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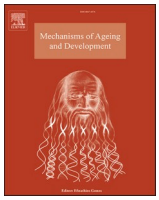

Navigating oligodendrocyte precursor cell aging in brain health

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ABSTRACT

Oligodendrocyte precursor cells (OPCs) comprise 5–8 % of the adult glial cell population and stand out as the most proliferative cell type in the central nervous system (CNS). OPCs are responsible for generating oligodendrocytes (OLs), the myelinating cells of the CNS. However, OPC functions decline as we age, resulting in impaired differentiation and inadequate remyelination. This review explores the cellular and molecular changes associated with OPC aging, and their impact on OPC differentiation and functionality. Furthermore, it examines the impact of OPC aging within the context of multiple sclerosis and Alzheimer's disease, both neurodegenerative conditions wherein aged OPCs exacerbate disease progression by impeding remyelination. Moreover, various pharmacological interventions targeting pathways related to senescence and differentiation are discussed as potential strategies to rejuvenate aged OPCs. Enhancing our understanding of OPC aging mechanisms holds promise for developing new therapies to improve remyelination and repair in age-related neurodegenerative disorders.

1. Introduction

In 2017, the number of individuals aged 60 and above reached 962 million, marking a profound increase compared to the 382 million people reported in 1980. This trend is expected to persist, likely resulting in a doubling of the aging population by 2050 (Nations, 2017). With the aging population comes a rise in neurodegenerative disorders, such as Alzheimer's disease (AD). Indeed, aging brains become more susceptible to neurodegeneration, as indicated by a brain volume decrease of 5 % per decade after 40 years of age. This decrease can be attributed to both gray and white matter changes (Peters, 2006).

The dynamic process of adaptive myelination, involving thickening, lengthening, complete removal, and *de novo* myelination, is essential for enabling myelin sheaths to adapt to various forms of brain activity, encompassing motor learning, cognitive processes and sensory tasks (Tripathi et al., 2017; Chapman et al., 2023; Wang et al., 2020; Hughes et al., 2018). Beyond the scope of adaptive myelination, generating new myelin sheaths becomes crucial in response to injury or disease, aiming to restore and replace damaged sheaths. The majority of myelin production is derived from the recruitment and subsequent differentiation

Abbreviations: OPC, oligodendrocyte precursor cell; CNS, central nervous system; AD, Alzheimer's disease; OL, oligodendrocyte; WML, white matter lesion; MS, multiple sclerosis; MTOR, mammalian target of rapamycin; P16, cyclin-dependent kinase inhibitor 2A; SASP, senescence-associated secretory phenotype; ECM, extracellular matrix; HDAC, histone deacetylase; ROS, reactive oxygen species; ETC, electron transport chain; ATP, adenosine triphosphate; TRPV1, transient receptor potential vanilloid 1; SVZ, subventricular zone; NSC, neural stem cell; NMDAR, N-methyl-D-aspartate receptor; BBB, blood-brain-barrier; TERC-KO, TERC knockout; AMPK, 5' AMP-activated protein kinase; PIEZO1, Piezo-type mechanosensitive ion channel component 1; PDGF-A, platelet-derived growth factor A; FGF-2, fibroblast growth factor 2; TET, ten-eleven translocase; DNMT, DNA methyltransferase; HDAC, histone deacetylases; MtDNA, mitochondrial DNA; RRMS, relapsing-remitting MS; PMS, progressive MS; IPSC, induced pluripotent stem cell; SA-β-Gal, senescence-associated β-galactosidase activity; HMGB1, high mobility group box 1; MBP, myelin basic protein; MRI, magnetic resonance imaging; MMSE, mini mental state exam; NPC, neural progenitor cell; NAWM, normal appearing white matter; APP, amyloid precursor protein.

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of oligodendrocyte precursor cells (OPCs), which, in conjunction with plastic pre-existing oligodendrocytes (OLs), establish a pool of myelinating OLs (Wang et al., 2020; Sams, 2021; Jeffries et al., 2016; Auer et al., 2018; Yeung et al., 2014). However, like many regenerative processes, the efficiency of OL generation declines in an age-dependent manner, making white matter lesions (WMLs) more apparent with aging, even in otherwise healthy individuals (Tripathi et al., 2017; Wang et al., 2020; Neumann et al., 2019a). Research indicates a modest 10 % reduction in pre-existing myelin in the corpus callosum of adult mice (8 months), while aged mice (20 months) experience a more substantial 30 % decrease in both the corpus callosum and optic nerve (Tripathi et al., 2017). A post-mortem study on the human corpus callosum shows similar results, with an initial steep increase in myelin levels up to the age of 5, reaching its peak at 17 years. Subsequently, there is a gradual decline with aging, resulting in a 25 % reduction in myelin volume by the age of 90 (Yeung et al., 2014). This decline results from less efficient myelin plasticity, concomitant with increased myelin degeneration (Wang et al., 2020; Lasiene et al., 2009; Shen et al., 2008). Consequently, demyelinated lesions contribute to cognitive difficulties, impacting learning and memory (Wang et al., 2020).

Although age-related mechanisms involved in impaired remyelination are not fully understood, research has identified several aging hallmarks, such as cellular senescence, changes in the microenvironment, mitochondrial damage, and oxidative stress as contributing factors (Shen et al., 2008). In this review, we will delve into the intricate mechanisms of OPC aging in both normal aging (Fig. 1) and age-related diseases, highlighting its crucial involvement in (re)myelination impairment. In the context of multiple sclerosis (MS), we will elaborate on the role of premature OPC aging and its effects on OPC differentiation and remyelination. Subsequently, we will discuss OPC aging in the context of AD, a prevailing form of dementia and one of the most common age-related diseases (Prince and Wimo, 2015). Additionally, we will provide insights into potential future treatment strategies directed at rejuvenating aged OPCs.

2. Transcriptional control of OPCs during myelination and post-injury remyelination

During the intricate process of CNS development, OPCs emerge from radial glial cells and neural stem cells. OPCs encounter several barriers to their terminal differentiation, mostly governed by the expression of *Sox5*, *Sox6*, *Hes5*, *Id2*, and *Id4*, which actively hinder differentiation and subsequent myelination. During developmental myelination, the Notch pathway emerges as a critical regulator of OPC fate. Early in development, axonal expression of the Notch ligand Jagg triggers proteolytic cleavage and nuclear translocation of Notch, resulting in the expression of *Hes5*. HES5 directly inhibits myelin gene expression and competes with pro-myelination factors like OLIG proteins for binding to the *Mbp* promotor, underscoring the delicate balance necessary for OPC maturation (Liu et al., 2006). WNT signaling, activates β-catenin, and thereby exerts an inhibitory effect on OPC maturation, although its role appears multifaceted. Studies indicate that mice lacking active β-catenin, can

