Journal of Integrative Neuroscience

J. Integr. Neurosci. **2023**; 22(4): 90
https://doi.org/10.31083/j.jin2204090

Review

Disease-Associated Oligodendrocyte: New Player in Alzheimer's Disease and CNS Pathologies

Peng Chen[1,†], ZhiLei Guo[2,†], Benhong Zhou[1,*]

[1]Department of Pharmacy, Renmin Hospital of Wuhan University, 430060 Wuhan, Hubei, China
[2]Department of Pharmacy, Wuhan Fourth Hospital, 430030 Wuhan, Hubei, China
*Correspondence: benhongzh@whu.edu.cn (Benhong Zhou)
[†]These authors contributed equally.

Academic Editor: Gernot Riedel
Submitted: 10 November 2022 Revised: 4 December 2022 Accepted: 12 December 2022 Published: 7 July 2023

Abstract

Considerable evidence has shown that the breakdown of myelin has been linked to Alzheimer's disease (AD). Considering the vulnerability of oligodendrocytes to Alzheimer's disease, the myelin sheath breakdown and degeneration are easily induced, suggesting that dysfunction of the oligodendrocytes could be the first step in the progression at the early AD before the occurrence of amyloid and tau pathology. It is considered that amyloid β-peptide (Aβ)-mediated oligodendrocyte dysfunction and demyelination could be manifested through neuroinflammation, oxidative stress, and neuronal ferroptosis. With the development of single-cell sequencing technology, an oligodendrocyte state that increased in association with central nervous system brain pathology (designated as disease-associated oligodendrocytes) has been identified. In the current review, we examine the possible roles of oligodendrocytes in cognitive decline and their molecular characteristics in AD. Altogether, our findings elucidate that targeting oligodendrocytes may be a novel treatment or prevention option for AD.

Keywords: Alzheimer's disease; oligodendrocytes; function; RNA sequencing

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia in the elderly, affecting over 45 million people worldwide [1]. It is a progressive neurodegenerative disorder that first affects learning and memory functions and then gradually impacts cognitive functions with behavioral damage [2]. The most common pathological features in Alzheimer's brains include accumulation of amyloid β-peptide (Aβ), neurofibrillary tangles (NFTs), abnormal mitochondrial function, gliosis, loss of synapses, neuron death, neuroinflammation, and oxidative stress, secondary to the toxic effects of Aβ and Tau [3]. Although the typical symptoms and disease characteristics are well-known, the underlying molecular mechanisms and drug targets remain unclear.

In recent years, majority of the research on neurodegenerative diseases has mainly focused on neurons; however, non-neuronal cells such as glial cells also play an important role in this complication [4]. Glial-like microglia and astrocyte-mediated chronic neuroinflammation and oxidative stress are the key intertwined pathological factors in brain aging and neurodegenerative diseases [5]. Although oligodendrocytes are one of the main types of glial cells in the central nervous system (CNS), their functions and effects on AD neurons are very different from microglia and astrocytes [6]. Like most glial cells, oligodendrocytes can provide neurons with many supporting processes, such as signal recognition [7], migration [8], ion energy supply [9], axon encapsulation [10], and regeneration and maintenance of myelin sheaths [11]. The central function of oligodendrocytes is to generate myelin, an extended membrane from the cell that wraps tightly around axons and is a prerequisite for promoting high-speed nerve conduction [12]. In addition, oligodendrocytes can directly support neurons and prevent cell death, especially by promoting myelin recovery, which is very beneficial for nerve repair after injury [13]. Extensive evidence confirmed that impaired myelin production because of an intrinsic failure of oligodendrocytes might initiate AD development [14].

The current study reviewed the role of myelin breakdown in cognitive decline and the signatures of oligodendrocytes in AD. An overview of oligodendrocyte pathogenic mechanisms in AD is provided, followed by an assessment of whether improving the oligodendrocyte function and inhibiting myelination will provide therapeutic benefits in AD.

2. Breakdown of Myelin in AD

Oligodendrocytes, developed from the well-characterized oligodendrocyte precursor cells (OPCs), are the myelin-forming glial cells of the CNS [15]. The primary purpose of oligodendrocytes, such as other glia, is to maintain and support the nervous system, neurons, and surrounding tissues through a substance called myelin composed of approximately 40% water and a dry mass of approximately 80% lipids and 20% proteins [16]. The oligodendrocyte makes contact with the axon and wraps

around it, thus forming a myelin sheath. These myelin sheaths form insulators on the surface of neurons to protect axons and allow electrical signals to travel more efficiently, reaching speeds of up to 322 km/s [17]. Thus, myelinated axons transmit signals more efficiently than unmyelinated single axons.

There is overwhelming evidence showing that when the immune system attacks oligodendrocytes, it can lead to aggravation of the pathophysiology of several disorders. These include stroke, schizophrenia, demyelinating diseases such as leukodystrophies, multiple sclerosis, white matter damage caused secondarily by such entities in the form of neoplasia, trauma, and infarction, and neurodegenerative diseases including Parkinson's disease, amyotrophic lateral sclerosis, brain aging, and AD [18–21].

