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► **To cite this version:**

Woojin Kim, María Cecilia Angulo. Unraveling the Role of Oligodendrocytes and Myelin in Pain. Journal of Neurochemistry, 2024, 10.1111/jnc.16206 . inserm-04734781

HAL Id: inserm-04734781

<https://inserm.hal.science/inserm-04734781v1>

Submitted on 14 Oct 2024

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REVIEW

Special Issue: Myelin

Unraveling the role of oligodendrocytes and myelin in pain

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Funding information

ANR CoLD, Grant/Award Number: ANR-20-CE16-0001-01; ANR Myelex, Grant/Award Number: ANR-21-CE37-0020-01; Fondation pour la Recherche Médicale, Grant/Award Number: EQU202103012626; National Research Foundation of Korea (NRF), Grant/Award Number: 2020R1A5A2019413 and RS-2023-00258816

Abstract

Oligodendrocytes, the myelin-producing cells in the central nervous system (CNS), are crucial for rapid action potential conduction and neuronal communication. While extensively studied for their roles in neuronal support and axonal insulation, their involvement in pain modulation is an emerging research area. This review explores the interplay between oligodendrocytes, myelination, and pain, focusing on neuropathic pain following peripheral nerve injury, spinal cord injury (SCI), chemotherapy, and HIV infection. Studies indicate that a decrease in oligodendrocytes and increased cytokine production by oligodendroglia in response to injury can induce or exacerbate pain. An increase in endogenous oligodendrocyte precursor cells (OPCs) may be a compensatory response to repair damaged oligodendrocytes. Exogenous OPC transplantation shows promise in alleviating SCI-induced neuropathic pain and enhancing remyelination. Additionally, oligodendrocyte apoptosis in brain regions such as the medial prefrontal cortex is linked to opioid-induced hyperalgesia, highlighting their role in central pain mechanisms. Chemotherapeutic agents disrupt oligodendrocyte differentiation, leading to persistent pain, while HIV-associated neuropathy involves up-regulation of oligodendrocyte lineage cell markers. These findings underscore the multifaceted roles of oligodendrocytes in pain pathways, suggesting that targeting myelination processes could offer new therapeutic strategies for chronic pain management. Further research should elucidate the underlying molecular mechanisms to develop effective pain treatments.

KEYWORDS

central nervous system, myelin, oligodendrocyte precursor cells, oligodendrocytes, pain

1 | INTRODUCTION

Oligodendrocytes, the myelin-producing glial cells in the central nervous system (CNS), play a crucial role in facilitating the rapid

conduction of action potentials along axons, thereby enabling efficient neuronal communication. As the principal architects of the myelin sheath, oligodendrocytes wrap axons in layers of lipid-rich membrane, which is essential for maintaining the integrity of neural

Abbreviations: CCI, chronic constriction injury; CNPase, cyclic nucleotide 3'-phosphodiesterase; MAG, myelin-associated glycoprotein; MBP, myelin basic protein; NG2, neural/glia antigen 2; OPC, oligodendrocyte precursor cells; PLP, myelin proteolipid protein; SCI, spinal cord injury.

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circuits and ensuring the proper functioning of the nervous system (Khelifaoui et al., 2024). The process of myelination not only enhances signal transmission speed but also contributes to the metabolic support of neurons, highlighting the multifaceted roles of oligodendrocytes in CNS health and disease (Benamer et al., 2020; Franklin & Ffrench-Constant, 2017; Moore et al., 2020; Saab & Nave, 2017). Pain, a complex sensory and emotional experience, serves as a critical biological warning system that signals harm or potential damage to the body (Raja et al., 2020). Acute pain typically acts as a protective mechanism, prompting avoidance behaviors and facilitating healing. In contrast, chronic pain, which persists beyond the normal healing time of an injury, reflects a malfunctioning of the nervous system and represents a substantial therapeutic challenge. The chronicity of pain suggests alterations not only at the level of peripheral nociceptors but also within the CNS, involving complex interactions between neurons and glial cells (Ji et al., 2013; Lonser et al., 2020; Waxman et al., 2020). However, while the roles of neurons and other glial cell types in pain are recognized, the involvement of oligodendrocytes and myelin in pain modulation is still limited compared to their established functions in neuronal support and axonal insulation and conduction (Borghi et al., 2019).

The role of oligodendrocytes in pain begins to emerge in the context of neuropathic pain, which arises from a lesion or disease affecting the somatosensory system. Neuropathic pain is often associated with oligodendrocyte loss or demyelination, the pathological loss of the myelin sheath surrounding neuronal fibers (Gritsch et al., 2014; Zarpelon et al., 2016). Such demyelination may disrupt normal sensory processing and can lead to aberrant signal transmission. Clinically, this dysregulation of sensory signals can manifest as hyperalgesia—an increased sensitivity to painful stimuli—and allodynia, the perception of pain in response to normally non-painful stimuli. The regeneration of myelin, or remyelination, represents a critical repair process that has been shown to influence pain perception, suggesting that promoting remyelination could be a promising therapeutic strategy for managing neuropathic pain (Borghi et al., 2019; Duffy et al., 2018).

Recent research has begun to unravel the intricate relationship between myelination processes and pain perception. Alterations in myelin structure and oligodendrocyte function may contribute to the pathophysiology of various chronic pain conditions. For instance, animal models have demonstrated that targeted manipulation of oligodendrocyte lineage cells can alter pain behaviors, implicating myelin dynamics in the modulation of pain pathways (Tao et al., 2013; Yang et al., 2018).

In this article, we aim to explore the complex relationship between oligodendrocytes, myelination, and pain. We will review the current understanding of the roles of oligodendrocytes in the CNS, the biological significance of myelination, and the impact of myelin dynamics on pain perception and chronic pain. Furthermore, we will discuss potential mechanisms underlying these relationships and consider future research directions in this field, highlighting

the critical importance of understanding myelin biology in developing effective treatments for chronic pain.