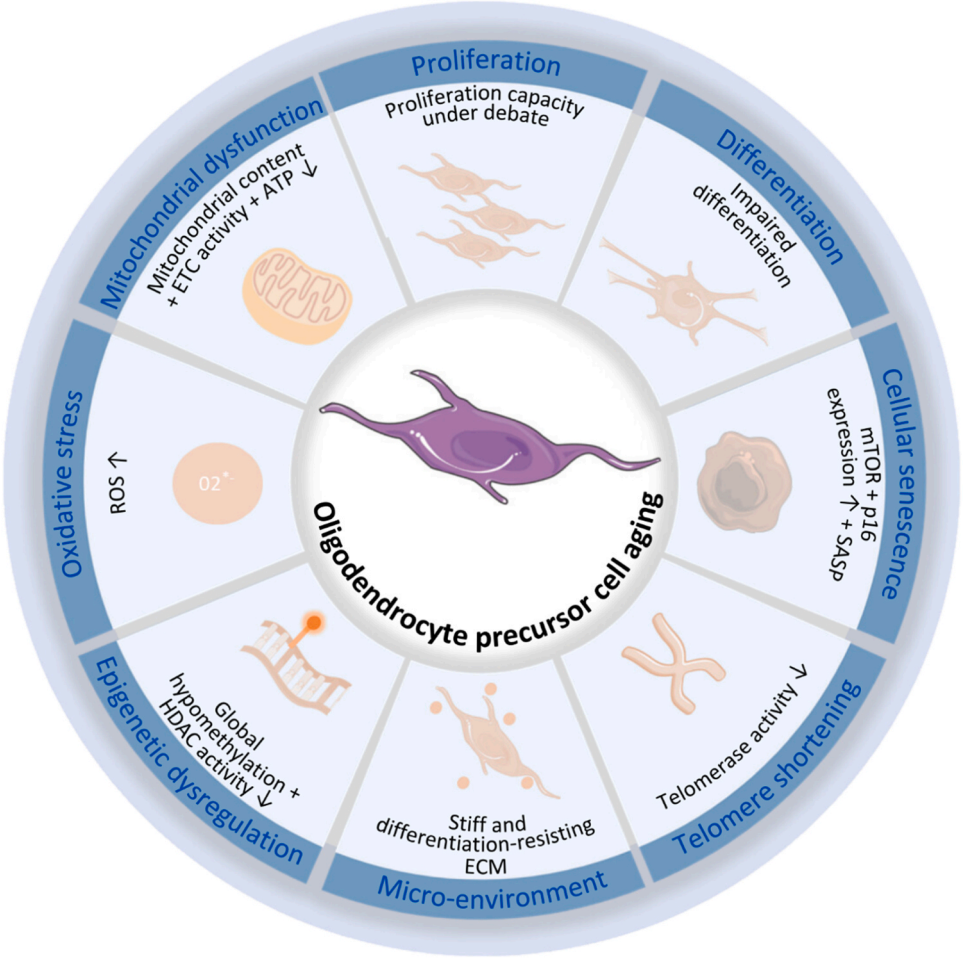

Fig. 1. Aging hallmarks of oligodendrocyte precursor cells (OPCs). Multiple intrinsic and extrinsic factors contribute to the functional decline of OPCs during aging. mTOR, mammalian target of rapamycin; p16, cyclin-dependent kinase inhibitor 2 A; SASP, senescence-associated secretory phenotype; ECM, extracellular matrix; HDAC, histone deacetylase; ROS, reactive oxygen species; ETC, electron transport chain; ATP, adenosine triphosphate.

delay OL differentiation (Feigenson et al., 2009; Dai et al., 2014a). Additionally, the SoxD proteins SOX5 and SOX6 antagonize SOX10, by competing for binding sites on the *Mbp* promoter. *Sox10*, expressed throughout the entire OL lineage, serves as a general marker for OLs, while *Sox5* and *Sox6* are prominently expressed in OPCs and are downregulated as differentiation progresses (Tiane et al., 2019).

Differentiation of OPCs is orchestrated by a network of positive regulators including OLIG1/2, NKX2.2, and SOX10 (Liu et al., 2006). NKX2.2 plays a dual role in OPC differentiation; it is already expressed during the OPC stage, however inadequate levels of NKX2.2 impair the terminal differentiation of OPCs into mature OLs (Feigenson et al., 2009; Dai et al., 2014a). On the other hand, myelination is promoted by OLIG2, which is expressed throughout the entire OL lineage, and by ASCL1, which is expressed during the specification of OL cells and later during terminal differentiation. SOX10, as previously discussed, competes with negative regulators of OPC differentiation such as SOX5/6 to directly bind the promoter region of myelin genes, enhancing their expression. YY1 is important for silencing inhibitory proteins such as ID4. MYRF, a recently discovered key regulator of CNS myelination, is only expressed in post-mitotic OL lineage cells and is therefore crucial for terminal differentiation. Together positive regulators of myelination promote the expression of myelin markers such as *Mbp* and *Plp (*Tiane et al., 2019*)*.

During remyelination following injury, adult OPCs are first activated to migrate to the site of damage. SOX2 plays a significant role in recruiting OPCs and promoting their proliferation at the lesion site. In addition to expansion, adult OPCs must differentiate, a process largely regulated by the same factors critical for developmental myelination. However, some differences exist. While OLIG2 is a key mediator of OPC differentiation during developmental myelination, OLIG1 plays a relatively minor role. In contrast, during remyelination in the adult brain, OLIG1 takes on a more prominent role in promoting OL differentiation and myelination. Furthermore, certain zinc finger proteins such as KLF9 and STAT3 are dispensable during developmental myelination but essential during remyelination (Sock and Wegner, 2019).

3. OPCs and normal aging

Cellular aging observed in OPCs involves structural and molecular changes that contribute to their functional decline. Consequently, OPC aging inevitably results in a reduction in OL numbers, leading to subsequent (re)myelination failure. In the following sections, we will explore the various factors associated with OPC aging (Tripathi et al., 2017; Shen et al., 2008).

3.1. Proliferative capacity

OPCs constitute 5–8 % of the adult glial cell population and stand out as the most proliferative cell type within the adult central nervous system (CNS) (Kuhn et al., 2019). While tissues typically experience a decline in regenerative capacity with aging, a human post-mortem study indicated a 12 % decrease in OPC numbers during the initial 5 years of development, followed by stability throughout the entire lifespan, up to 90 years of age (Wang et al., 2020; Yeung et al., 2014). In addition to the consistent numbers of OPCs, research in the monkey brain revealed that the proliferative activity of OPCs remains unaltered with aging (Dimovasili et al., 2023). In mice, a decrease in mature OLs within the motor cortex was observed between 13 and 18 months of age, while OPC numbers remained unaffected (Wang et al., 2020). Conversely, other murine studies suggest reducing OPC numbers during natural aging (Spitzer et al., 2019; Segel et al., 2019; Luan et al., 2021). Additionally, it has been demonstrated that old adult human (60–75 years), but not old adult mouse OPCs (1 year) exhibit reduced expression of platelet-derived growth factor receptor A (PDGFR-A), a membrane protein crucial for OPC proliferation regulation, suggesting decreased proliferative activity (Seeker LA et al., 2023; Windener et al., 2024).