2.1 Myelin Pathology in AD: A Macroscopic View

Myelin is formed by oligodendrocytes in the CNS and Schwann cells in the peripheral nervous system. The myelin sheath is a layer of fat and protein that covers the axon of a nerve cell, enabling the electrical impulses between nerve cells to travel back and forth rapidly [22]. Myelin is essential for healthy brain functioning, and myelin wraps around axons to increase neural signaling speed, enabling complex neuronal mechanisms underlying learning and cognition [23]. There is growing evidence that myelin disruption is an important factor contributing to the age-related loss of brain plasticity and repair responses [24]. There is close agreement between neuropsychology, neuropathology, and imaging measures suggesting that the process of myelin breakdown begins in adulthood, accelerates with human aging, and underlies age-related cognitive declines, and the most potent risk factor of dementia-causing disorders, such as AD, is age [25]. *In vivo* AD models have shown that alterations of myelin morphology and oligodendrocyte development appear before the formation of amyloid and tau pathologies. However, these alterations might be highly associated with different mutations in the AD models [26]. It has been reported that oligodendrocytes were more vulnerable to stressors in the presence of AD-associated presenilin-1 (PS1) mutations and in embryonic neurons, amyloid precursor protein (APP) mutations may interfere with myelination *via* axon-mediated signaling to oligodendrocytes in 3xTg-AD models while others do not so [27,28].

2.2 Aβ-Induced Oligodendrocyte Dysfunction

Amyloid β-peptide plaques have been confirmed to be the pathological hallmark of AD, and multiple lines of evidence have linked Aβ with AD-associated neuronal degeneration. Numerous studies have proposed that Aβ alters myelinating oligodendrocyte functions and induces toxicity in AD [29].

The direct toxicity generated by pathological Aβ peptides alone or combined with the signals produced by degenerating neurons leads to oligodendrocytes compromise, which participates in the disease process [30]. The response of OPCs to Aβ, such as demyelination, increased proliferation, reactive microglia triggering, and default response to any brain injury, is described in several studies [31]. Furthermore, in the initial phase of AD, the reactions of OPCs to the increased differentiation of oligodendrocytes are also described. The myelin disruption induced by Aβ-mediated toxicity is associated with the spatial and temporal progress of cognitive disorder in the AD model *in vivo* during the early pre-symptomatic stages [32]. As shown in some *in vitro* studies, a new pathogenic mechanism underlying oligomer-mediated leukopenia degeneration may impair myelin maintenance and regeneration of adult OPCs, consequently leading to cumulative damage to myelin axons and to nerve disconnection [33]. Oligodendrocyte precursor cells, potential sources for myelin defect repair, have different outcomes in AD-associated mouse models and human AD pathology because of their specific response to amyloid plaque deposition [25]. AD-associated presenilin-1 mutations increase Aβ-induced myelin damage and oligodendrocyte dysfunction in the pre-symptomatic phase of early AD [34]. Here, we show that the PS1 mutation made mouse OPCs vulnerable to Aβ-induced cell differentiation. In addition, PS1 expression is closely related to OPC function and the distribution of myelin basic protein (MBP), a process further exacerbated by the exposure to Aβ [35]. Furthermore, demyelination was observed where the Aβ plaques were the most abundant. In preclinical and sporadic AD cases, focal loss of oligodendrocytes in neocortical gray matter was relevant to the core of Aβ plaques [36]. As demonstrated in immunoreactive research, high levels of Aβ tend to be positively correlated with marker expression in oligodendrocytes (there are three types of myelin basic proteolipid protein: galactocerebroside, myelin glycoprotein, and myelin/oligodendrocyte glycoprotein), implicating that Aβ plaque formation may be preceded by neuronal/oligodendrocytic degeneration [37]. However, contradictory literature indicates that oligodendrocyte survival, myelination, and OPCs seem to be affected by Aβ [38]. Acute inflammation induced by Aβ enhanced remyelination-related transcription signals and rapidly cleared myelin debris. Along with the visibly distinct outcomes between an AD-related mouse model and human AD pathology, APP/PS1 mice had a greater number of oligodendrocyte lineage cells, and a decrease in oligodendrocyte number was found in the postmortem human cortex of patients with AD [34,39]. In addition, defects in myelin integrity and amount were prevalent in APP/PS1 mice at six months of age but were normalized in control mice at nine months [40]. There is a possibility of repair from newly formed oligodendrocytes in APP/PS1 mice, but in human AD, this response from oligodendrocyte progenitors does not seem as evident.

2.3 Oligodendrocyte and Neurofibrillary Tangles (NFTs)

Neurofibrillary tangles, known as pathological hallmarks of AD, are intracellular aggregates of hyperphosphorylated tau protein known as microtubule-associated proteins. Brains affected by AD are also commonly affected by NFTs, especially in the hippocampus and entorhinal cortex [41]. A hippocampus and temporal cortex with NFTs can also be observed in normal elderly individuals and patients suffering from other neurodegenerative diseases [42]. Clinical symptom severity and the degree of neuronal death increase the number of NFTs with aging.

