., 2015; Dimri et al., 1995).

Apoptosis with DNA fragmentation in cells of the oligodendroclial lineage is frequent in MS plaques (Ozawa et al., 1994), where high levels of reactive oxygen species (ROS) are generated by inflammatory cells as they attack myelin. Furthermore, higher levels of 8-hydroxyguanine, a major product of such damage, are found in OGDs in demyelinating lesions (Haider et al., 2011) These findings hint at an association between age-related myelin loss and OGD genomic integrity, suggesting that OGDs may long suffer oxidative stress and DNA damage prior to the more extensive loss of myelin.

These observations raise the question whether OGDs, like neurons, have age-related deficits in DNA repair such as low antioxidant mechanisms (Chow & Herrup, 2015). OGDs possess low levels of intracellular antioxidant glutathione and mitochondrial manganese superoxide dismutase as compared to those observed in astrocytes (Ekoue et al., 2017; Juurlink, 1997), which makes OGDs particularly vulnerable to free radical damage and cell death (Back et al., 1998). This scenario should also worsen with age, as the level of γ-glutamylcysteine synthetase, the glutathione-producing enzyme, declines (Liu et al., 2004). Similarly, oxidative stress stimulates the activation of sphingomyelinase, generating the release of ceramide. Once ceramide is generated, several molecules including Bcl-2, SAPK, PKB/Akt, and KSR become involved downstream in the apoptotic pathway (Ruvolo, 2003). Similarly, as enzymes responsible for DNA repair decline with age and in cells undergoing replicative senescence (Place et al., 2005; Wagner et al., 2001), cumulative oxidative damage to DNA may exceed the ability of the repair machinery, causing irreparable DNA damage that ultimately leads to senescent OGD death. Furthermore, several enzymes involved in DNA repair also play critical roles in the differentiation of the oligodendroglial lineage. For example, histone deacetylases 1 and 2 (HDAC1/2), which participate in the repair of DNA double strand breaks (Lee & Paull, 2005; Miller et al., 2010) followed by histone methylation, promote OGD maturation, myelin gene expression (Shen et al., 2008b), and OPC differentiation (Allen et al., 2001; Carlessi et al., 2009; Liu et al., 2014). Indeed, the levels of histone deacetylation correlate with the expression of transcriptional inhibitors Hes5 and Id4 and the persistent expression of precursor stage markers such as Sox2; (Shen et al., 2008a). This overlapping function of HDAC1/2 may be critical to continuous myelin remodeling (McKenzie et al., 2014). It should be pointed out that the enzymatic activities of HDAC1/2 in these competing functions are exhausted by aging. In line with this view, differentiating OGDs treated *in vitro* with HDAC inhibitors have shown a pattern of gene expression similar to that observed in the aging brain, which indicates that aging modifies oligodendroglial lineage cells by affecting chromatin conformation and inducing changes in gene expression (Shen et al., 2008a).

Proteomic OPC analysis has demonstrated a ∼50% difference between young and aged cells (de la Fuente et al., 2020). Data from this study indicated that the levels of myelin-associated proteins and those associated with oxidative phosphorylation, inflammatory responses, and actin cytoskeletal organization increased with age. Furthermore, unlike myelin proteins, cholesterol biosynthesis-related enzymes were decreased in aged OPCs, and aged phagocytes exhibited reduced capacity to clear and recycle cholesterol and remove myelin debris (Cantuti-Castelvetri et al., 2018). These alterations are critical not only for age-associated remyelination failure but also for new myelinating OGD formation and myelin plasticity (Hill et al., 2018; Hughes et al., 2018). Moreover, aged OPCs have shown higher expression of aggregates of misfolded proteins (May et al., 2014), which can interfere with OPC differentiation and alter basal cellular energy, therefore further contributing to age-associated remyelination failure.