The disparity in OPC numbers and proliferation capacity reported in different studies implies that the proliferative changes in aged OPCs may be contingent on the species and brain region assessed. Yeung et al. proposed that in humans, the number of adult OLs remains more static, with a generation rate at least 100 times lower than that observed in mice. Moreover, they emphasized that remyelination in humans relies more on pre-existing OLs, in contrast to rodents, as the turnover of OLs is insufficient to account for the observed adaptability of white matter in response to external stimuli in humans (Yeung et al., 2014). A study by Neely et al. showed in a transient receptor potential vanilloid 1 (TRPV1) transgenic zebrafish model for demyelination that pre-existing OLs produce a limited number of new myelin sheaths (an average of only 2 per cell) and often misdirect new myelin towards neuronal cell bodies instead of axons. A similar mistargeting of myelin was observed in human post-mortem MS samples, suggesting a potential decrease in the myelination efficiency of pre-existing OLs (Neely et al., 2022).

3.2. Differentiation capacity

The renewal of damaged myelin sheaths can occur through the combined efforts of newly formed OLs and pre-existing OLs (Sams, 2021; Jeffries et al., 2016; Auer et al., 2018). Newly formed OLs primarily originate from OPCs, with a minor contribution from subventricular zone (SVZ)-derived neural stem cells (NSCs) (Neely et al., 2022; Capilla-Gonzalez et al., 2015). In response to myelin damage, OPCs are typically recruited and triggered to differentiate into mature OLs, initiating remyelination (Hughes et al., 2018; Sim et al., 2002). While the differentiation capacity of SVZ-derived NSCs remains relatively intact with aging, this does not seem to be the case for OPC differentiation (Luan et al., 2021; Neely et al., 2022). Impaired OPC differentiation leads to a decrease in OL density, as evidenced by a substantial reduction in myelin basic protein (MBP) expression, a key structural protein of myelin, in aged mice (Luan et al., 2021). In an animal model of cortical MS induced by myelin oligodendrocyte glycoprotein (Mog) (Christodoulou et al., 2024) immunization, after demyelination, 80 % of the pre-existing OLs survived. This observation highlights the resilience of mature OLs and confirms a possible contribution to the repair process. Unfortunately, existing OLs are unable to meet the high demand for myelin production, therefore the turnover of OLs is imperative for the remyelination and survival of axons (Mezydlo et al., 2023; Zhi et al., 2023). Intriguingly, previous research on zebrafish has indicated that existing OLs can even impede the formation of new OLs, emphasizing the necessity of OL death and clearance to allow novel OPC differentiation (Neely et al., 2022).

The aging-associated inability of OPCs to differentiate properly is due to a disturbance in OPC patterning gene (e.g. *homeodomain protein NK2 homeobox 2 (Nkx2.2), Oligodendrocyte transcription factor 1/2 (Olig1/2)*) expression, concomitant with an upregulation in the expression of genes related to aging (e.g. *Mechanistic target of rapamycin (Mtor), Cyclin-dependent kinase inhibitor 2 A (P16^{INK4A})*) (Shen et al., 2008; Neumann et al., 2019b). A Rhesus monkey model of normal aging (20–30 years) revealed that *NKX2.2* is downregulated in aged OPCs. NKX2.*2* is a crucial transcription factor for OPC differentiation, which is normally upregulated during the active phase of demyelination to initiate remyelination (Dimovasili et al., 2023; Fancy et al., 2004). *Cnp, Mag, and Olig1* are three other factors involved in the remyelination process that were found to be upregulated following demyelination in young, but not old mice (Shen et al., 2008). Furthermore, *Sirt2*, an essential factor in promoting OPC differentiation, exhibits upregulation during both developmental stages and remyelination in newborn and adult mice. However, *Sirt2* expression in OPCs remains unaltered in aged mice following demyelination. Remarkably, Sirt2 acts as a repressor of Id4, which together with Id2, acts as an OPC differentiation inhibitor (Jastorff et al., 2009). *In vitro* transcriptional repression of *Id2/Id4* results in improved OPC differentiation, as evidenced by Tiane et al (Tiane et al., 2021). With aging, OPC N-methyl-D-aspartate (NMDA) receptor

(NMDAR) and voltage-gated sodium channel densities decrease, leading to a disturbed neural activity-dependent myelination, i.e., the process by which the electrical activity of neurons influences the degree of myelination (Spitzer et al., 2019). As OPCs differentiate into OLs, they exert a high metabolic demand. Nevertheless, oxidative phosphorylation and respiratory electron-transport pathways are suppressed in aged OPCs, which are inherent aging hallmarks that may lead to restricted differentiation (Luan et al., 2021).

Next to general OPC gene expression alterations, it has been reported that OPCs display increased regional heterogeneity with age, meaning that their differentiation potential may be diminished in a region-dependent manner (Seeker LA et al., 2023; Vigano et al., 2013). In this context, a first distinction can be made between white- and gray matter-derived OPCs. While murine OPCs derived from white matter were capable of differentiation in both white and gray matter environments, gray matter-derived OPCs exhibited less efficient differentiation (Vigano et al., 2013). Furthermore, within the white matter, Seeker et al. observed two distinct OPC clusters and six OL clusters after single nucleus RNA sequencing in samples derived from human adults (Lampron et al., 2015). The OPC_A cluster showed increased *SLC22A3* and *PAX3* expression, the latter of which plays a crucial role in promoting remyelination, as shown in a murine spinal cord lesion model (Seeker LA et al., 2023; Zhu et al., 2011). While the OPC_A cluster was primarily associated with the cerebellum and spinal cord, the OPC_B cluster was mainly located in the primary motor cortex and marked by increased *NELL1* expression, a gene potentially involved in OPC differentiation. Moreover, the researchers identified 871 differentially expressed genes between the OPC_A and OPC_B clusters, indicating variation in their molecular fingerprints and associated biological processes, including glial differentiation, suggesting that OPCs derived from different regions of the adult CNS vary in their differentiation and function. The same study examined post-mortem OPCs from elderly people and concluded that age-related differences in oligodendroglia are largely confined to OPCs (Seeker LA et al., 2023). Spitzer et al. demonstrated that the electrophysiological characteristics of OPCs undergo changes during aging and exhibit considerable diversity across various brain regions (Lampron et al., 2015). They demonstrated that at the onset of OPC differentiation, the densities of voltage-gated sodium channels and NMDARs reached their peak. However, these densities decrease with age. This reduction in receptor densities leads to reduced excitability in response to changes in neuronal activity, subsequently resulting in a diminished potential for differentiation, as evidenced by *in vitro* experiments blocking the NMDAR. It is important to note that this electrophysiological activity is region-dependent, as not all OPCs exhibit the same receptor densities. Consequently, the extent to which OPCs rely on neuronal activity-dependent differentiation may differ (Spitzer et al., 2019).

3.3. Emerging functions of OPCs in the adult brain

In the developing brain, the proliferation and differentiation of OPCs are primarily driven by the high demand for myelin sheaths vital for the maturation of the CNS. In the adult brain, OPCs remain the most proliferative cell type, constituting about 70 % of the BrdU-positive cells (Dawson et al., 2003). Although it was previously believed that the main role of OPCs in adults was to differentiate into OLs and contribute to remyelination, recent studies suggest that OPCs have additional pivotal functions. This can explain their high proliferation rate despite a relatively low differentiation rate in the adult brain.