Tau hyperphosphorylation and accumulation frequently occur in neurons but were also found in non-neuronal glial cells [43]. Mice with the G272V mutation (mutations in tau) developed oligodendroglial fibrillary lesions similar to those seen in human tauopathies [44]. In oligodendrocyte cytoplasm, tau-positive fibrillary tangles resemble NFTs in terms of argyrophilia and antigenicity to tau and ubiquitin [45]. Despite this, the role of oligodendrocytes in NFT formation is still not fully understood. This suggests that oligodendrocyte dysfunction and NFTs share a similar background in that axonal dysfunction can neither transmit nor conduct electrical signals using myelin [46]. However, the specific causality between oligodendrocyte dysfunction and NFTs remains unclear.

Inflammation and oxidative stress are common pathophysiological factors that cause oligodendrocyte dysfunction and NFT formation in AD. According to some researchers, inflammation and oxidative stress induced by NFTs may contribute to oligodendrocyte dysfunction [47]. Therefore, it is important to investigate whether oligodendrocyte dysfunction is either a cause or a consequence of NFTs in AD. The exact role that oligodendrocytes play in NFT pathogenesis remains unknown.

3. Oligodendrocyte-Mediated Neuron Ferroptosis

The oligodendrocytes of the CNS contain the greatest concentration of iron as it is required for both myelination and metabolic enzyme activity [48]. According to quantitative analyses, iron accumulation in neurons and glial cells was significantly increased in postmortem brains affected by AD [49]. As a result, Olig2-positive oligodendrocytes had an iron content that increased by a factor of ~2.5 [48,50]. Furthermore, oligodendrocytes contain ferritin heavy chains, which provide neurons with antioxidant protection against iron-induced cytotoxicity [51]. Ferroptosis caused by rapid iron mobilization from ferritin led to oligodendrocyte loss, demyelination, and demyelination in a multiple sclerosis (MS) cuprizone-induced model [48]. It is likely that lipid peroxidation and oligodendrocyte loss mediated by rapid mobilization of ferritin can also contribute to ferroptosis in neurons affected by AD. Because of the close physical contact between neurons and oligodendrocytes under pathological conditions such as demyelination in aging, oligodendrocytes become a natural pool for loading iron to neurons and induced neuron ferroptosis [52].

4. Disease-Associated Oligodendrocyte (DOL) in AD

When referring to dementia diseases, especially AD and brain aging, it was observed that substantial age-related myelin has been changed and destructed in models based on deceased patients' brains and on mice [53]. Although oligodendrocytes play a non-trivial role in the brain, it remains unclear whether and how their fate is altered in AD and, if so, in an etiologically dependent or pathologically conserved manner [54]. Recently, Kenigsbuch M *et al*. [55], using scRNA-seq, identified a transcriptional state (DOLs) among oligodendrocytes as a response to deviations from homeostasis in the CNS. This transcriptome module seems to exist in different pathological states, and its elements may be closely related to the occurrence of human diseases.

In a 5xFAD model of amyloidosis in 10-month-old mice, DOLs appeared alongside some other pathological changes including Aβ plaque formation, reactive gliosis, mitochondrial dysfunction, synaptic collapse, gliosis, inflammation, and cognitive impairment [55]. These findings suggested that oligodendrocyte response to damage in 5xFAD is due to the activation of other glial cells, such as microglia and astrocytes, suggesting that this could be the result of a cumulative injury [56,57].

Although DOLs were found in the vicinity of Aβ plaques, they appeared a long time after plaque accumulation; however, *in vitro* results showed that stimulation of Aβ is insufficient to induce its conversion. Furthermore, these experimental results are consistent with observations in animal models without amyloid accumulation *in vivo*, arguing against Aβ as a sufficient trigger of this cellular state. Of interest, the presence of DOLs in plaque-rich brain regions is also attributed to other factors, such as damage-related molecular patterns, a class of metabolic factors released by dying cells, and inflammation [58]. Interestingly, in an alternative model of amyloidosis, transcriptomic features similar to DOL features were also observed using spatial transcriptomic analysis of plaque niches, further supporting the notion that a rich plaque microenvironment contributes to the maintenance of this cellular state [59].

4.1 DOL and Disease-Associated Astrocyte (DAA)

The overlap of transcriptomic features between DOL and DAA suggests that despite fundamental differences between functions of astrocytes and oligodendrocytes, they share similar damage response molecular pathways (Serpina3n, C4b, and Ctsb upregulation). Microglial responses appear to be more pathologically specific, such as disease-associated microglia (DAM) observed in amyloidosis, but not in tau pathology [60]. Notably, some genes, such as C4b, are also found as common features of both astrocytes and oligodendrocytes [61]. Therefore, further studies are