Mitochondrial dysfunction may prove a major aging mechanism. Like nuclear DNA, mitochondrial DNA (mtDNA) is constantly exposed to damaging agents. Accumulation of ROS is one of the main factors explaining mitochondrial damage in aging (Harman, 2001). Because mtDNA is extremely vulnerable to oxidative stress, mtDNA damage accumulates progressively throughout life, generating deficits in oxidative phosphorylation and, consequently, an increase in ROS production. This increase in ROS in turn heightens mtDNA damage, which results in the accumulation of mtDNA mutations leading to progressive cellular dysfunction and ultimately causing oxidative stress-induced cell death. Moreover, a growing body of evidence has demonstrated that impairments in mtDNA repair may contribute to the accumulation of DNA damage associated with aging (Chen et al., 2002). Alterations in these repair mechanisms makes them less efficient in OGDs and microglia than in astrocytes (Hollensworth et al., 2000). Moreover, impaired proteasome function has been associated with aging and neurodegenerative process. Decreased levels of proteasome activity during aging produce alterations in mitochondrial membrane potential, the release of cytochrome c, and the activation of death-related caspases 3 and 9, leading to cellular apoptosis (Goldbaum et al., 2006).

The Impact of Aging on Remyelination

The aging-associated decline in regenerative processes is a well-established phenomenon in many tissues (López-Otín et al., 2013). Similarly, although post-development oligodendrogenesis continues throughout life, extensive evidence demonstrates that efficiency decreases with age (Barnabé-Heider et al., 2010; Kang et al., 2010), as does the rate of OPC proliferation and differentiation into mature OGDs in rodents (Sim et al., 2002; Young et al., 2013). Worth highlighting, age-related failure in remyelination plays a critical role in axonal degeneration in MS,

contributing to progressive phase entry regardless of age of onset. These findings suggest that deficient remyelination and disease progression are closely linked to each other (Confavreux & Vukusic, 2006; Goldschmidt et al., 2009).

The effects of age on remyelination have been studied using an ethidium bromide model of local demyelination (Woodruff & Franklin, 1999). In this model, remyelination proceeded to completion in younger animals but was slower in older ones. This age-related phenomenon was reflected by a delay in the reappearance of MBP and PLP transcripts within the lesions of old animals as compared to young. Interestingly, the process was not affected by OPC availability but was rather impaired by slower recruitment of OPCs to demyelinated areas and a significant delay in the differentiation of recruited OPCs into remyelinating OGDs (Sim et al., 2000; Woodruff & Franklin, 1999). However, there appears to be a limiting phase for recruited OPC differentiation, as an increase in the supply of OPCs after the demyelination process does not increase remyelination efficiency in old animals (Shen et al., 2008b; Woodruff et al., 2004)

Many of the OPC processes that determine proliferation, migratory capacity, response to different metabolites, and differentiation may be mediated by epigenetic mechanisms such as histone post-translational modifications or DNA methylation (Moyon et al., 2021; Shen et al., 2008b). Changes in the epigenome in response to different stimuli, internal or external, are critical in the regulation of remyelination in aging, conditioning a unique transcriptome that modulates differential gene expression in OPCs over time (Dansu et al., 2021). Different factors have been proposed to explain deficient remyelination. OPC aging is associated with low density of voltage-gated sodium (Nav) channels, a lack of NMDAR, and high density of AMPA/kainate receptors, as well as the lengthening of the cell cycle with a decrease in the differentiation potential of OPCs. Therefore, this state may be thought to represent a "quiescent" state (Spitzer et al., 2019). Moreover, growth factors participate in the proliferation, migration, and differentiation of OPCs. PDGF and FGF-2 take part in OPC motility and proliferation and have therefore been associated with the recruitment phase. On the other hand, IGF-1 and TGF-β show an expression peak at the beginning of OPC differentiation (Franklin & Hinks, 1999). Interestingly, this peak coincides with the maximum expression of macrophages. These findings suggest that a delay in the expression of PDGF may cause a delay in recruitment, while an impairment in the production of TGF-β and IGF-1 in older animals may damage the differentiation of OPCs (Franklin et al., 2002). However, increased IGF-1 levels triggered by adenoviral vectors in old animals do not accelerate the remyelination process, which indicates that either IGF-1 is not a critical factor or its expression must occur in conjunction with other growth factors (O'Leary et al., 2002).

Changes in the production of growth factors could also imply differences in the status of cell groups in the CNS along the remyelination process. For example, reactive astrocytes generated during demyelination/remyelination secrete a number of factors that facilitate different steps in the remyelination process including OPC proliferation, differentiation and myelination. Among these soluble factors are PDGF, FGF2, IGF-1, leukemia inhibitory factor-like protein (LIF), ciliary neurotrophic factor (CNTF), metalloproteinase-1, and endothelin-1 (Hinks & Franklin, 1999; Kiray et al., 2016; Komoly et al., 1992; Redwine & Armstrong, 1998).

