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MICROGLIA AND OLIGODENDROGLIA IN ALZHEIMER'S DISEASE

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Alzheimer's disease is the most common form of dementia, characterized by the accumulation of β-amyloid plaques, neurofibrillary tangles composed of hyperphosphorylated tau protein, loss of synaptic connections and neurons, and pronounced neuroinflammation. Traditionally, the pathogenesis of Alzheimer's disease was associated with neuronal death; however, accumulating evidence over the past decade convincingly demonstrates the critical role of glial cells — primarily microglia and oligodendrocytes — in the development, progression, and clinical manifestations of the disease.

Microglia, as innate immune cells of the central nervous system, and oligodendrocytes, responsible for axonal myelination and trophic support, not only respond to pathological changes in Alzheimer's disease but actively shape the microenvironment that either supports neuronal integrity or promotes neurodegeneration. In this context, studying the functional state, molecular activation mechanisms, and intercellular interactions of these glial cells is essential for understanding the pathogenesis of Alzheimer's disease and developing new therapeutic strategies.

The consequences of microglial and oligodendrocyte malfunction are closely interconnected functionally and pathophysiologically. Chronically reactive microglia can negatively affect the differentiation of oligodendrocyte precursor cells, while an excess of cytokines (TNF-α, IL-1β) inhibits remyelination. Conversely, damaged oligodendrocytes synthesize proteins that further activate microglia, creating a vicious cycle of glial malfunction. This interaction generates a pathological microenvironment characterized by sustained inflammation, oxidative stress, metabolic instability, and loss of neuronal function. Given this dynamic, it becomes clear that therapeutic strategies should not be limited to the removal of amyloid plaques or tau protein, but should also aim to restore the functional activity of glial cells, particularly microglia and oligodendrocytes.

Thus, microglia and oligodendrocytes are active participants in the pathogenesis of Alzheimer's disease. Their malfunction — especially chronic microglial activation and the loss of oligodendrocyte myelinating capacity — contributes to the progression of neurodegeneration. Understanding the molecular mechanisms of glial malfunction opens new opportunities for the development of targeted therapies, including modulation of microglial activation, support of energy metabolism, and promotion of remyelination — promising directions in the fight against Alzheimer's disease.

| Keywords: Alzheimer's disease, neurodegeneration, oligodendrocytes, microglia, neuroprotection, glial cells, neuroinflammation, amyloid plaques, neurofibrillary tangles.

| Introduction

Alzheimer's disease (AD) was first described by the German psychiatrist and neuropathologist Alois Alzheimer. In his report at the 37th Conference of Psychiatrists of Southwest Germany in 1906, he presented findings of plaques and neurofibrillary tangles after histopathological examination of the brain of one of his long-term psychiatric patients (Alzheimer, 1907; Kaltschmidt et al., 2024). To this day, these two biomarkers (amyloid plaques and neurofibrillary tangles) remain the main neuropathological hallmarks of AD (Kaltschmidt et al., 2024; Chaikovsky et al., 2022; Nevmerzhytska & Yaremenko, 2024). The accumulation of these features is accompanied by a cascade of pathological processes, such as neuroinflammation, synaptic malfunction, bioenergetics disturbances, vascular abnormalities, etc. These ultimately lead to neuronal death (Zhang et al., 2024). Other pathogenetic factors of AD include acetylcholine deficiency, oxidative stress, dysregulation of trace elements and lipid metabolism, glutamate imbalance, insulin resistance, gut microbiome disruption, mitochondrial malfunction, and impaired autophagy (Beata et al., 2023; Thakral et al., 2023; Nevmerzhytska 2025; Zhang et al., 2024).

The brain of a healthy adult human contains approximately 80 billion glial cells (Verkhratsky & Butt, 2023; Yu et al., 2024). The functions of neuroglia in the central nervous system (CNS) have been widely studied and include neuronal support and metabolism, assistance in development, and the clearance of pathogens and dead neurons (Verkhratsky & Butt, 2023). Recent findings have shown that the glia-to-neuron ratio in the human brain is approximately 1:1 (von Bartheld et al., 2016; Verkhratsky & Nedergaard 2018). This ratio remains constant across developmental stages and in the healthy brain (Yu et al., 2024). It is also important to note that the neuron-to-non-neuronal cell ratio in the CNS varies by region and differs between humans and mice (Verkhratsky & Butt, 2023).

There is substantial evidence to suggest that investigating neuroglial alterations in AD provides a foundation for understanding and treating this disorder (Verkhratsky & Butt, 2023). In response to diverse stimuli, glial cells can adopt a spectrum of activation states that confer either neurotoxic or neuroprotective properties (Liu et al., 2024). These states may either exacerbate or mitigate disease progression, depending on the context (Liu et al., 2024).