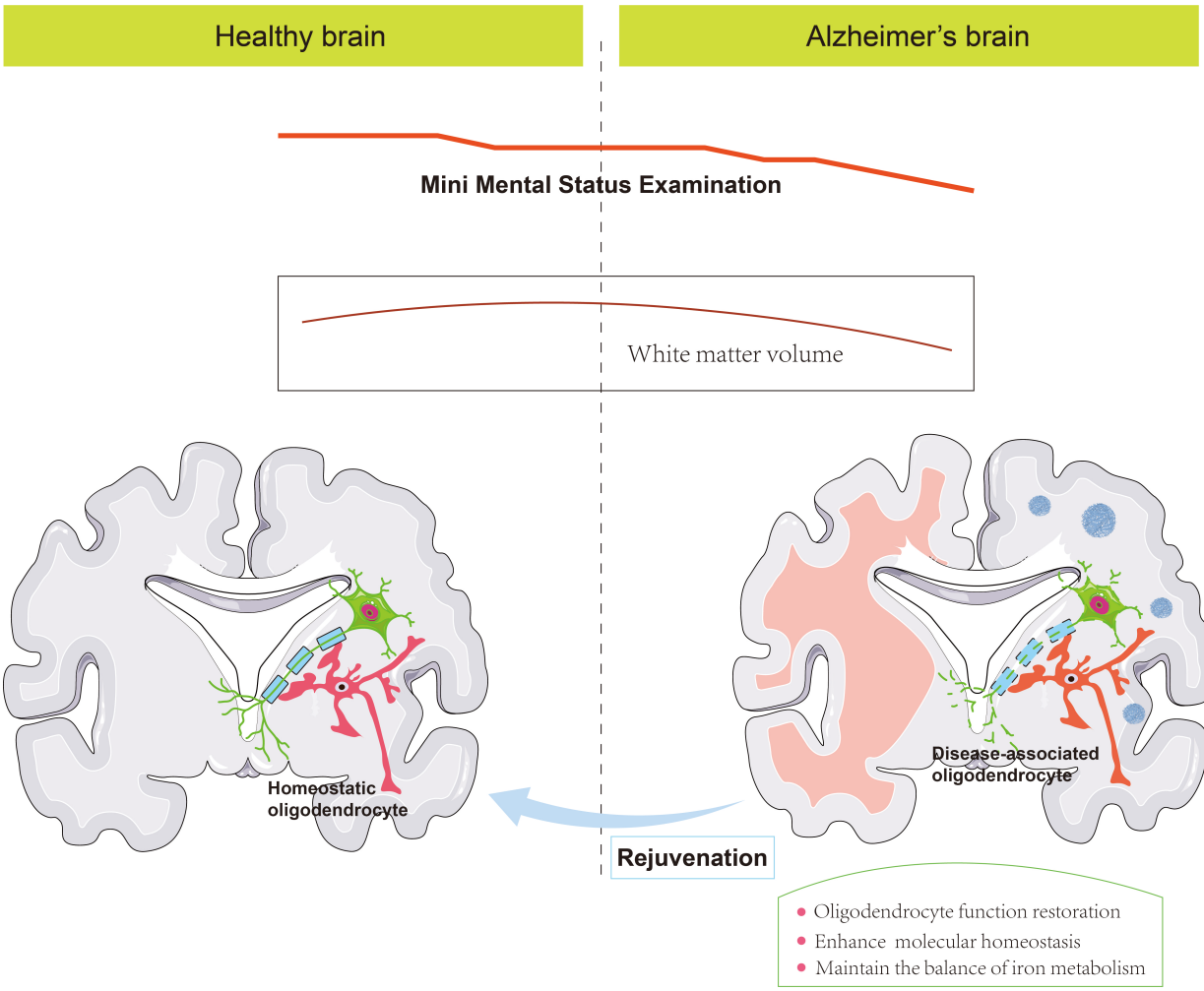

Fig. 1. Hypothesis of targeting the Disease-Associated Oligodendrocyte (DOL) for AD treatment. We used the Mini Mental Status Examination (MMSE) to represent cognitive function for Alzheimer's disease (AD). White matter volume demonstrates a u-shaped pattern, with decreases with the progression of AD, as is also the case for cognitive function. Homeostatic oligodendrocytes are converted to DOLs, which accelerates cognitive decline. Interestingly, the damage can be reversed through targeting of the DOL.

needed to determine the role of these responses and their targeting in the development of effective treatments for CNS diseases.

4.2 Does Targeting DOL Prove Beneficial to Cognitive Decline?

Interestingly, SERPINA3+ oligodendrocytes in human postmortem AD brains were observed using immunohistochemistry [62]. Transcriptomics results have revealed that a high level of *SERPINA3* signature in proximity to macrophages is associated with inflammation, suggesting that neuroinflammation and damage can potentially induce increased expression of *SERPINA3* [63]. However, the presence of only a single marker in the immunohistochemistry may not be sufficient to determine the degree of similarity between these cells and mouse DOLs. Furthermore, spatial transcriptomics could not fully characterize this marker and it lacked single cell resolution. Notably, it was found that the proportion of SERPINA3+ cells in the brain has been associated with Mini-Mental State Examination (MMSE) scores, suggesting *SERPINA3* may be an indicator of impaired cognitive function. A notable effect of *Serpina3n* is that it inhibits granzyme B, thereby protecting cells against CD8+ T-cell-induced cytotoxicity [64]. Furthermore, it promoted plaque aggregation *in vitro* [65]. Further research is required to better understand the role of DOLs, particularly *Serpina3n/SERPINA3*, and their relevance to human diseases.