Recent research has shown that OPCs play a significant role in sculpting neural circuits during development and remodeling them in adults by forming synapses with neurons. OPCs possess both glutamatergic and cholinergic channels, enabling communication with neurons via neurotransmitters (Sams, 2021). During the development of neuronal circuits, OPCs strengthen, support, and protect synapses that become active. Conversely, when signaling is weak, OPCs may eliminate or remodel these synapses. Although neuron-OPC synapses are still present in the adult brain, their number decreases as the brain matures, consistent with changes in the composition of glutamatergic and cholinergic receptors on OPCs (Moura et al., 2021). Notably, cholinergic signaling drives OPC proliferation, while glutamatergic signaling following demyelination promotes OPC differentiation. Therefore, age-related axonal instability or a decrease in neuronal activity might impair remyelination due to reduced glutamatergic activation of OPCs (Sams, 2021).

Following CNS injury, while astrocytes primarily contribute to glial scar formation, OPCs also play a significant role in this process. During glial scar formation, OPCs upregulate NG2 expression, which inhibits axonal regeneration. OPC-specific depletion of the β-catenin gene, which blocks NG2-OPC proliferation, has been shown to enable axonal regeneration, implying that OPCs contribute to the inhibition of neuronal repair within glial scars (Rodriguez et al., 2014). Furthermore, OPCs contribute to immune responses, for example, by initiating extracellular matrix (ECM) degradation and opening the blood-brain barrier (BBB), allowing immune cell infiltration (Seo et al., 2013). However, how these emerging functions change with aging and how they impact age-related dysfunction of OPC differentiation is not well understood.

4. Molecular mechanisms behind OPC aging

4.1. Cellular senescence

Senescence is often used as a synonym for aging and refers to a state wherein the cell cycle is arrested, rendering cells incapable of further division. Cellular senescence only constitutes one facet of the complex aging process that serves a crucial physiological role in preventing tumor formation (Sams, 2021). Extensive research has focused on peripheral tissues where cell turnover is robust, leading cells to enter replicative senescence after a finite number of divisions (Yu et al., 2020; McHugh and Gil, 2018). However, in the CNS, cellular turnover is less abundant, especially in post-mitotic cells such as neurons, which cease division after CNS development. OPCs, however, are the most active proliferating cells of the CNS and can proliferate and differentiate during the whole course of life to provide newly formed OLs (Zhang et al., 2019). Nevertheless, aging often leads to senescence in OPCs, impairing their differentiation towards OLs. This acquired deficiency was confirmed by the upregulation *Mtor* which is important in regulating several cellular processes such as growth and proliferation, and is linked to cellular senescence (Neumann et al., 2019b; Chen et al., 2009). Furthermore, $P16^{INK4A}$ and cyclin-dependent kinase 1a (P21), both representing tumor suppressor and cell cycle regulators, have been designated to be important in the induction of cellular senescence in OPCs (Safwan-Zaiter et al., 2022; Ogrodnik et al., 2021). A study using directly converted human OLs (65–71 years) demonstrated heightened expression of both $P16^{INK4A}$ and *P21* genes, compared to young and adult controls (Windener et al., 2024). This finding was confirmed in several murine models, showing that with aging, the number of $P16^{INK4A}$-positive OPCs increases in aged rats (20–24 months) (Neumann et al., 2019b). Additionally, the OPC population of aged INK-ATTAC transgenic mice (an inducible model to clear senescent cells, aged 25–29 months) exhibited the highest proportion of $P16^{INK4A}$-positive cells in the hippocampus, accompanied by elevated expression of the senescence marker P21 (Ogrodnik et al., 2021).

In addition to a low proliferation rate, the senescent state is recognized by the secretion of pro-inflammatory factors known as the senescence-associated secretory phenotype (SASP).

These secreted factors can influence the function of surrounding cells by paracrine signaling (Sams, 2021). Cells of the OL lineage are surrounded by other types of glial cells, such as astrocytes and microglia, which were found to undergo P16 ^{INK4A} -and P21-dependent cellular senescence when aging (Ogrodnik et al., 2021; Balasubramanian et al.,

2021). Additionally, microglial senescence has been associated with the suppression of OPC differentiation (Luan et al., 2021). White matter-associated senescent microglia display upregulation of inflammatory and phagocytic genes, while homeostatic markers are downregulated (Safaiyan et al., 2021). Furthermore, endothelial cells and pericytes, important components of the BBB, enter a senescent state with biological aging, compromising BBB integrity and allowing for changes in the micro-environment of brain cells (Knopp et al., 2023; Yamazaki et al., 2016).

4.2. Telomere shortening

During each cell division, the DNA at the very end of the chromosome cannot be replicated and is henceforth lost in the daughter cells, resulting in a slow and gradual shortening of the chromosome. To protect the genetic material, each chromosome end consists of a region with repetitive nucleotide sequences, so-called telomeres (Saretzki, 2018). Telomere shortening is counterbalanced by telomerases, which add nucleotides to the chromosome ends, thereby prolonging the lifespan of the cell. Both the telomerase activity and the telomere length decrease with aging, and this phenomenon can induce senescence signaling pathways. A comparison between post-mortem brain samples of infants and adults indicated that telomere shortening happens in both neurons and glial cells, with the shortening being most pronounced in white matter regions (Tomita et al., 2018). Moreover, *in vitro*, the differentiation of OPCs into mature OLs has been associated with lower telomerase activity (Caporaso and Chao, 2001). Notably, a study conducted by Yang et al. demonstrated that complete inactivation of telomerase, using a premature aging mouse model with a telomerase RNA component (TERC) knockout (TERC-KO), led to disrupted OPC differentiation. TERC, an essential RNA component in telomerase, was specifically targeted for knockout, resulting in telomerase inactivity. The TERC-KO resulted in downregulation of *Olig2* and *Sox10* in OPCs, two pivotal regulators of the differentiation process of OPCs (Yang et al., 2022). A decrease in differentiation cues, as observed in a mouse model for telomerase silencing, resulted in a lower count of mature OLs and, subsequently thinner myelin sheaths, as demonstrated by Jaskelioff et al. Upon endogenous reactivation of telomerase, normal levels of mature OLs were restored, reversing the hypomyelination phenotype (Jaskelioff et al., 2011). Taken together, these findings indicate that maintaining optimal telomerase activity is crucial to prevent a senescent phenotype and support the differentiation capacity of OPCs, ensuring optimal functionality (Yang et al., 2022; Jaskelioff et al., 2011).