In this review, we will examine the general characteristics of microglia and oligodendroglia, as well as their states in AD.

| Microglia

General characteristics of microglia

Microglia are cells of the innate immune system of the CNS, originating from the yolk sac and migrating into the CNS during early embryogenesis. These cells constitute 5–10% of the total brain cell population (Shippy et al., 2024; Giovannini et al., 2021). Microglial cells play a dynamic role in coordinating responses between the immune system and cognitive functions (Giovannini et al., 2021; Uddin & Lim 2022). They participate in neural tissue homeostasis, neuronal protection, development, differentiation, survival, synaptic plasticity, and neuronal metabolism (AmeliMojarad et al., 2024). Microglia constantly monitor the neuronal microenvironment and secrete cytokines, chemokines, and growth factors in response to pathological changes, altering their phenotype and neuronal activity (Soelter et al., 2024; Augusto-Oliveira et al., 2019; Liu et al., 2024).

Microglia–neuron interactions are mediated through intercellular signalling pathways, including purinergic signalling, cytokines, neurotransmitters, and neuropeptides (De Schepper et al. 2021; Xie et al., 2024). The microglia's ability to maintain its protective function is significantly reduced in a proinflammatory microenvironment (Giovannini et al., 2021).

Microglia in ageing

The reduction of microglial cells in the aged human brain was noted as early as the 1970s and is considered one of the most important markers of CNS ageing, since microglia exhibit the most prominent morphological changes (Verkhratsky & Butt, 2023). Ageing is associated with an increase in dystrophic/atrophic microglia, which appear in nearly all brain regions (Uddin & Lim 2022; Makarenko et al., 2024; Streit et al., 2020; Verkhratsky & Butt, 2023). In the ageing brain, microglial processes become shorter and less branched, and the soma volume increases, which may indicate impending pathology. Degeneration of these cells reduces the neuroprotective capabilities of microglia and contributes to the development of neurodegenerative processes (Makarenko et al., 2024).

During ageing, especially in the context of pathology, there is an increase in dark microglia, i.e., cells with electron-dense cytoplasm and nucleoplasm, as well as other ultrastructural markers of oxidative stress (Makarenko et al., 2024). Aged microglia become more sensitive to inflammatory stimuli and can promote the

progression of Alzheimer's disease (Merighi et al., 2022; Hu et al.,2021). The cGAS–STING pathway, a fundamental driver of inflammageing, facilitates microgliosis, thereby fostering chronic inflammation, neurotoxicity, and cognitive decline (Gulen et al., 2023; Liu, 2024). Moreover, ageing is characterized by impaired Ca^{2+} signalling within microglial cells, which limits their responsiveness to both physiological and pathological challenges (Makarenko et al., 2024).

Microglia in Alzheimer's disease

At early stages of AD, microglia internalise and degrade Aβ and tau from the extracellular space. However, as the disease progresses, inflammation and oxidative stress can lead to persistent microglial activation, iron overload, neurotoxicity, and neurodegeneration (Merighi et al., 2022; Fan et al., 2017). Thus, in early AD, microglia play a protective role by removing Aβ, inhibiting tau hyperphosphorylation, and producing neurotrophic factors (Uddin & Lim, 2022; Merighi et al., 2022; Feng et al., 2020; Gratuze et al., 2018). Impaired microglial function and inadequate response to Aβ are associated with an increased risk of rapid AD progression (Uddin & Lim, 2022).

In the late stages of Alzheimer's disease, the accumulation of Aβ and tau inhibits the protective functions of microglia (Sun et al., 2024). Microglial malfunction is further exacerbated by the abundance and size of amyloid plaques (Sun et al., 2024). According to the literature, microglia are capable of engulfing and degrading pathogenic tau species; however, they may also contribute to the propagation of tau pathology (Merighi et al., 2022) and release pro-inflammatory factors (Kaltschmidt et al., 2024; Giovannini et al., 2021). The release of such pro-inflammatory mediators promotes neuronal injury either directly or indirectly through the activation of neurotoxic astrocytes. Neuroinflammation can also impair the differentiation of oligodendrocyte precursor cells and, consequently, trigger demyelination (Uddin & Lim, 2022).

Increased reactive oxygen species and loss of neurotrophins can exacerbate neurodegeneration. Two competing signalling pathways exist within neurons following TNF stimulation: a neuroprotective NF-κB–regulated pathway and an apoptotic caspase-8–mediated one. When NF-κB is inhibited, the pro-apoptotic signal predominates, leading to neuronal apoptosis (Kaltschmidt et al., 2024; Zhang et al., 2024).