4.3 Is Aging an Activating Factor for DOL Formation?

In experimental allergic encephalomyelitis (EAE), oligodendrocyte progenitors (OPC) and mature oligodendrocytes with similar characteristics are phagocytic, present antigens on MHC-II, and stimulate CD4+ T cells [66]. Unlike EAE, scRNA-seq analysis of the transcriptomic profile of mature oligodendrocytes (GalC+) in 5xFAD revealed upregulation of the MHC-I pathway but not of the MHC-II pathway. Therefore, CD8+ T cells are more likely to inter-

act with the immune system than CD4+ T cells. In addition, a recent study suggests that OPC may age in the presence of amyloidosis [67]. The authors have not found any evidence of senescence markers at the transcriptome level in mature oligodendrocytes. However, a more in-depth description of OPC is needed to answer these questions. Consistent with observations in the 5xFAD model, the expression levels of DOL genes in EAE were found to increase with disease progression, supporting the idea that DOL signaling expression and damage accumulation are related.

5. Conclusions

A variety of factors contribute to oligodendrocyte function, such as aging, aluminum toxicity, small vessel disease, white matter stress, and pathology and/or NFTs associated with AD [68]. During this process of neurodegeneration, there is a prolonged pathological assault on oligodendrocytes, leading to myelin breakdown. The oligodendrocytes that form myelin are derived from morphologically complex precursor cells. Various cognitive declines that are hypothetically linked to aging, including Alzheimer's dementia, are caused by myelin breakdown. Several scientific studies have demonstrated that myelination patterns and oligodendrocyte status are significantly altered before the development of amyloid and tau pathologies [69]. Myelin dysfunction of oligodendrocytes and Aβ-mediated toxicity may be further aggravated by oxidative stress, neuroinflammation, and/or dysregulated iron metabolism. Moreover, as a novel phenotype, disease-associated oligodendrocytes share common molecular pathways in different neurodegenerative disease conditions, indicating that diseases of the CNS share potential common pathological mechanisms [70]. Based on the above findings, we hypothesize that cognitive impairment and white matter degeneration in AD brain are caused by dysfunction of DOLs, and that regulating this phenotype can rejuvenate AD brain pathology (Fig. 1).

However, further research is required to understand the mechanisms underlying the disruption of oligodendrocytes and myelin in AD. For example, it is necessary to investigate whether inhibiting oligodendrocyte dysfunction and myelin breakdown is a favorable treatment target for AD. Despite several preclinical studies supporting this hypothesis, clinical data is lacking. Therefore, elucidating these specific mechanisms may contribute to a better understanding of AD and may help to prevent and treat the disease.

Author Contributions

PC, ZG, and BZ conceptualized and designed the study. PC wrote the manuscript. PC and ZG designed the figures. BZ reviewed the manuscript. All authors contributed to editorial changes in the manuscript. All authors have read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This work was supported by grants from the National Natural Science Foundation of China (31770381) and Scientific Research Fund of Wuhan Municipal Health Commission (WZ20D07).

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Mantzavinos V, Alexiou A. Biomarkers for Alzheimer's Disease Diagnosis. Current Alzheimer Research. 2017; 14: 1149–1154.

[2] Tan C, Yu J, Tan L. Biomarkers for preclinical Alzheimer's disease. Journal of Alzheimer's Disease. 2014; 42: 1051–1069.

[3] Golde TE. Disease-Modifying Therapies for Alzheimer's Disease: More Questions than Answers. Neurotherapeutics. 2022; 19: 209–227.

[4] Cornell J, Salinas S, Huang H, Zhou M. Microglia regulation of synaptic plasticity and learning and memory. Neural Regeneration Research. 2022; 17: 705–716.

[5] Tcw J, Qian L, Pipalia NH, Chao MJ, Liang SA, Shi Y, *et al*. Cholesterol and matrisome pathways dysregulated in astrocytes and microglia. Cell. 2022; 185: 2213–2233.e25.

[6] Sadick JS, O'Dea MR, Hasel P, Dykstra T, Faustin A, Liddelow SA. Astrocytes and oligodendrocytes undergo subtype-specific transcriptional changes in Alzheimer's disease. Neuron. 2022; 110: 1788–1805.e10.

[7] Allen NJ, Lyons DA. Glia as architects of central nervous system formation and function. Science. 2018; 362: 181–185.

[8] Kang M, Yao Y. Laminin regulates oligodendrocyte development and myelination. Glia. 2022; 70: 414–429.

[9] Raffaele S, Boccazzi M, Fumagalli M. Oligodendrocyte Dysfunction in Amyotrophic Lateral Sclerosis: Mechanisms and Therapeutic Perspectives. Cells. 2021; 10: 565.

[10] Chen K, Wellman SM, Yaxiaer Y, Eles JR, Kozai TD. In vivo spatiotemporal patterns of oligodendrocyte and myelin damage at the neural electrode interface. Biomaterials. 2021; 268: 120526.