Likewise, macrophages recruited in large numbers along remyelination for myelin debris clearance have also been associated with the production of IGF-1 and TGF-β, favoring the differentiation of OPCs (Diemel et al., 1998; Hinks & Franklin, 2000). Notably, the response of macrophages/microglial cells is delayed in old as compared to young animals, which determines two key phenomena: first, there is a delay in the production of growth factors and, second, there is a failure in the removal of myelin residues that limits the remyelination process. The decline in myelin debris clearance by microglia cells during aging has been associated with different mechanisms, including increased expression of CD22 and a decrease in transcription factor RXR-α and chemokine receptor CX3CR1 (Lampron et al., 2015; Natrajan et al., 2015; Pluvinage et al., 2019). Aged microglial cells also have a reduced ability to recycle cholesterol into the extracellular space. The reduction in cholesterol availability limits the differentiation of OPCs into mature OGDs and contributes to the age-related remyelination failure (de la Fuente et al., 2020). Overall, microglial cells are important regulators of OGD proliferation and differentiation.

Astrocytes and macrophages/microglial cells interact with each other conditioning a feedback process. While astrocytes produce pro-myelinating factors, they also secrete chemokines capable of increasing the recruitment of macrophages/microglial cells (Merrill & Benveniste, 1996).

Environmental Factors Influencing Demyelination and Remyelination Failure During Aging

While intrinsic cellular aging mechanisms can impact the processes of demyelination and remyelination, intercellular interactions and alterations in the extracellular environment occurring with aging can also affect the differentiation of OPCs and the ability of mature OGDs to support myelin maintenance, internode remodeling, and remyelination.

Microglial Cells

Demyelinating lesions present an important number of activated microglia preferentially located in their core, where they can secrete growth factors, cytokines and chemokines, as well as stimulate phagocytosis to remove myelin debris