This supports the heterogeneous role of microglial reactivity in the pathogenesis of Alzheimer's disease, as moderate stimulation gives rise to a protective microglial phenotype, observed during the preclinical stages of AD, whereas excessive activation leads to a neurotoxic phenotype, which emerges in the clinically manifest and progressive stages of the disease (Fig. 1, Fan et al., 2017; Hamelin et al., 2016; Merighi et al., 2022).

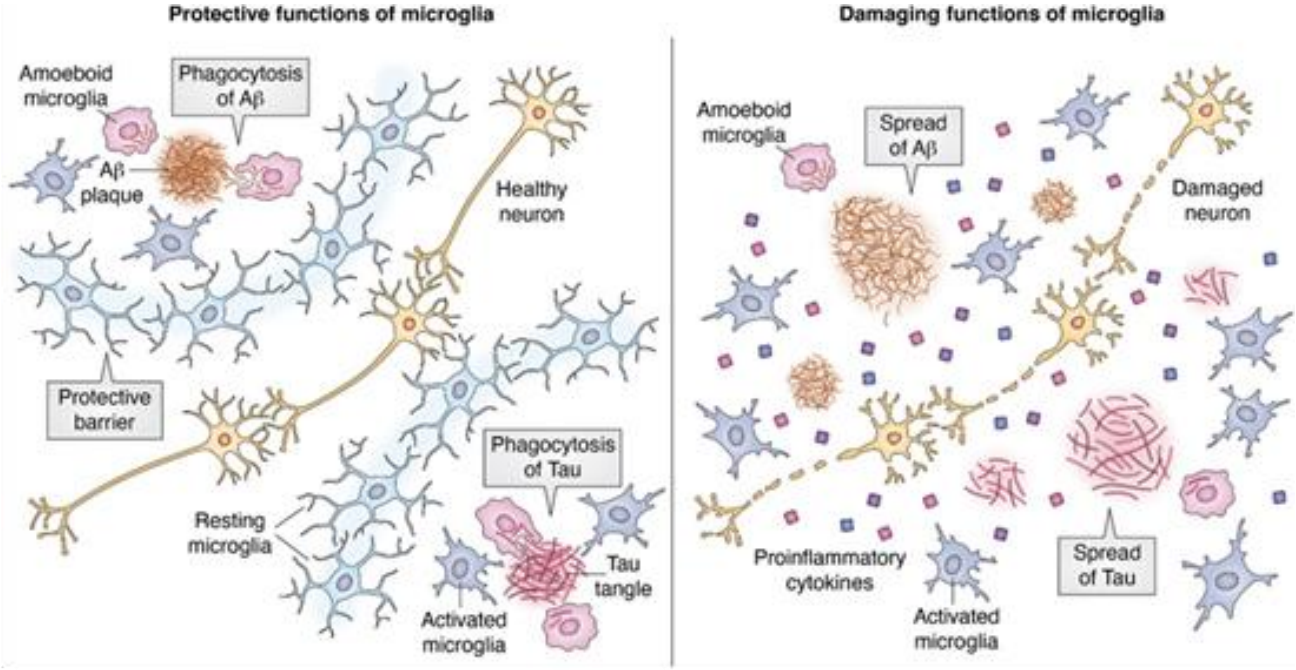

Figure 1. Dual functions of microglia in AD (Shippy et al., 2024). This article is in open access https://www.jbc.org/article/S0021-9258(24)01807-6/fulltext

Microglia-mediated neuroinflammation is increasingly recognized as one of the principal factors contributing to the progression of AD (Zhang et al., 2024). Lifestyle factors, such as diet, sleep patterns, physical activity, and the microbiota, influence the regulation of microglial states and neurodegeneration in both animal models and humans. Preliminary findings have clearly demonstrated the importance and impact of the gut microbiome on microglial phenotype and pathology in models of neurodegenerative diseases (Madore et al., 2020).

Microglial Phenotypes

The pathology of microglia exhibits extensive heterogeneity, encompassing reactive, dystrophic, and malfunctional phenotypes. Microglial reactivity, triggered by mechanical, chemical, or biological insults to the central nervous system, follows a progressive sequence of alterations that generate multiple reactive phenotypes, reflecting the specific nature and progression of the underlying pathological changes. Dystrophic microglia, commonly observed during ageing, experience a decline in their protective functions, thereby contributing to the onset and progression of age-related neurodegenerative processes (Streit et al., 2009; Verkhratsky & Butt, 2023).

A novel form of microglia, known as dark microglia, has been described in the literature. (Bisht et al., 2016; Merighi et al., 2022; Sarlus et al.,2017; Verkhratsky & Butt, 2023). These cells are termed dark due to their appearance under electron microscopy. Dark microglia exhibit low expression of Iba1, CX3CR1, and P2Y12 markers, but high expression of CD11b and the phagocytic marker 4D4 in their processes surrounding synapses. Dark microglia associate with senile plaques also express TREM2 (Bisht et al., 2016; Verkhratsky & Butt, 2023).