[11] Neely SA, Williamson JM, Klingseisen A, Zoupi L, Early JJ, Williams A, *et al*. New oligodendrocytes exhibit more abundant and accurate myelin regeneration than those that survive demyelination. Nature Neuroscience. 2022; 25: 415–420.

[12] Chen J, Wang F, Huang N, Xiao L, Mei F. Oligodendrocytes and myelin: Active players in neurodegenerative brains? Developmental Neurobiology. 2022; 82: 160–174.

[13] Lee S, Rezzonico MG, Friedman BA, Huntley MH, Meilandt WJ, Pandey S, *et al*. TREM2-independent oligodendrocyte, astrocyte, and T cell responses to tau and amyloid pathology in mouse models of Alzheimer disease. Cell Reports. 2021; 37: 110158.

[14] Xiao Y, Petrucco L, Hoodless LJ, Portugues R, Czopka T. Oligodendrocyte precursor cells sculpt the visual system by regulating axonal remodeling. Nature Neuroscience. 2022; 25: 280–284.

[15] Clayton BLL, Tesar PJ. Oligodendrocyte progenitor cell fate and function in development and disease. Current Opinion in Cell Biology. 2021; 73: 35–40.

[16] Kim WS, Hsiao JT, Bhatia S, Glaros EN, Don AS, Tsuruoka S, *et al*. ABCA8 stimulates sphingomyelin production in oligodendrocytes. The Biochemical Journal. 2013; 452: 401–410.
[17] Cohen CCH, Popovic MA, Klooster J, Weil M, Möbius W, Nave K, *et al*. Saltatory Conduction along Myelinated Axons Involves a Periaxonal Nanocircuit. Cell. 2020; 180: 311–322.e15.
[18] Xu S, Lu J, Shao A, Zhang JH, Zhang J. Glial Cells: Role of the Immune Response in Ischemic Stroke. Frontiers in Immunology. 2020; 11: 294.
[19] Hase Y, Horsburgh K, Ihara M, Kalaria RN. White matter degeneration in vascular and other ageing-related dementias. Journal of Neurochemistry. 2018; 144: 617–633.
[20] Zang C, Liu H, Ju C, Yuan F, Ning J, Shang M, *et al*. *Gardenia jasminoides J. Ellis* extract alleviated white matter damage through promoting the differentiation of oligodendrocyte precursor cells *via* suppressing neuroinflammation. Food & Function. 2022; 13: 2131–2141.
[21] Nave KA, Werner HB. Myelination of the nervous system: mechanisms and functions. Annual Review of Cell and Developmental Biology. 2014; 30: 503–533.
[22] Bonetto G, Belin D, Káradóttir RT. Myelin: A gatekeeper of activity-dependent circuit plasticity? Science. 2021; 374: eaba6905.
[23] Morelli AM, Chiantore M, Ravera S, Scholkmann F, Panfoli I. Myelin sheath and cyanobacterial thylakoids as concentric multilamellar structures with similar bioenergetic properties. Open Biology. 2021; 11: 210177.
[24] Gupta M, Weaver DF. Microsecond molecular dynamics studies of cholesterol-mediated myelin sheath degeneration in early Alzheimer's disease. Physical Chemistry Chemical Physics. 2021; 24: 222–239.
[25] Butt AM, Rivera AD, Fulton D, Azim K. Targeting the Subventricular Zone to Promote Myelin Repair in the Aging Brain. Cells. 2022; 11: 1809.
[26] Desai MK, Sudol KL, Janelsins MC, Mastrangelo MA, Frazer ME, Bowers WJ. Triple-transgenic Alzheimer's disease mice exhibit region-specific abnormalities in brain myelination patterns prior to appearance of amyloid and tau pathology. Glia. 2009; 57: 54–65.
[27] Pak K, Chan SL, Mattson MP. Presenilin-1 mutation sensitizes oligodendrocytes to glutamate and amyloid toxicities, and exacerbates white matter damage and memory impairment in mice. Neuromolecular Medicine. 2003; 3: 53–64.
[28] Truong PH, Ciccotosto GD, Merson TD, Spoerri L, Chuei MJ, Ayers M, *et al*. Amyloid precursor protein and amyloid precursor-like protein 2 have distinct roles in modulating myelination, demyelination, and remyelination of axons. Glia. 2019; 67: 525–538.
[29] Aires V, Ziegler-Waldkirch S, Friesen M, Reichardt W, Erny D, Loreth D, *et al*. Seed-induced Aβ deposits in the corpus callosum disrupt white matter integrity in a mouse model of Alzheimer's disease. Frontiers in Cellular Neuroscience. 2022; 16: 862918.
[30] Agosta F, Dalla Libera D, Spinelli EG, Finardi A, Canu E, Bergami A, *et al*. Myeloid microvesicles in cerebrospinal fluid are associated with myelin damage and neuronal loss in mild cognitive impairment and Alzheimer disease. Annals of Neurology. 2014; 76: 813–825.