4.3. Micro-environment

The impact of growth factors released by neighboring cells significantly influences cellular behavior. It is known that the production and release of growth factors generally decreases with aging, which leads to impaired activity of progenitor cells. The OPC environment shows substantial disparities between early and late life (Segel et al., 2019; Luan et al., 2021). Notably, by changing a differentiation-impairing environment towards a differentiation-promoting environment, aged OPCs reacquire the ability to differentiate. This was shown by a heterochronic parabiosis model comparing young and aged animals, where soluble factors derived from the blood of young animals were administered to aged animals (Ruckh et al., 2012). The replacement of an aged with a young environment resulted in a remarkable tenfold increase in the rate of OPC differentiation (Ruckh et al., 2012; Zheng et al., 2023). In addition, caloric restriction, which is often applied in experimental animal settings to attenuate aging processes, has been shown to enable aged animals to (re)myelinate with the same efficiency as young animals. The same effect could be phenocopied by administering a 5' AMP-activated protein kinase (AMPK) agonist, metformin, which was shown to be able to reverse aging hallmarks in aged OPCs (Neumann et al., 2019b). The importance of a young environment was also highlighted in a study where serum-derived exosomes of aged animals exposed to an enriched environment boosted OPC proliferation and differentiation in brain slice cultures from aged rats to the same extent as exosomes derived from young animals. This improved OPC differentiation led to elevated MBP expression and enhanced myelination, evidenced by thicker myelin sheaths (Pusic and Kraig, 2014).

Next to chemical factors, also physical factors play a role. OPCs are mechanosensitive, which means that their proliferation, cell survival, migration and differentiation capacity depend on the mechanical stiffness of the ECM (Segel et al., 2019; Zheng et al., 2023; Jagielska et al., 2012). In a study by Segel et al., impaired differentiation of aged OPCs could be attributed to the stiffening of the micro-environment, secondary to an increased fibronectin content (Zheng et al., 2023; van Schaik et al., 2022). Piezo-type mechanosensitive ion channel component 1 (PIEZO1) is a mechanosensitive ion channel that regulates cell density and stem-cell activation (Segel et al., 2019; Zheng et al., 2023). This protein was found to display increased expression with advancing age. A CRISPR/Cas9-induced *Piezo1* knockout was able to increase the differentiation rate of aged OPCs by abolishing the calcium transients, and therefore mimicking the young, less stiff environment (Segel et al., 2019). In this stiff environment, there is an accumulation of myelin debris caused by the loss of myelin exceeding the capacity for compensatory remyelination. The clearance of myelin is further impeded by senescent phagocytes, resulting in compromised clearance of the myelin debris, which hampers the recruitment and differentiation of OPCs (Lampron et al., 2015).

Microglia and astrocytes, alongside OPCs, play crucial roles as regulators of myelination. Age-related changes in these glial cells can significantly contribute to the failure of remyelination, as they are also part of the OPC micro-environment (Hughes, 2021). Following demyelination, microglia typically function as phagocytes to clear myelin debris. However, in aged animals, microglia exhibit delayed recruitment, reduced process complexity, altered granularity, and increased expression of senescence genes, such as $P16^{INK4A}$ (Balasubramanian et al., 2021; Neumann et al., 2009). Moreover, with the accumulation of myelin debris during aging, microglia become less efficient in processing myelin, leading to insoluble inclusions that result in a pro-inflammatory microglial phenotype. This phenotype is characterized by an increased production of reactive oxygen species (ROS) and the secretion of pro-inflammatory cytokines (Neumann et al., 2009; Marschallinger et al., 2020). Consequently, these pro-inflammatory microglia can trigger the induction of reactive, pro-inflammatory astrocytes (Galatro et al., 2017). As such, astrocytes, which normally promote OPC proliferation and differentiation through the release of factors like PDGF-A and fibroblast growth factor 2 (FGF-2), change their function with aging. Altogether, age-related changes in microglia and astrocytes, coupled with their transition to a pro-inflammatory state, directly influence the behavior of aged OPCs, contributing to impaired remyelination (Rawji et al., 2020).

4.4. Epigenetic regulation

Cumulative evidence implies that pro-differentiation signals rely predominantly on the micro-environment, which primarily influences the cell at the epigenetic level. With aging, the OPC niche changes; therefore, epigenetic alterations are hypothesized to have a pivotal role in differentiation failure (Tiane et al., 2019). Epigenetics is defined as changes in gene expression that do not involve alterations in the DNA sequence. The development and the regulation of OL differentiation as well as their aging process depend on epigenetic regulation (Dansu et al., 2021). DNA methylation is one of the most variable epigenetic modifications throughout life (Kane and Sinclair, 2019). DNA hypomethylation has been associated with the onset and progression of neurodegenerative diseases and cellular changes accompanying natural aging (Kaur et al., 2022).

While DNA methylation is regulated by DNA methyltransferases

(DNMTs), two ten-eleven translocases (TETs) regulate DNA hydroxymethylation and demethylation. Research indicates an age-dependent role for DNMTs in the OL lineage, where neonatal DNA methylation relies mainly on DNMT1 to copy methylation during cell division, and adult methylation depends on DNMT3A for *de novo* methylation. Following demyelination in adult and aged animals, increased expression of *Dnmt3a* suggests its pivotal role in regulating OPC proliferation and differentiation. On the other hand, recent studies highlight TET1, and not TET2/3, as the primary DNA hydroxymethylation enzyme influencing OPC differentiation, as evidenced by inefficient myelin repair and axomyelinic swellings in TET1 knockout models (Kaur et al., 2022). Contrasting myelination involving hypermethylation, aging is associated with global DNA hypomethylation in OPCs, primarily attributed to decreased levels of DNMT1, with no significant alterations in the expression levels of TET enzymes in aging animals (Zhou et al., 2019; Egawa et al., 2019; Moyon et al., 2021).

Next to DNA methylation, histone modification profiles are known to differ between aged and newborn OPCs (Dansu et al., 2024). Histone deacetylases (HDACs) play a pivotal role in the regulation of gene expression by removing acetyl groups from histone tails, leading to a more condensed chromatin structure and subsequent transcriptional repression. OPCs prominently express HDAC1/2 isoforms, which are integral to the regulation of myelination processes. The inhibition of HDAC1/2 activity has been shown to hinder the process of remyelination in the brains of young mice. Interestingly, aging has been linked to a diminished capacity to recruit HDACs to the promoter region (Shen et al., 2008). This decreased HDAC recruitment results in the inability to eliminate histone acetyl marks (Dansu et al., 2024). These altered histone acetylation patterns lead to the binding of RNA polymerase II and the subsequent increased expression of genes acting as transcriptional brakes, including *Sox2* and *Hes5 (*Shen et al., 2008*)*. For instance, aged OPCs exhibit higher expression of H4K20me3, and its inhibition leads to increased expression of myelin genes such as *Plp* and *Mbp*. This suggests that H4K20me3 helps maintain the progenitor state in aged OPCs by suppressing the expression of certain myelin genes (Dansu et al., 2024).

4.5. Oxidative stress and mitochondrial dysfunction

The differentiation of OPCs is characterized by an increased metabolic and mitochondrial demand, as evidenced by their elevated oxygen consumption and ATP generation compared to mature OLs (Meyer and Rinholm, 2021). Demyelination is followed by an increase in both the number and size of mitochondria in OPCs, accompanied by increased electron transport chain (ETC) activity. Additionally, there is a rise in damage to mitochondrial DNA (mtDNA) and nuclear DNA, partly attributed to increased ROS levels associated with demyelination and increased mitochondrial activity (Spaas et al., 2021; Zhao et al., 2022).