The disease-associated microglia (DAM) phenotype typically emerges in the context of accumulating neuronal apoptotic bodies and myelin debris in AD (Merighi et al., 2022; Krasemann et al., 2017; Xie et al.,2024) as well as other neurodegenerative diseases (frontotemporal dementia and amyotrophic lateral sclerosis). DAM is dependent on the triggering receptor expressed on myeloid cells 2 (TREM2) and predominantly expresses markers such as ApoE, transmembrane protein 119 (TMEM119), P2Y12purinergic receptor, chemokine receptor CX3CR1, cystatin 7 (CST7), and Axl (Sun et al., 2024).

The microglial neurodegenerative (MGnD) phenotype is characterized by specific markers, including C-type lectin domain family 7 member A (Clec7a), galectin-3 (Lgals3), glycoprotein NMB (Gpnmb), integrin alpha X (Itgax), app1, fatty acid-binding: elevated levels of apoptotic neurons and depend on the TREM2-ApoE pathway (Sun et al.,2024; Merighi et al., 2022; Xie et al., 2024). Interestingly, this microglial subtype shows reduced sensitivity to TGFβ signalling and plays a protective role in the initial response to neuronal damage, particularly in the ageing brain and in neurodegenerative diseases such as AD (Sun et al.,2024). MGnD possesses the capacity to phagocytose pathogens, toxic chemicals, dead or damaged neurons, and to amplify inflammatory processes (Merighi et al., 2022; Qin et al., 2021).

The MGnD and DAM phenotypes are characterized by the expression of chemokines that may promote the recruitment of inflammatory monocytes and the activation of astrocytes (Liddelow et al., 2017). The association of MGnD/DAM microglia with Aβ plaques is well established; however, key questions remain regarding the potential protective versus neurotoxic functions of these cells (Madore et al., 2020).

Other microglial subtypes described in the literature include activated response microglia (ARM), lipid droplet–accumulating microglia (LDAM), white matter–associated microglia (WAM) (Sun et al.,2024; Kaur et al., 2024), interferon-responsive microglia (IRM), and human AD–associated microglia (HAM), all of which are closely linked to AD (Kaur et al., 2024).

Other microglial changes in Alzheimer's disease

As highly reactive immune cells in the brain, microglia play an important role in regulating brain iron metabolism (Xu et al., 2025; Ryan et al., 2023). Microglia control iron levels through the iron regulatory protein (IRP)–iron response element (IRE) system (Xu et al., 2025). Under neuroimmune activation, the number of divalent metal transporter 1 (DMT1) molecules on microglial and neuronal surfaces increases, promoting ferroptosis due to iron overload (Xu et al., 2025; Sharawy et al., 2022). NF-κB–mediated proinflammatory cytokines also activate microglia in response to excess iron (Xu et al., 2025). Elevated iron levels can induce iron-rich Aβ plaque formation and contribute to microglial proliferation and neurotoxicity (Xu et al., 2025; Kenkhuis et al., 2021).

Trace elements such as zinc play a crucial role in brain function and immunity, and zinc dyshomeostasis has been implicated in AD pathogenesis. Zinc activates microglia, promoting neuroinflammation, while zinc deficiency accelerates cognitive decline by activating the NLRP3 inflammasome. Interventions that modulate zinc concentration or target key zinc-related genes, as well as gene therapy strategies utilizing engineered ZFPs, may

provide alternative therapeutic avenues for AD (Shippy et al., 2024).

Lithium deficiency alters the expression in microglia of several AD risk genes identified in GWAS, including APOE, Trem2, Bin1, Picalm, Clu, and Cd33 (Aron et al., 2025; Qiu et al., 2025). These expression changes are associated with elevated microglial activation markers such as CD68, as well as increased production of numerous proinflammatory cytokines and chemokines, which are also elevated in AD (Aron et al., 2025; Heneka et al., 2025). Furthermore, lithium deficiency impairs microglial phagocytosis and Aβ degradation, a phenotype linked to Aβ deposition in AD (Aron et al., 2025; Romero-Molina et al., 2022). These findings indicate that endogenous lithium supports microglial homeostatic function and prevents proinflammatory alterations associated with AD (Aron et al., 2025; Qiu et al., 2025).

| Oligodendroglia

General Characteristics

Oligodendroglia refers to all cells of the oligodendrocyte lineage, characterized by the expression of specific transcription factors such as OLIG2 and SOX10. This category encompasses mature oligodendrocytes, oligodendrocyte precursor cells (OPCs) and satellite oligodendrocytes (Fig. 2, Verkhratsky & Butt, 2023).