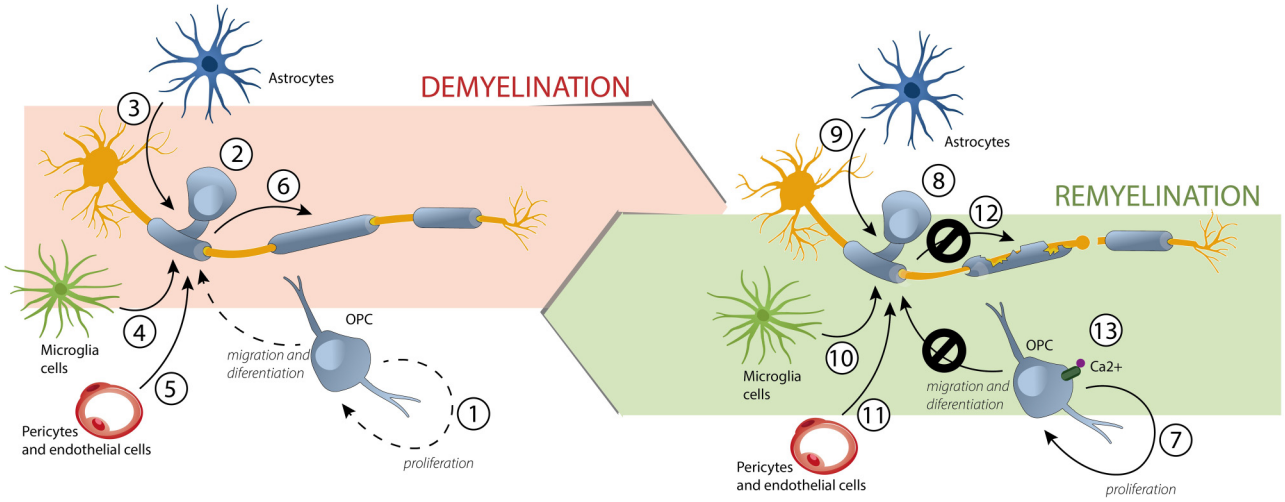

Figure 1. Main factors which condition the demyelination/remyelination processes during aging. (1) Impairment of OPC proliferation, migration, and differentiation occur with aging. (2) Several cellular processes affect OGDs during age-related demyelination, including nuclear and mitochondrial DNA damage, replication stress, and increased oxidative stress. These factors condition the expression of factors p21 and p16, which determine cell cycle blockage. Enzymes involved in DNA repair and antioxidant mechanisms are also impaired. (3) Senescence also affects neighboring cells; for example, astrocytes are characterized by a state of growth arrest and an increase in the production of a complex secretome (known as the senescence-associated secretory phenotype, SASP), represented mainly by IL-6, TNF-α, CXCL10, CXCL5 and the complement fractions C3 and C4B. In addition, astrocytes decrease glycogen metabolism with a drop in lactate levels and show a significant decrease in cholesterol synthesis. They also present failures in iron homeostasis and a decrease in FGF2 production, which in turn reduces the differentiation of OPCs. (4) Aged microglial cells enter a state of growth arrest, are deficient in the phagocytosis of myelin debris, produce pro-inflammatory factors such as IL-1, IL-6, TNF-α, CCL4, and MIF, and increase the production of ROS, which leads to lipid peroxidation. (5) Pericytes and endothelial cells alter the expression of tight junction proteins such as ZO-1 and claudin-5, which leads to a breakdown of the blood-brain-barrier and allows peripheral leukocytes into the CNS. (6) Reciprocal communication between axons and OGDs is affected, as evidenced by the disruption of paranodal junctions and a decrease in internode size. Altogether, these factors worsen the demyelination process. With age (7) (8), the rate of OPC proliferation, migration, and differentiation into mature OGDs decreases and remyelination is slower. Many of these events are mediated by epigenetic mechanisms (e.g., histone methylation). The aging of OPCs is associated with a low density of Nav channels, a lack of NMDAR, and high expression of AMPA/kainate receptors. Moreover, there is a delay in the production of growth factors and an increase in the expression of p16 and p21, which produces a blockage of the cell cycle. (9) Astrocytes also show a decrease in growth factor production (e.g., PFGF, IGF-1, and FGF-2). (10) Microglial cells present a delay in the production of IGF-1 and TGF-β, as well as failure in myelin debris phagocytosis and cholesterol recycling. (11) There is a decrease in the number of pericytes which determines a decrease in the differentiation of OPCs. (12) The demyelination process leads to a loss of axon trophic support by OGDs. (13) The OPC microenvironment stiffens with age, mainly at the expense of the extracellular matrix. This mechanical change contributes to lower proliferation and differentiation of OPCs, a process mediated by the mechanoresponsive ion channel PIEZO1.

(Cignarella et al., 2020; Neumann et al., 2009). Aged microglia exhibit characteristic features of senescence, including SA β-gal expression, shorter telomeres, and growth arrest (Yu et al., 2012). Different microglial populations are present from embryogenesis to old age, and some of them expand following demyelinating injuries. Although the greatest microglial heterogeneity is observed at young ages, some subtypes persist throughout life or increase in the aged brain (Hammond et al., 2019). Of note, with aging, microglia become deficient in phagocytosis and partially lose their ability to acquire a regulatory phenotype (Miron et al., 2013). Furthermore, aging microglia decreases their ability to break down myelin debris in the lysosomes, leading to the formation of insoluble, lipofuscin-like inclusions (Safaiyan et al., 2016). By contrast, RNA expression patterns of microglia isolated from old demyelinating animals have shown particular clusters that express *Ccl3, Ccl2, Ccl4, Ccl7, Ccl9, Ccl12, CD74, il1b, il6 and Tnf* (Sierra et al., 2007; Voet et al., 2019), many of which can be highly damaging to the CNS. For example, *il1b, il*6 and *Tnf* are harmful for myelin, and peripheral immune cells attracted by microglia expressing chemokine CCL4 can target myelin and exacerbate pathology (Gadani et al., 2015). Likewise, macrophage inhibitory factor (MIF) and its receptor CD74 may prolong the pro-inflammatory effects of microglial cells, contributing to the progression of MS and experimental autoimmune encephalomyelitis (EAE; Rijvers et al., 2018). Moreover, in aging animals, microglial cells secrete more ROS in MS lesions and myelin injury models, which determines elevated lipid peroxidation (Michaels et al., 2020; O'Neil et al., 2018). Activated microglia in the aging process induces astrocyte activation by secreting TNF-α, IL-1α, and the complement fraction C1q (Liddelow et al., 2017). In agreement, the aging-induced up-regulation of

reactive astrocyte genes is significantly reduced in mice lacking IL-1α, TNF, and C1q (Clarke et al., 2018). Reactive astrocytes further induce the death of neurons and OGDs (Liddelow et al., 2017). Overall, the environment determined by microglial cells in aging lesions is likely responsible for much of the immune-mediated OGD damage.