Aged OPCs exhibit significant changes in their mitochondrial function. While previous studies indicated that aged OPCs have lower ATP levels and reduced cellular respiration (Luan et al., 2021; Neumann et al., 2019b), recent research by Windener et al. contradicts this, showing increased mitochondrial function in aged mouse OPCs (1 year) and directly converted human OLs (65–71 years). Windener et al. found higher maximal mitochondrial respiration, increased spare capacity and higher ATP levels compared to adult human OLs. Along with the downregulation of only a few mitochondrial genes, they concluded that mitochondrial dysfunction is not a major factor in aging within the OL lineage (Windener et al., 2024). Interestingly, mitochondria in aged OPCs produce more ROS, which may result from the mitochondrial dysfunction and the consequent increased electron leakage from the ETC, or from the heightened mitochondrial activity required to meet the higher energy demands of aged cells (Windener et al., 2024; Neumann et al., 2019b). Elevated ROS levels inevitably lead to significant oxidative stress-induced damage to nuclear DNA and mtDNA (Neumann et al., 2009). DNA damage influences gene expression, including activation of the $P16^{INK4A}$/*P53* senescence pathways in OPCs (Sams, 2021). Additionally, exposure to ROS during *in vitro* OPC differentiation decreased the expression of positive OL markers (e.g., *SOX10, SHH, and HDAC3*), while negative regulators (e.g. *ID2 and ID4*) were elevated. Finally, elevated ROS levels could also be involved in mediating epigenetic dysregulation seen in aged OPCs (Spaas et al., 2021).

5. OPC aging and disease

5.1. Multiple sclerosis

With 2.8 million cases reported in 2020, MS is the most prevalent demyelinating neurodegenerative disorder of the CNS (Walton et al., 2020). The most common form of MS is relapsing-remitting MS (RRMS), characterized by episodes of inflammation damaging the myelin sheaths of the neuronal axons followed by periods of remission. During these remission phases, OPCs play a crucial role by generating new OLs to remyelinate the demyelinated lesions. However, over time, patients transition to a progressive (PMS) phase, characterized by gradual worsening of the neurologic symptoms and accumulation of disability without intermittent periods of repair (Ghasemi et al., 2017). The worsening of the symptoms results from excessive demyelination which is not followed by remyelination, consequently leading to increased axonal damage. Although the cause of the transition from RRMS to PMS is not well understood, it is known that impaired OPC differentiation, rather than OPC recruitment or proliferation, plays a pivotal role in hampering remyelination. Indeed, evidence suggests that the OPC density increases in demyelinated MS lesions, indicating that migration and proliferation do not have a primary role in the transition towards PMS (Chang et al., 2002; Nicaise et al., 2019; Zhang et al., 2021). The fact that despite these elevated OPC numbers, one observes low OL numbers suggests that impaired OPC differentiation is key in this context (Neumann et al., 2019b).

As MS is typically diagnosed between the ages of 20–30, it is traditionally not regarded as an age-related disease. Yet, recent research has underscored the crucial role of age-related characteristics in impaired OL differentiation and, therefore, MS progression. Consequently, MS is now recognized as a disorder involving premature aging (Ghasemi et al., 2017; Nicaise et al., 2019). Studies employing demyelination models in rodents and zebrafish have elucidated the significant impact of aging on compromised remyelination following demyelination induction. Investigations comparing the remyelination potential between young and old animals reveal a diminished and slower repopulation of lesions with mature OLs, resulting in thinner and less myelin sheaths (Sim et al., 2002; Munzel et al., 2014; Gingele et al., 2020). Recent evidence on induced pluripotent stem cell- (iPSCs) derived neural progenitor cells (NPCs) of PMS patients revealed that these NPCs neighboring OPCs in PMS lesions exhibit signs of senescence, indicated by the expression of $P16^{INK4A}$ and senescence-associated β-galactosidase activity (SA-β-Gal). Notably, these senescent cells release high mobility group box 1 (HMGB1), a pro-inflammatory compound that disrupts gene expression patterns within OPCs, leading to impaired OPC maturation. The impact of HMGB1 on gene expression is particularly pronounced at the epigenetic level, where it negatively influences the expression of helicases and specific histones (Nicaise et al., 2019).

Evidence indicates that after demyelination, the cellular environment of OPCs is “poisoned,” thus inhibiting differentiation. Therefore, mimicking a youthful environment can stimulate OPC differentiation. Caloric restriction stands out as a highly effective intervention in influencing the aging process by positively affecting the cellular environment. The positive effects of dietary restriction were highlighted by Neuman et al., who involved aged rats with focal demyelination (Neumann et al., 2019b). In this research, the rats were subjected to alternate-day fasting (ADF), revealing a remarkable twofold increase in mature OL density at both 21 and 50 days post lesion induction, in contrast to animals fed *ad libitum*. Subsequently, the fasting animals exhibited nearly complete remyelination, a stark contrast to the *ad*

libitum-fed animals, where remyelination was confined to the lesion border. The beneficial effects of an ADF diet were linked to a decrease in *Cdkn2a*, reduced DNA damage, lower levels of phosphorylated p70S6K, and elevated ATP levels, collectively contributing to a more youthful, rejuvenated phenotype. Recognizing the clinical challenges of implementing dietary restriction, the researchers investigated metformin, an AMPK-activating and fasting mimetic. The study demonstrated a reduction in aging hallmarks, accompanied by increased AMPK activity, enabling aged OPCs to undergo differentiation once again. Notably, metformin treatment in *ad libitum* animals resulted in remyelination to the same extent as observed in ADF animals, surpassing the levels achieved in the control group (Neumann et al., 2019b). Currently, the ongoing clinical MACSiMiSE-BRAIN trial is aimed at assessing whether metformin, as an add-on treatment, is able to delay disease progression in PMS patients (De Keersmaecker et al., 2024).

In terms of epigenetic dysregulation, DNA methylation alterations seem to play a substantial role in MS, as chronically demyelinated MS lesions have been reported to display over 8000 differentially methylated CpGs when compared to normal appearing white matter (NAWM) (Tiane et al., 2023a). Moreover, it was shown that OPCs obtained from lesions showed global hypermethylation in comparison with NAWM-derived OPCs (Tiane et al., 2023b; Moyon and Casaccia, 2017). Next to impaired OPC differentiation, the low myelogenic capacity of both surviving and newly differentiated OLs plays a pivotal role in remyelination failure. Although NAWM-derived OLs show normal levels of H3k27 histone activator, which is associated with transcriptional activation, OLs derived from inactive lesions exhibit low or undetectable levels of this activator. Instead, lesion-derived OLs display increased expression of transcriptional silencers such as H3K27me3 and H3K9me3, suggesting a state of epigenetic suppression (Liu et al., 2024). Epigenetic-silencing inhibitor-1 (ESI1), initially reported as a HDAC3 inhibitor, has been shown to effectively reduce these transcriptional silencers while increasing H3K27ac levels. The epigenetic modulation by ESI1 promotes the synthesis of myelin components by condensation of the master regulators of lipid and cholesterol metabolism, SREBP1/2. Following toxin-induced demyelination, ESI1 treatment increased the number of myelinating OLs and the thickness of myelin sheaths, indicating enhanced remyelination. In experimental autoimmune encephalomyelitis (EAE)-treated mice, ESI1 treatment resulted in greater remyelination in the lumbar spinal cord, the predominant site of demyelination in this model. This was accompanied by reduced disease severity and improved clinical symptoms such as motor recovery and visual function (Liu et al., 2024). These findings highlight the potential of epigenetic interventions at the OPC and OL levels to enhance remyelination in MS.