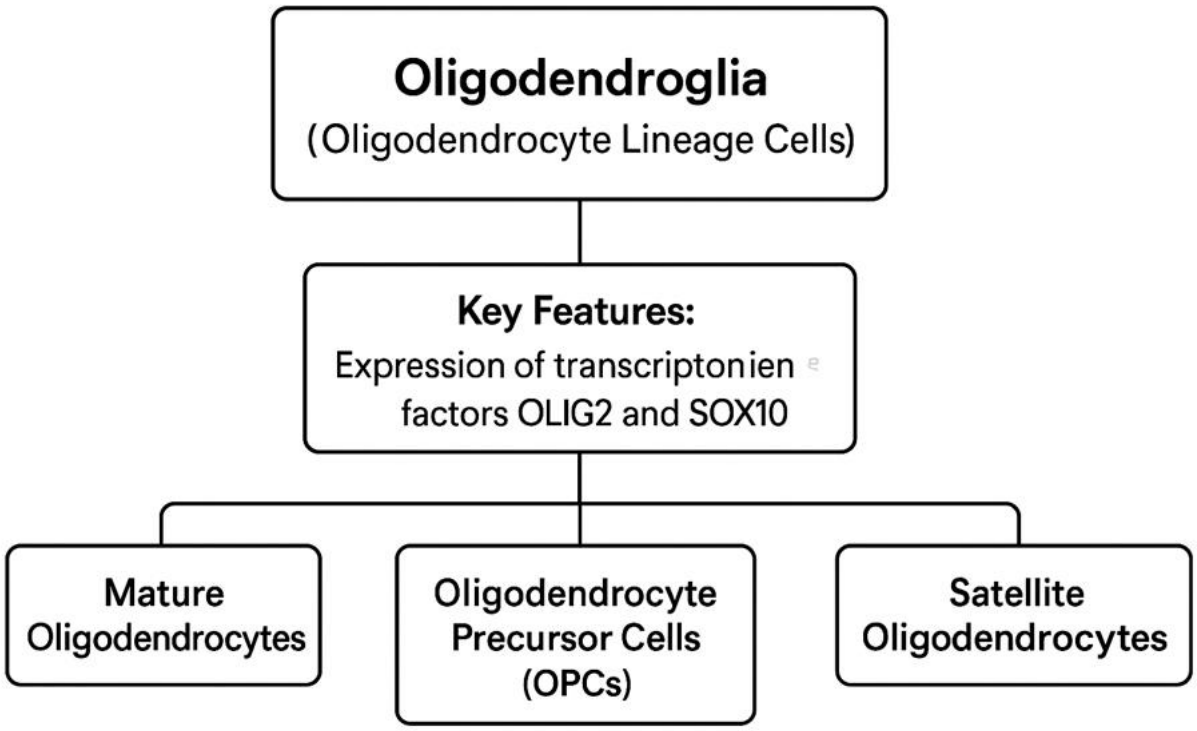

Figure 2. General characteristics of oligodendroglia.

All these cells are myelin-forming neuroglia (Chen et al., 2023; Clayton et al., 2021) and constitute ~ 50% of all neuroglial cells in the CNS of humans (Chaikovsky et al. 2022; Verkhratsky & Butt, 2023). Oligodendrocytes, which originate from OPCs, enwrap axons to form the myelin sheath, thereby facilitating the rapid conduction of electrical impulses (Cohen et al. 2020). Myelin is essential for proper brain function, as its presence around axons enhances the speed of neural signalling, enabling the execution of complex neuronal mechanisms required for learning and cognition (Niu et al., 2025a; Chen et al. 2023). Additionally, oligodendrocytes provide homeostatic and metabolic support to axons, contributing to their development and regeneration (Chaikovsky et al. 2022; Nevmerzhytska 2025). The differentiation process of oligodendrocytes has been well characterized in the literature (Chaikovsky et al. 2022; Verkhratsky & Butt, 2023)

A crucial function of oligodendrocytes, like other neuroglial cells, is the support of neuronal functioning (Wang et al, 2024). Oligodendrocytes perform protective roles, particularly when other cell types such as microglia

are overwhelmed (Kedia & Simons, 2025). Moreover, oligodendrocytes maintain systemic, metabolic, and molecular homeostasis in the nervous system (including glutamate metabolism), and participate in the regulation of the neuro-glio-vascular unit (Verkhratsky & Butt, 2023).