[31] Behrendt G, Baer K, Buffo A, Curtis MA, Faull RL, Rees MI, *et al*. Dynamic changes in myelin aberrations and oligodendrocyte generation in chronic amyloidosis in mice and men. Glia. 2013; 61: 273–286.
[32] Desai MK, Mastrangelo MA, Ryan DA, Sudol KL, Narrow WC, Bowers WJ. Early oligodendrocyte/myelin pathology in Alzheimer's disease mice constitutes a novel therapeutic target. The American Journal of Pathology. 2010; 177: 1422–1435.
[33] Horiuchi M, Maezawa I, Itoh A, Wakayama K, Jin L, Itoh T, *et al*. Amyloid β1-42 oligomer inhibits myelin sheet formation in vitro. Neurobiology of Aging. 2012; 33: 499–509.
[34] Nasrabady SE, Rizvi B, Goldman JE, Brickman AM. White matter changes in Alzheimer's disease: a focus on myelin and oligodendrocytes. Acta Neuropathologica Communications. 2018; 6: 22.
[35] Desai MK, Guercio BJ, Narrow WC, Bowers WJ. An Alzheimer's disease-relevant presenilin-1 mutation augments amyloid-beta-induced oligodendrocyte dysfunction. Glia. 2011; 59: 627–640.
[36] Mitew S, Kirkcaldie MTK, Halliday GM, Shepherd CE, Vickers JC, Dickson TC. Focal demyelination in Alzheimer's disease and transgenic mouse models. Acta Neuropathologica. 2010; 119: 567–577.
[37] Feng W, Zhang Y, Sun P, Xiao M. Acquired immunity and Alzheimer's disease. Journal of Biomedical Research. 2022. (online ahead of print)
[38] Singhrao SK, Neal JW, Piddlesden SJ, Newman GR. New immunocytochemical evidence for a neuronal/oligodendroglial origin for corpora amylacea. Neuropathology and Applied Neurobiology. 1994; 20: 66–73.
[39] Povala G, Bellaver B, De Bastiani MA, Brum WS, Ferreira PCL, Bieger A, *et al*. Soluble amyloid-beta isoforms predict downstream Alzheimer's disease pathology. Cell & Bioscience. 2021; 11: 204.
[40] Yang H, Jiang L, Zhang Y, Liang X, Tang J, He Q, *et al*. Anti-LINGO-1 antibody treatment alleviates cognitive deficits and promotes maturation of oligodendrocytes in the hippocampus of APP/PS1 mice. The Journal of Comparative Neurology. 2022; 530: 1606–1621.
[41] Lang J, Maeda Y, Bannerman P, Xu J, Horiuchi M, Pleasure D, *et al*. Adenomatous polyposis coli regulates oligodendroglial development. The Journal of Neuroscience. 2013; 33: 3113–3130.
[42] Sarkar S. Neurofibrillary tangles mediated human neuronal tauopathies: insights from fly models. Journal of Genetics. 2018; 97: 783–793.
[43] Zhang M, Wang X, Jiang F, Wang W, Vincent I, Bu B. Mitotic epitopes are incorporated into age-dependent neurofibrillary tangles in Niemann-Pick disease type C. Brain Pathology. 2010; 20: 367–377.
[44] Ferrer I, Gomez-Isla T, Puig B, Freixes M, Ribé E, Dalfó E, *et al*. Current advances on different kinases involved in tau phosphorylation, and implications in Alzheimer's disease and tauopathies. Current Alzheimer Research. 2005; 2: 3–18.
[45] Götz J, Tolnay M, Barmettler R, Chen F, Probst A, Nitsch RM. Oligodendroglial tau filament formation in transgenic mice expressing G272V tau. The European Journal of Neuroscience. 2001; 13: 2131–2140.
[46] Nishimura M, Tomimoto H, Suenaga T, Namba Y, Ikeda K, Akiguchi I, *et al*. Immunocytochemical characterization of glial fibrillary tangles in Alzheimer's disease brain. The American Journal of Pathology. 1995; 146: 1052–1058.
[47] Papuć E, Rejdak K. The role of myelin damage in Alzheimer's disease pathology. Archives of Medical Science. 2018; 16: 345–351.
[48] Cai Z, Xiao M. Oligodendrocytes and Alzheimer's disease. The International Journal of Neuroscience. 2016; 126: 97–104.
[49] Jhelum P, Santos-Nogueira E, Teo W, Haumont A, Lenoël I, Stys PK, *et al*. Ferroptosis Mediates Cuprizone-Induced Loss of Oligodendrocytes and Demyelination. The Journal of Neuroscience. 2020; 40: 9327–9341.
[50] Friedrich I, Reimann K, Jankuhn S, Kirilina E, Stieler J, Sonntag M, *et al*. Cell specific quantitative iron mapping on brain slices by immuno-μPIXE in healthy elderly and Parkinson's disease. Acta Neuropathologica Communications. 2021; 9: 47.
[51] Wang Z, Yuan L, Li W, Li J. Ferroptosis in Parkinson's disease:

glia-neuron crosstalk. Trends in Molecular Medicine. 2022; 28: 258–269.
[52] Mukherjee C, Kling T, Russo B, Miebach K, Kess E, Schifferer M, *et al*. Oligodendrocytes Provide Antioxidant Defense Function for Neurons by Secreting Ferritin Heavy Chain. Cell Metabolism. 2020; 32: 259–272.e10.
[53] Baldacchino K, Peveler WJ, Lemgruber L, Smith RS, Scharler C, Hayden L, *et al*. Myelinated axons are the primary target of hemin-mediated oxidative damage in a model of the central nervous system. Experimental Neurology. 2022; 354: 114113.
[54] Wyss-Coray T, Rogers J. Inflammation in Alzheimer disease-a brief review of the basic science and clinical literature. Cold Spring Harbor Perspectives in Medicine. 2012; 2: a006346.
[55] Kenigsbuch M, Bost P, Halevi S, Chang Y, Chen S, Ma Q, *et al*. A shared disease-associated oligodendrocyte signature among multiple CNS pathologies. Nature Neuroscience. 2022; 25: 876–886.
[56] Oakley H, Cole SL, Logan S, Maus E, Shao P, Craft J, *et al*. Intraneuronal beta-amyloid aggregates, neurodegeneration, and neuron loss in transgenic mice with five familial Alzheimer's disease mutations: potential factors in amyloid plaque formation. The Journal of Neuroscience. 2006; 26: 10129–10140.
[57] Keren-Shaul H, Spinrad A, Weiner A, Matcovitch-Natan O, Dvir-Szternfeld R, Ulland TK, *et al*. A Unique Microglia Type Associated with Restricting Development of Alzheimer's Disease. Cell. 2017; 169: 1276–1290.e17.
[58] Habib N, McCabe C, Medina S, Varshavsky M, Kitsberg D, Dvir-Szternfeld R, *et al*. Disease-associated astrocytes in Alzheimer's disease and aging. Nature Neuroscience. 2020; 23: 701–706.
[59] Venegas C, Heneka MT. Danger-associated molecular patterns in Alzheimer's disease. Journal of Leukocyte Biology. 2017; 101: 87–98.
[60] Chen W, Lu A, Craessaerts K, Pavie B, Sala Frigerio C, Corthout N, *et al*. Spatial Transcriptomics and in Situ Sequencing to Study Alzheimer's Disease. Cell. 2020; 182: 976–991.e19.
[61] Lee S, Meilandt WJ, Xie L, Gandham VD, Ngu H, Barck KH, *et al*. Trem2 restrains the enhancement of tau accumulation and neurodegeneration by β-amyloid pathology. Neuron. 2021; 109: 1283–1301.e6.
[62] Deczkowska A, Matcovitch-Natan O, Tsitsou-Kampeli A, Ben-Hamo S, Dvir-Szternfeld R, Spinrad A, *et al*. Mef2C restrains microglial inflammatory response and is lost in brain ageing in an IFN-I-dependent manner. Nature Communications. 2017; 8: 717.
[63] Ji J, Qian L, Zhu Y, Wu Y, Guo J, Ma G, *et al*. Serpina3c protects against high-fat diet-induced pancreatic dysfunction through the JNK-related pathway. Cellular Signalling. 2020; 75: 109745.
[64] Haile Y, Carmine-Simmen K, Olechowski C, Kerr B, Bleackley RC, Giuliani F. Granzyme B-inhibitor serpina3n induces neuroprotection in vitro and in vivo. Journal of Neuroinflammation. 2015; 12: 157.
[65] Zhou Y, Song WM, Andhey PS, Swain A, Levy T, Miller KR, *et al*. Human and mouse single-nucleus transcriptomics reveal TREM2-dependent and TREM2-independent cellular responses in Alzheimer's disease [published correction appears in Nature Medicine. 2020; 26: 981]. Nature Medicine. 2020; 26: 131–142.
[66] Falcão AM, van Bruggen D, Marques S, Meijer M, Jäkel S, Agirre E, *et al*. Disease-specific oligodendrocyte lineage cells arise in multiple sclerosis. Nature Medicine. 2018; 24: 1837–1844.
[67] Zhang P, Kishimoto Y, Grammatikakis I, Gottimukkala K, Cutler RG, Zhang S, *et al*. Senolytic therapy alleviates Aβ-associated oligodendrocyte progenitor cell senescence and cognitive deficits in an Alzheimer's disease model. Nature Neuroscience. 2019; 22: 719–728.
[68] Masters CL, Bateman R, Blennow K, Rowe CC, Sperling RA, Cummings JL. Alzheimer's disease. Nature Reviews Disease Primers. 2015; 1: 15056.
[69] Hashimoto R, Hori K, Owa T, Miyashita S, Dewa K, Masuyama N, *et al*. Origins of oligodendrocytes in the cerebellum, whose development is controlled by the transcription factor, Sox9. Mechanisms of Development. 2016; 140: 25–40.
[70] Pandey S, Shen K, Lee S, Shen YA, Wang Y, Otero-García M, *et al*. Disease-associated oligodendrocyte responses across neurodegenerative diseases. Cell Reports. 2022; 40: 111189.