5.2. Alzheimer's disease

Accumulating evidence implicates white matter abnormalities in neurodegenerative diseases such as AD, the most common type of dementia. Both demyelination and microstructural changes in the myelin sheath have been associated with AD. For example, immunostainings of the cortex and hippocampus derived from AD patients and APP/PS1 mice, representing a transgenic mouse model for AD, show a decreased surface area of MBP, an essential component of the myelin sheaths (Vanzulli et al., 2020). Cerebral CT and magnetic resonance imaging (MRI) scans of patients with AD and mild cognitive impairment show a loss of myelin as indicated by hyperintense lesions in periventricular and deep white matter areas (Garnier-Crussard et al., 2022; Kao et al., 2019) as well as impairments in white matter tract integrity (Mayo et al., 2017; Xiao et al., 2022). These alterations were highly correlated with cognitive performance, as examined by e.g. the mini-mental state examination (MMSE).

Concerning alterations in the oligodendroglial lineage, the number of OLIG2-positive cells, which includes OPCs and mature oligodendrocytes, has been shown to be decreased in AD post-mortem brain tissue (Behrendt et al., 2013) and in transgenic Tg2576 mice (Lorenzini et al., 2020). APP/PS1 mice also exhibited a loss of mature OLs in the hippocampus, particularly in the CA3 and CA4. Excessive loss of these mature OLs has been suggested to be due to impairments in OPC proliferation or differentiation, causing insufficient repopulation of the OLs. The differentiation capacity of the OPCs, however, has been reported to remain intact in APP/PS1 mice (DeFlitch et al., 2022). The proliferation capacity of these precursor cells appears to depend on the AD model type and age (Zou et al., 2023). Various studies investigating the APP/PS1 mouse model reported an increase in OPC density at ages between 2 and 15 months (Behrendt et al., 2013; Li et al., 2013; Wu et al., 2017). Within the same mouse model, a decreased OPC density has been observed at ages of 9–14 months (Chacon-De-La-Rocha et al., 2020). Another transgenic AD mouse model, i.e., 3xTg-AD, showed a similar decrease in OPC density at 6 and 24 months (Vanzulli et al., 2020). The OPCs in these mice were hypertrophic, characterized by an increased cell body volume and surface.

The exact relation between OPC dysfunction and AD disease progression remains to be elucidated. In comparison to other glial cells, oligodendroglial cells are especially vulnerable to various AD pathologies, including hallmarks such as oxidative stress (Spaas et al., 2021), neuroinflammation, amyloid beta plaques, and neurofibrillary tangles (Zhang et al., 2019; Roth et al., 2005; Desai et al., 2011). These pathological hallmarks can induce oligodendroglial cell death and senescence (Nasrabady et al., 2018). It was found that glial cells, particularly microglia, showed high levels of β-galactosidase and P16, indicating increased senescence in AD samples compared to non-disease controls. Increased senescence was also observed in OLs and astrocytes, but there was little evidence for this in OPCs. Additionally, differential expression analysis revealed upregulated pathways related to 'senescence initiators' and 'regulation of cellular senescence' in OLs. This study also identified seven different subpopulations of OLs with varying susceptibility to senescence. Notably, subpopulations one and four, which were indicative of immature OLs, showed substantial increase in the expression of senescence genes in AD samples (Fancy et al., 2024).

Conversely, OL dysfunction can predispose the CNS to the development of AD pathology (Cai and Xiao, 2016). Indeed, OLs contribute to the production (Mot et al., 2018) and clearance (Li et al., 2013) of amyloid beta. Myelin dysfunction promotes the accumulation of amyloid beta and increases the cleavage of the amyloid precursor protein (APP) in an AD model (Depp et al., 2023). Altogether, there is ample evidence of a role of OL and white matter dysfunction in the development and course of AD.

5.3. Current treatments and future perspectives

Brain aging is primarily characterized by the shrinkage of the entire brain and changes in both white and gray matter. Consequently, MRI analysis can provide a rough estimate of a person's brain biological age. Over the past few decades, several biomarkers have been developed to predict brain aging, with blood epigenetic age being one of the most well-studied markers for predicting cognitive decline (Higgins-Chen et al., 2021). However, predicting aging at the cellular level of OPCs remains challenging. For instance, versican (VCAN), a large ECM proteoglycan was found to be downregulated in the prefrontal cortex and plasma levels of aged humans, and is derived from OPCs (Niu et al., 2023). This suggests its potential role as an aging marker. Moreover, senescence-associated biomarkers show promise. Despite this progress, identifying OPC-specific biomarkers continues to be a significant challenge.

Therapies targeting different aging mechanisms have been developed (Fig. 2). There are two main classes of therapeutics targeting senescence (senotherapeutics): senolytics and senomorphics. The former aims to kill senescent cells, often by targeting anti-apoptotic pathways. Although the use of senolytics has been shown to improve general health, prolonged administration of these agents can cause global

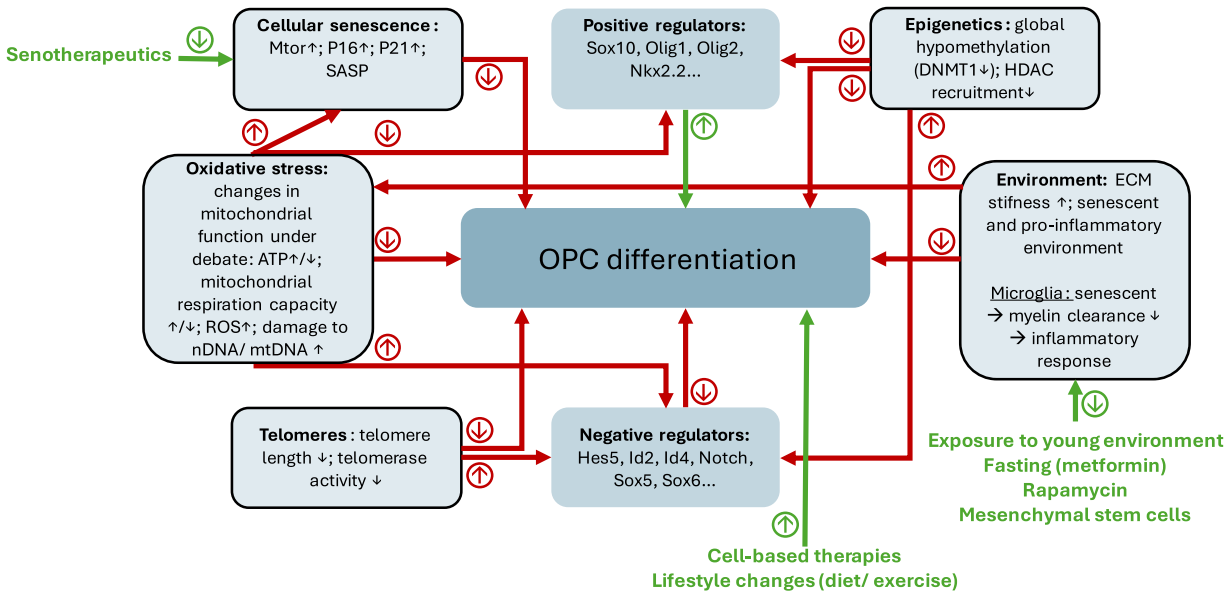

Fig. 2. Interference of aging hallmarks during OPC aging.