OPCs, also known as NG2-glia, O2A cells, synantocytes, or polydendrocytes, are resident neural stem cells in the CNS derived from the subventricular zone, which proliferate, migrate, and populate the CNS (Butt et al., 2025; Zou et al., 2023). OPCs constitute a heterogeneous subpopulation of oligodendroglia that persists into adulthood and performs diverse functions, including neuromodulation, vascularization, angiogenesis, and coordinated interactions with astrocytes in the development and maintenance of the blood–brain barrier (BBB) (Rossi et al., 2024; Zou et al., 2023; Chaikovsky et al., 2022). Reactive OPCs can differentiate into astrocytes, neurons (Rossi et al., 2024; Akay et al., 2021), and other cell types (Chaikovsky et al., 2022). Their reactions and functions are tightly regulated by multiple signalling pathways, including Notch and PI3/Akt, which are known to be dysregulated in AD (Rossi et al., 2024; Hirschfeld et al., 2022).

OPCs establish direct synaptic contacts with axons and facilitate transient activation of ion channel receptors on their processes (Kedia & Simons, 2025; Soelter et al., 2024; Fang et al., 2023), thereby modulating neuronal synaptic activity (Yu et al., 2024; Soelter et al., 2024; Chaikovsky et al., 2022), promoting the restoration of neuronal communication after injury, and preserving cognitive function (Yu et al., 2024; Auguste et al., 2022; Zou et al., 2023). Activation of these receptors also links neuronal activity with both proliferation and differentiation of OPCs into mature oligodendrocytes (Kedia & Simons, 2025; Li et al., 2024; Yu et al., 2024; Soelter et al., 2024). Under pathological conditions, impaired OPC proliferation and migration compromise their differentiation into mature oligodendrocytes (Zou et al., 2023; Skaper et al., 2019), contributing to myelin degeneration and other pathological alterations in neurodegenerative diseases (Zou et al., 2023).

Oligodendroglia in ageing

Ageing is associated with a reduction in white matter volume and the number of oligodendrocyte progenitor cells (Makarenko et al., 2024). These cells lose their capacity to differentiate into mature oligodendrocytes, resulting in myelin degradation, loss of myelinated axons, and diminished remyelination potential. These alterations correlate with the emergence and severity of cognitive decline in ageing (Makarenko et al., 2024; Verkhratsky & Butt, 2023). Demyelination and the suppression of oligodendrocyte proliferation and differentiation contribute to amyloid-β deposition (Dimovasili et al., 2023; Depp et al., 2023).

Some researchers report that the total number of OPCs does not significantly decline with age; however, their regenerative capacity diminishes, especially in pathological conditions (Verkhratsky & Butt, 2023). Pronounced changes in oligodendroglial gene expression are a hallmark of brain ageing (Verkhratsky & Butt, 2023). The migratory potential of neural stem cells (NSCs), capable of differentiating into OPCs, is limited by NSC ageing (Zou et al., 2023).

Some data suggest that the number of oligodendrocytes increases with age, at least in certain brain regions. However, the rate and nature of age-dependent oligodendroglial growth vary across species, brain areas, and the temporal context in which oligodendrocyte numbers are assessed (Kedia & Simons, 2025). Importantly, degeneration of white matter with focal myelin pathology is a normal feature of brain ageing (Kedia & Simons, 2025). In humans, white matter volume peaks around 40–50 years of age, followed by a gradual decline (Kedia & Simons, 2025; Bethlehem et al., 2022; Makarenko et al., 2024).

Oligodendroglia in Alzheimer's disease

Contrary to the traditional view of oligodendrocytes as passive bystanders in AD pathology, growing evidence indicates their active participation and early response, even during the preclinical stages of the disease (Kedia & Simons, 2025; Sadick et al., 2022; Xie et al., 2024). Far from being inert players, oligodendrocytes play a dual role in AD pathogenesis, potentially offering protective mechanisms during early disease stages and contributing to disease progression at symptomatic and late stages (Niu et al., 2025b; Kedia & Simons, 2025).

In AD, oligodendrocyte malfunction and demyelination result in white matter atrophy in the CNS (Verkhratsky & Butt, 2023; Xu et al., 2025; Chen et al., 2023; Sadick et al., 2022). However, the etiology of this malfunction remains debated. The traditional view suggests amyloid-induced oligodendrocyte malfunction and demyelination arise due to the accumulation of senile plaques, which initiate neuroinflammation and oxidative stress (Verkhratsky & Butt, 2023; Butt et al., 2019; Chen et al., 2023; Aires et al., 2022; Rossi & Bovenkamp, 2024). Other authors argue that oligodendrocyte malfunction

precedes amyloid and tau pathology (Chaikovsky et al., 2022; Butt et al., 2019).