Astrocytes

With age, astrocytes show SA-ß-gal activity and increased expression of p53–p21–RB and $p16^{INK4A}$-RB pathways and consequently enter growth arrest, all features of reminiscent senescence (Bitto et al., 2010). In demyelination and remyelination, astrocytes play pivotal roles in the support and nourishment of cells of the OGD lineage. However, these functions are dynamic and can vary according to different time points or triggers, resulting in different biological effects (Li et al., 2016).

There is growing evidence that astrocytes function as immune cells which exacerbate their activity with aging. Aged astrocytes are able to increase the secretion of pro-inflammatory cytokines and chemokines including CXCL10 and CXCL5, which serve as chemoattractant for peripheral T cells and neutrophils, respectively (Clarke et al., 2018; Sofroniew et al., 2018; Sorensen et al., 2018; Xie et al., 2010). In addition, old astrocytes increase the production of components C3 and C4B of the complement, thus participating in inflammatory processes, opsonization, and cell lysis (Sofroniew, 2014).

OGDs utilize lactate by oxidation and lipogenesis, which are required to synthesize myelin. In the period of increased activity, lactate is provided by astrocyte-derived glycogen (Brown et al., 2003). As glycogenesis is confined to astrocytes, these cells represent the only glycogen repository in the mammalian CNS (Cataldo & Broadwell, 1986). Therefore, a decrease in glycogen metabolism in old astrocytes can induce an energetic deficit in neighboring cells of the oligodendroglial lineage. Likewise, in the old brain, OGDs have a high demand for iron for oxidative metabolism and as a cofactor for enzymes involved in ATP, cholesterol, and lipid synthesis (Cheli et al., 2020). Given that astrocytes are also considered the main iron regulators in the CNS (Dringen et al., 2007), a failure in the mechanisms of iron homeostasis in old astrocytes may represent a further detrimental factor to neighboring OGDs.

Although OGDs produce cholesterol for myelin synthesis, they also require cholesterol from astrocytes for this function (Camargo et al., 2017). Cholesterol synthesis is impaired in aging astrocytes due to the down-regulation of the limiting cholesterol synthesis enzyme HMG-COA reductase and cholesterol transporters, including LDL receptor (Madison, 2016). As a consequence, OGDs do not receive an adequate amount of cholesterol in aging, which results in reduced myelin synthesis. Finally, the decrease in the production of basic fibroblast growth factor 2 (bFGF-2) by aged astrocytes disturbs OPC differentiation (Bernal & Peterson, 2011). Altogether, alterations in several astrocyte-derived factors have an important effect on neighboring oligodendroglial lineage cells during aging.

Pericytes and Endothelial Cells

Pericytes contribute to maintaining the physiological environment in white matter. Along with endothelial cells, astrocytic end-feet processes, smooth muscle cells, and perivascular microglia help preserve the integrity of the blood-brain-barrier (BBB; Sweeney et al., 2019). Electron microscopy studies have revealed the accumulation of osmiophilic material in senescent pericytes, and their loss is demonstrated by a decrease in PDGF receptor-β expression in white matter along aging (Farkas & Luiten, 2001; Montagne et al., 2018). In addition, the NF-κB pathway is activated, which induces astrocyte secretion of inflammatory factors such as nitric oxide, IL-6, TNF-α, and matrix metalloproteinases (Zhang, 2008) and acts directly on tight junction proteins ZO-1 and claudin-5, triggering brain endothelial degeneration and allowing leukocyte entry into CNS tissue (Lamberti et al., 2001; Stamatovic et al., 2008). Taken together, these findings indicate that pericyte and endothelial cells degenerate in the aging process, leading to BBB breakdown and altering white matter environment homeostasis.