dysregulation of proliferation and other cellular processes, potentially leading to cancer. Hence, senolytics are administered using a 'hit and run' strategy, wherein they are administered intermittently prior to a period of rest to mitigate this potential risk (Zhang et al., 2023). Senomorphics act on signaling pathways that alter the senescent phenotype, suppressing the production of SASP compounds and bringing them back to a more rejuvenated state without clearance of the senescent cells. As aforementioned, the senescent phenotype in OPCs is generally characterized by impairments in their ability to differentiate into mature OLs, while their proliferation capacity and density are preserved during normal aging. Senolytics would, therefore, not be desirable in the context of myelin deficits, as it would lead to an overall loss of the OPC population. Senomorphic agents, on the other hand, could potentially be used to reverse the senescent profile of OPCs, rendering them more prone to differentiation and remyelination.

Various pharmacological agents have been implemented to target the inner machinery of OPCs, regulating their differentiation capacity. Metformin, a pro-differentiation compound, is being applied to render OPCs more responsive to pro-differentiation cues, thereby promoting the rejuvenation of OPCs and restoring myelination (Neumann et al., 2019b). Further, OPC aging has been associated with low cellular nicotinamide adenine dinucleotide levels, which blocks the nuclear entry of SIRT2, a histone deacetylase that normally drives the expression of the mature oligodendrocyte-associated MBP. Supplementation with a nicotinamide adenine dinucleotide precursor, Beta-MNM, promoted the nuclear entry of SIRT2 and enhanced OPC differentiation. Supplementation of OPC cultures with recombinant human HMGB1, a chromatin protein that regulates inflammation and is essential for repairing damaged DNA, induced OPC maturation in a dose-dependent manner (Shen et al., 2008). Rapamycin, traditionally known for its immunosuppressant and antiproliferative properties and currently acknowledged as a senomorphic agent, has been used to induce differentiation in various cell types by inhibiting the mTOR pathway (Chen et al., 2009). Rapamycin treatment of primary progressive MS-derived NPCs indirectly promoted the differentiation of OPCs. This effect is achieved by reducing the expression of key cellular senescence markers, such as $p16^{INK4A}$ and SA-β-gal, and by abrogating HMGB1, a SASP factor. HMGB1 has been shown to directly influence OPC maturation, and its reduction enhances the ability of NPCs to provide pro-differentiation cues to OPCs (Nicaise et al., 2019). When OPCs were directly treated with rapamycin, they did not show enhanced differentiation capacity, attributed to the requirement of mTOR signaling for OPC differentiation. Thus, while rapamycin can create a repair-permissive environment by alleviating senescence in NPCs and indirectly supporting OPC differentiation, it does not directly aid the differentiation process of OPCs themselves (Nicaise et al., 2019; Dai et al., 2014b; Tyler et al., 2009).

Other strategies focusing on the micro-environment and other glial cells, rather than directly targeting OPCs, have also proven to be promising, as they can effectively modulate OPC senescence and differentiation. The H1-antihistamine and antimuscarin clemastine have been used in different neurodegenerative diseases, including AD and MS, to simultaneously reduce microglia-associated neuroinflammation, enhance neuronal plasticity, and promote maturation and differentiation of oligodendroglial cells (Jiang et al., 2023). Clemastine treatment enhanced both OPC and OL densities in APPswe/PS1dE9 mice (Xie et al., 2021). Similarly, clemastine has been shown to be able to increase the number of OPCs in the cortex, corpus callosum, and hippocampus of aged mice and enhance myelination and spatial memory (Wang et al., 2020).

A challenge for the application of current senotherapeutics in neurodegenerative diseases is the need to cross the BBB. Furthermore, most compounds are not selective for one cell type, and their effects differ widely between different cell types, resulting in side effects (Zhang et al., 2023; Melo Dos Santos et al., 2024). Improving selectivity of the compounds and targeting OPC aging could specifically reduce systemic side effects while retaining the beneficial effects on myelination and cognitive functioning. Another approach to overcoming these barriers is the use of cell-based therapies. Progenitor cells derived from the adult human subcortical white matter have shown the ability to differentiate into OLs in the demyelinated lesions of rats following toxin-induced demyelination. Within weeks, the implanted progenitors differentiated into OLs and developed myelin-associated antigens (Windrem et al., 2002). Additionally, various types of stem cells, including hematopoietic and mesenchymal stem cells, have shown efficacy in enhancing remyelination in models of MS. While both are effective in promoting remyelination, mesenchymal stem cells also contribute to improving the toxic environment of MS lesions by for instance suppressing inflammation, modulating neurotransmission, reducing the formation of gliotic scars, and promoting angiogenesis (extensively reviewed by Christodoulou et al.) (Christodoulou et al., 2024).

A growing number of studies indicate the potential effects of non-pharmacological interventions as well. Lifestyle changes, including dietary interventions and physical exercise, have shown promise. Fasting, which induces acute changes in energy availability, produces a robust

transcriptional response in OL lineage cells. Refeeding promotes OL differentiation by upregulating mTORC1 and increasing OL cell size, a characteristic of cells preparing for myelination (Kohnke et al., 2021). Conversely, a high-fat diet increases oxidative stress levels, leading to OPC loss in mice (Langley et al., 2020). Additionally, physical exercise in mice following acute demyelination improved the remyelination process by enhancing OPC recruitment, subsequent differentiation, and myelin production (Maugeri et al., 2023). Therefore, lifestyle changes could enhance OPC function and remyelination.

6. Conclusion

OPCs have been extensively studied for their proliferative and differentiation mechanisms. Recent findings indicate that cellular aging plays a significant role in hindering OPC differentiation in both normal aging and neurodegenerative disorders such as MS and AD. Various characteristics contribute to the decline in OPC function with age, affecting remyelination efficiency in MS and AD. Existing treatments, which aim to directly promote OPC differentiation or improve the micro-environment, often fall short due to their lack of specificity and inability to penetrate the BBB. Hence, a more profound comprehension of the aging process of OPCs could lead to the development of innovative strategies to rejuvenate these cells and facilitate effective myelin repair in age-related neurological disorders, with a potential key role for epigenetics.

CRediT authorship contribution statement

Lisa Koole: Writing – review & editing, Writing – original draft, Conceptualization. **Freddy Leenders:** Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Tim Vanmierlo:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization. **Daniel van den Hove:** Writing – review & editing, Supervision. **Assia Tiane:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization. **Helena Slaets:** Writing – review & editing.

Declarations of interest

none

Data availability

No data was used for the research described in the article.

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