Oligodendrocyte malfunction and demyelination promote amyloid production and tau propagation, ultimately leading to neurodegeneration and dementia (Kedia & Simons, 2025; Chen et al., 2023; Depp et al., 2023; Sasmita et al., 2024). Oligodendroglial impairment may also contribute to axonal and neuronal degeneration, exacerbating disease progression (Verkhratsky & Butt, 2023; Zou et al., 2023).

Olig2, a marker of the oligodendrocyte lineage, is reduced in the brains of AD patients (Kawade & Yamanaka, 2024; Behrendt et al., 2013). The expression of oligodendrocyte-related genes such as myelin basic protein (MBP), myelin-associated glycoprotein (MAG), claudin 11 (CLDN11), myelin oligodendrocyte glycoprotein (MOG), and CNP is also decreased in postmortem AD brains (Kawade & Yamanaka, 2024).

Radiological markers of white matter damage appear as early as 22 years before the predicted age of symptom onset in individuals with AD-related mutations (Lee et al., 2016; Nasrabady et al., 2018; Kedia & Simons, 2025). Alterations in axonal conductivity due to demyelination or axonal injury directly or indirectly contribute to cognitive decline (Nasrabady et al., 2018). In addition to structural damage, chemical alterations occur in white matter during AD, including the loss of proteins and cholesterol. A reduction in myelin proteins such as MBP, PLP, and CNPase in white matter reflects oligodendrocyte and myelin sheath abnormalities and is observed in AD brains. In animal models, white matter malfunction and changes in myelin marker expression are among the earliest pathological features (Nasrabady et al., 2018). These findings support the objective presence of myelin loss in the white matter of AD patients (Kawade & Yamanaka, 2024).

The potential for oligodendrocytes to synthesize β-amyloid in AD remains controversial. Some researchers report a lack of definitive evidence that oligodendrocytes produce β-amyloid, despite findings that they express APP and β-secretase in vitro (Verkhratsky & Butt, 2023). Other studies show that transcripts for APP and amyloidogenic enzymes in oligodendrocytes suggest their possible contribution to Aβ synthesis in AD (Sasmita et al., 2024; Ishii et al., 2024). Recent evidence indicates that human oligodendrocytes not only synthesize Aβ but may also generate it in quantities exceeding those produced by neurons (Rajani et al., 2024). Importantly, selective suppression of oligodendrocyte-derived Aβ has been shown to ameliorate brain morphology in AD and facilitate neuronal functional recovery in an in vivo mouse model (Rajani et al., 2024).

Furthermore, even at the earliest stages of AD, oligodendrocyte precursor cells (OPCs) exhibit impaired migratory capacity, defective differentiation (Yu et al., 2024), and reduced biological activity (Zou et al., 2023). Such malfunction compromises remyelination processes and contributes to synaptic impairment in the AD brain (Butt et al., 2019). This has led to the hypothesis that a vicious cycle of myelin loss and failed regeneration from NG2 glia plays a key role in the development of AD (Butt et al., 2019). Therapeutic strategies targeting NG2 glia are likely to have a beneficial impact on myelination and neuroprotection in AD (Butt et al., 2019).

Notably, the literature describes a population of cells referred to as disease-associated oligodendrocytes (DAO) (Chen et al., 2023; Park et al., 2023). Their formation is triggered by several signalling pathways and transcription factors, including members of the nuclear factor κB (NF-κB) family, signal transducer and activator of transcription (STAT), and interferon regulatory factor (IRF) (Kenigsbuch et al., 2022; Kedia & Simons, 2025), as well as extracellular signal–regulated kinases (ERK1 and ERK2), among others (Kedia & Simons, 2025; Xie et al., 2024; Park et al., 2023). Using immunohistochemistry, OLIG2+ SERPINA3N+ oligodendrocytes were identified in amyloid plaque-enriched regions of post-mortem brain tissue from AD patients (Kenigsbuch et al., 2022; Kedia & Simons, 2025; Xie et al., 2024). Even during normal ageing, a relatively large proportion of oligodendrocytes, particularly in white matter, transition into the disease-associated state (Kedia & Simons, 2025; Kaya et al., 2022). Thus, the presence of DAO reflects a reactive response to brain injury and ageing in general (Kedia & Simons, 2025).

In 5xFAD mice, oligodendrocytes that increased in number in areas of brain pathology expressed SERPIN3A/SERPINA3 in affected cortical regions and near Aβ plaques. Moreover, SERPIN3A/SERPINA3 expression was also observed in the brains of human AD patients, and its levels correlated with cognitive decline [(Kenigsbuch et al., 2022; Kawade & Yamanaka, 2024). Another study demonstrated, using single-cell RNA sequencing in AD mouse models, the existence of three distinct DAO subtypes: DA1 (disease-associated 1, linked to immunogenic genes and elevated inflammatory gene expression), DA2 (associated with genes influencing oligodendrocyte survival), and IFN (associated with interferon response genes) (Pandey et al., 2022; Kawade & Yamanaka, 2024). DA1 and DA2 were localized to areas outside demyelinating lesions, with DA1 repopulating remyelinated areas. However, the patterns of

oligodendrocyte activation observed in human AD patients differed from those seen in AD mouse models (Pandey et al., 2022; Kawade & Yamanaka, 2024).