Neurons and OGD Interactions

A reciprocal communication between neurons and OGDs is essential to control OGD development and myelin synthesis. Growing evidence supports the notion that axons control the development of myelinating glial cells, promoting the proliferation of OPCs and the survival of mature OGDs (Barres & Raff, 1999). Indeed, OGD death occurs selectively in transected optic nerves in which axons degenerate (Barres et al., 1993). Furthermore, studies demonstrate that PLP trafficking to the plasma membrane is under neuronal control (Trajkovic et al., 2006). Different neuron-derived survival signals have been proposed to explain the differentiation of OGDs, including electrical and contact-mediated neuronal signals, as well as biophysical characteristics of the axon (Corfas et al., 2004; Rosenberg et al., 2008; Stevens et al., 2002). Several growth and trophic factors such as PDGF-A, FGF-2, IGF-1, BDNF, neurotrophin-3, and CNTF—produced by both neurons and astrocytes—have been shown to regulate OGD development (Baron et al., 2005; Barres & Raff, 1994; Miller, 2002; Wong et al., 2013). Age-related neuronal changes such as mitochondrial alterations, increase in oxidative stress, and disrupted paranodal junctions causing cytoskeletal deficiency in the axonal cytoplasm can impact myelin integrity (Stahon et al., 2016; Takagishi et al., 2016; Tönnies & Trushina, 2017). Conversely, once myelination is complete, the long-term integrity of axons depends on OGD energy supply. Oligodendroglial support requires, in

addition to glucose import through glial glucose transporters, the subsequent release of lactate and/or pyruvate into the peri-axonal space (Lee et al., 2012). Thus, it is plausible that failures in these mechanisms can cause axonal degeneration, as shown in mouse mutants lacking certain myelin-specific proteins. For example, studies employing PLP null mice (Griffiths et al., 1998) and Cnp1 mutant mice (Lappe-Siefke et al., 2003) revealed axon loss without significant demyelination, suggesting that OGDs support axon survival through a myelin-independent mechanism (Fünfschilling et al., 2012).

Additional environmental factors are also responsible for remyelination failure. The OPC microenvironment becomes stiff with age, fundamentally at the expense of extracellular matrix remodeling. This mechanical change is sufficient to cause an age-related decrease in the proliferation and differentiation of OPCs, a process mediated by the mechanoresponsive ion channel PIEZO1 (Jagielska et al., 2017; Segel et al., 2019). These changes have been reversed, and remyelination thus enhanced, by exposing old mice to a more youthful systemic environment via heterochronic parabiosis (Conboy & Rando, 2012). In these studies, young monocytes/macrophages recruited in the early phase of remyelination restored the survival, proliferation, and differentiation capacity of endogenous OPCs (Ruckh et al., 2012). Similarly, the clearance of myelin debris by microglial cells and remyelination can also be restored in old mice by up-regulating scavenger receptor CD36 (Rawji et al., 2020). Calorie restriction by intermittent fasting, as well as exposure of OPCs to the 5′ AMP-activated protein kinase (AMPK) agonist metformin, also lead to a recovery in OPC responsiveness. After treatments, OPCs exhibited increased expression of *Pdgfra,* had lower expression of the senescent-associated gene *Cdkn2a*, and showed less DNA damage. In sum, an increase in the number of OPCs and enhanced responsiveness of aged OPCs to pro-differentiation factors make these cells permissive toward remyelination (Neumann et al., 2019).

Conclusions and Future Perspectives

The spontaneous regenerative phenomenon that follows demyelination/remyelination becomes more complex and heterogeneous with aging. This tightly regulated process is influenced by several cell types, as well as by the microenvironment surrounding demyelination areas (Figure 1).

During demyelination, issues present in OGDs in aging include: (i) a decrease in lipid to protein ratio, (ii) nuclear and mtDNA damage conditioned by impairment in DNA repair mechanisms (iii) increase in oxidative stress-induced cell death as a result of decreased protective anti-oxidant mechanisms, and (iv) cell-cycle blockade. Remyelination, on the other hand, is affected by a decrease in OPC proliferation rate, in migration, and in differentiation into mature OGDs. Many of these processes may be mediated by epigenetic mechanisms. Moreover, aging of OPCs is associated with a low density of Nav channels, a lack of NMDAR, and high expression of AMPA/kainate receptors, representing a "quiescent state" in which cell cycle arrest is evident. Finally, both demyelination and remyelination are affected by neighboring cells and environmental factors. Astrocytes and microglial cells can produce pro-inflammatory factors during demyelination. The failure of remyelination observed during aging is also associated with a decline in the production of growth factors by astrocytes and microglial cells, as well as a decrease in myelin debris phagocytosis and cholesterol recycling. At the same time, the extracellular matrix becomes stiffer, which contributes to a lower proliferation and differentiation of OPCs.