Other oligodendrocyte changes in Alzheimer's disease

Oligodendrocytes contain the highest concentration of iron, as it is essential for both myelination and metabolic enzyme activity (Chen et al., 2023; Cai et al., 2016). While iron is a crucial cofactor in myelin synthesis, it also promotes lipid peroxidation and activates ferroptosis (Xu et al., 2025; Cheli et al., 2020). The low levels of antioxidants in oligodendrocytes, such as glutathione (GSH), further exacerbate neuronal ferroptosis (Xu et al., 2025; Fan et al., 2021). In addition, oligodendrocytes contain ferritin heavy chains that provide neurons with antioxidant protection against iron-induced cytotoxicity (Chen et al., 2023; Wang et al., 2022). Lipid peroxidation and oligodendrocyte loss mediated by rapid ferritin mobilization may contribute to ferroptosis in neurons affected by AD (Chen et al., 2023; Mukherjee et al., 2020). Lithium deficiency decreases the expression of myelin-related genes in oligodendrocytes and reduces the levels of myelin-associated proteins. Fluoromyelin staining has demonstrated significant myelin loss in 3xTg mice after prolonged lithium deficiency. This was associated with a reduction in oligodendrocyte numbers, OPCs, and axons in 3xTg mice. Electron microscopy revealed thinner myelin sheaths in lithium-deficient mice, indicating that endogenous lithium supports the maintenance of myelin integrity and normal myelination of nerve fibers (Aron et al., 2025).

| Conclusions and future perspectives

Neuroglial cells, particularly microglia and oligodendrocytes, play a crucial role in the development and progression of Alzheimer's disease, far beyond their traditionally perceived supportive functions in the central nervous system. Both cell types are actively involved in the pathogenesis, responding to β-amyloid, hyperphosphorylated tau protein, and age-related as well as inflammatory changes in the microenvironment. Under physiological conditions, microglia act as the primary immune effectors of the brain, performing neuroprotective functions, including phagocytosis, regulation of synaptic remodeling, and control of inflammatory processes. However, under chronic exposure to pathological proteins, their activation takes on a destructive character: microglia adopt a pro-inflammatory phenotype, reduce their ability to clear toxic proteins, and release cytokines that exacerbate neuroinflammation and neurodegeneration. Oligodendrocytes and their precursors ensure myelination, trophic support, and metabolic maintenance of neurons. In AD, these functions are impaired: demyelination, suppression of remyelination, decreased expression of the glucose transporter GLUT1, disrupted lactate metabolism, and imbalances in iron and lithium homeostasis are observed. These alterations reduce neuronal conductivity, create an energy deficit in neurons, and contribute to oxidative stress, which further aggravates neurodegenerative processes.

The combined malfunction of microglia and oligodendrocytes creates a vicious cycle of glial pathology in which inflammation, myelination deficits, and metabolic disturbances mutually reinforce one another.

Future scientific investigations should focus both on the molecular mechanisms of microglial activation and on the interactions between microglia and other central nervous system cell types in the context of neuroinflammation control and neuroplasticity. One key area of interest is the differential characterization of microglial heterogeneity, particularly the identification of specific microglial subpopulations and, potentially, their targeted modulation to promote neuroprotection. Another promising direction is the study of signalling pathways that regulate microglial switching between distinct functional states, as well as the use of microglial markers as biomarkers for AD, both for early diagnosis and for monitoring therapeutic efficacy. The therapeutic potential of microglia lies not in simply 'switching off' inflammation, but rather in the delicate modulation of their functional state aimed at restoring homeostasis in the neuroglial environment.

Strategies aimed at delaying OPC senescence, enhancing myelin repair processes, and initiating OPC differentiation hold considerable promise for AD treatment. Combining approaches that target OPCs and/or their microenvironment may produce a synergistic effect and improve therapeutic outcomes in AD patients. It is essential to deepen our understanding of how oligodendrocytes respond to and function at different stages of AD. Further research is required to investigate the balance between myelin degeneration and remyelination in Alzheimer's disease and related conditions.

| Conflicts of interest

The author declares no conflict of interest.

| Author Contributions

Both authors contributed equally to the conception, writing, and revision of this manuscript. All authors have read and approved the final version.

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