Understanding the molecular mechanisms that regulate lineage transitions from OPCs to mature myelinating OGDs poses different obstacles. First, although the CNS retains significant potential for myelin synthesis, molecular and biochemical mechanisms leading to inadequate remyelination are only partially known. Second, several hallmarks have been postulated to explain common denominators of aging in mammals. Some could be initiating triggers, the damaging effects of which accumulate progressively over time. These primary hallmarks include: DNA damage, mtDNA mutations and telomere loss, epigenetic alterations, and defective protein homeostasis (proteostasis). Another group of hallmarks exert opposite effects, depending on their intensity. At low levels, they could be beneficial, but at high levels they could become progressively deleterious, in a process partly promoted by the primary hallmarks. This the case for example of senescence, which protects organisms from cancer, but in excess can promote aging. Likewise, optimal nutrient-sensing and anabolism are obviously important, but in excess can become pathological. Finally, beyond intrinsic cell alterations, aging also involves changes in intercellular communication. These include changes in both communication between different cell groups, and in the composition of the extra-cellular environment, ultimately affecting the mechanical properties of the tissues (López-Otín et al., 2013). Because these different features occur simultaneously and are interconnected, elucidating the main hallmarks that affect demyelination and remyelination processes during aging will require future studies. Third, it is essential to discover which intracellular pathways mediate extracellular signaling, and how they intertwine. There is data to support a critical role in the regulation of OPCs differentiation and remyelination following demyelinating injury, for three highly conserved intracellular signaling pathways: Wnt/β-catenin, PI3K/AKT/mTOR and ERK/MAPK (Gaesser & Fyffe-Maricich, 2016). It is likely these pathways do not act in isolation, but rather as part of a larger signaling network. Therefore, how these different signaling pathways interact with the aging process needs to be better understood. Furthermore, strength and duration of signaling, can be a key determinant of subsequent biological outcomes. Therefore, future research should include investigation of

the potential role of these pathways, their interactions, as well as the level and timing of their activation during aging

Finally, a better understanding of the molecular mechanisms and signaling pathways that drive the processes of demyelation/remyelination have emerged from studies in animal models. Therefore, a crucial question for future studies is whether experimental results obtained in rodents are also relevant to human OGDs and myelin disorders.

Overall, future studies need to be undertaken to address these limitations and develop effective treatments that allow myelin repair upon aging. Single cell sequencing technologies may have special impact on understanding demyelination/remyelination processes during aging by facilitating the evaluation of genetic and epigenetic changes specifically accumulated by OPCs and OGDs (Gundry & Vijg, 2012). These studies will allow comparative genomic studies between young and elderly individuals. Additionally, molecular analysis of the genome-environment interactions modulating age-related changes will help identify pharmaceutical targets that can impact demyelinating diseases during aging (de Magalhães et al., 2010; Heyn et al., 2012). Since rodent models do not reproduce all the characteristics of MS in humans, and young animals are studied at an age at which regenerative myelin capacity is optimal, *in vivo* studies with gain or loss-of-function in non-human primate models would be necessary to prove causal evidence of individual hallmarks (Gems & Partridge, 2013). However, as previously mentioned, we do not know whether results from animal models are relevant to humans. Furthermore, forced expression of signaling proteins may not truly reflect physiological states, and results from experiments using these techniques should be interpreted with caution. To overcome the previous limitations, generation of human induced pluripotent stem cells (iPSC) and brain organoids could provide experimental approaches identifying signaling pathways involved in OGDs development and demyelination/remyelination processes (Marton et al., 2019). These experiments could be further complemented by studying post-mortem tissue gene expression in iPSC-derived OGDs (Adams et al., 2021).

In humans, response to putatively remyelinating drugs decreases with age (McMurran et al., 2022), and yet we must acknowledge that most clinical trials exclude patients over the age of 55. Future studies assessing remyelination should be conducted in cohorts of a broader age range. As the number of elderly people with MS grows clinical trials with this type of design are likely to play an important role in improving strategies to promote remyelination.

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Author Contribution

JC: Conceptualization, Writing original draft, Writing—Review & Editing; **MCY:** Writing original draft, Writing—Review & Editing.

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