2 | BIBLIOGRAPHIC APPROACH

A systematic search was performed for all studies investigating the impact of pain, oligodendrocytes, and myelination, utilizing PubMed and Google Scholar databases as well as the MEDLINE records of the National Library of Medicine up to January 2024 (Figure 1). Keywords used for the search included 'pain', 'neuropathic pain', 'oligodendrocyte', and 'myelin'. The initial query yielded 1081 articles. After removing duplicates, bibliographic entries, study protocols, clinical trials, and non-English studies, 501 articles remained for abstract screening. Studies lacking quantifiable pain measurement data, or evidence of changes in oligodendrocytes and myelination within the central nervous system were further excluded. This process culminated in the inclusion of 12 studies meeting the criteria for comprehensive analysis (Figure 1). This limited number of articles shows that the involvement of oligodendrocytes in pain is still largely underexplored and warrants further investigation.

3 | OLIGODENDROCYTES IN PAIN

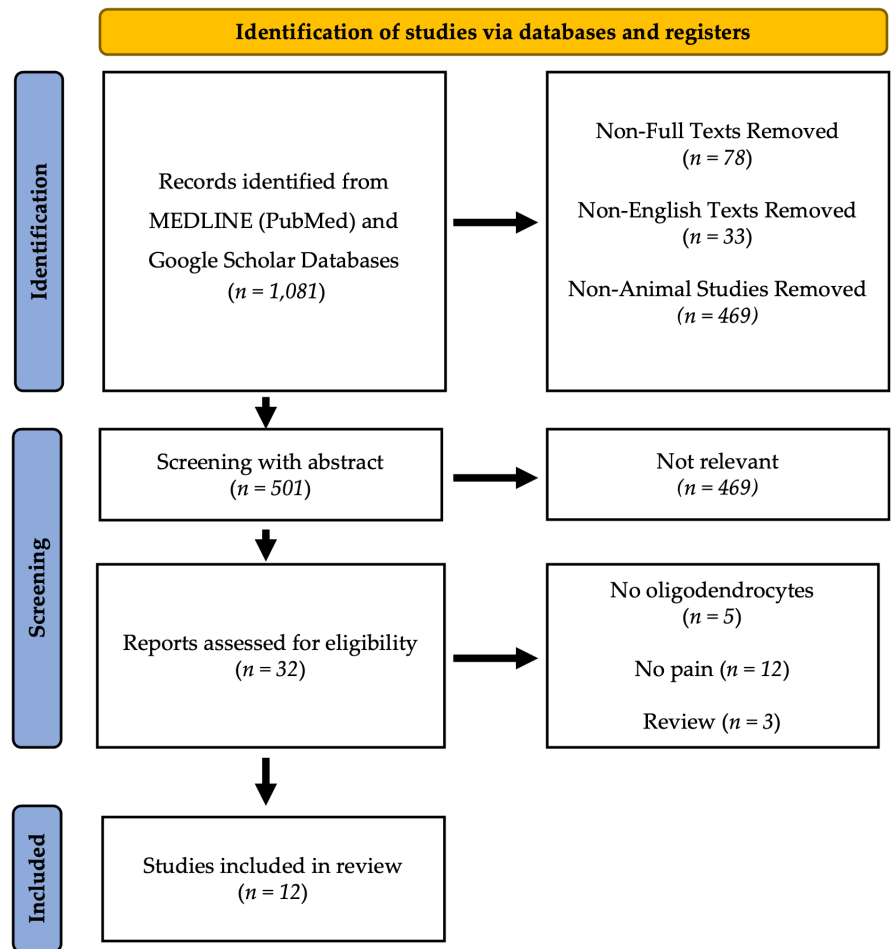
3.1 | The role of oligodendrocytes and pain in the spinal cord

In the nervous system, the spinal cord plays a pivotal role in pain processing. It functions as the primary conduit for sensory information traveling from the body to the brain, where pain is perceived (Colloca et al., 2017; D'Mello & Dickenson, 2008). When potentially harmful stimuli are detected, sensory neurons convey signals to the dorsal horn of the spinal cord. Here, these signals undergo an initial processing and modulation, which includes the amplification or dampening of the pain signals before they ascend to the brain by the activities of both excitatory and inhibitory interneurons present in the spinal cord (Helms & Johnson, 2003).

The spinal cord also houses glial cells such as astrocytes and microglia, which significantly influence pain processing (Jessen, 2004). Astrocytes, the most abundant type of glial cells in the CNS, contribute to the amplification of pain signals by releasing cytokines and chemokines in response to injury or inflammation (Ji et al., 2013). Microglia, the resident immune cells of the CNS, are activated in response to similar stimuli. Upon activation, microglia release proinflammatory factors that can potentiate synaptic transmission in pain pathways, leading to heightened pain sensitivity, a phenomenon known as central sensitization (Inoue & Tsuda, 2009; Lee & Kim, 2020). While the roles of astrocytes and microglia in the spinal cord are relatively well documented, the specific contributions of oligodendrocytes and the myelination process in modulating pain are less understood. This section outlines the current understanding



FIGURE 1 Flowchart of the article-inclusive protocol. Identification through searches of MEDLINE (PubMed) and Google Scholar yielded 1081 articles, which were screened by abstract and full-text examinations. Finally, our review ultimately included 12 articles that explored the impact of oligodendrocytes and myelination on pain in rodent models.



of the functions of oligodendrocytes in pain within the spinal cord (Figure 2).

3.1.1 | Peripheral nerve injury and spinal cord oligodendrocyte lineage cells

Diverse animal models of peripheral nerve injury are used to clarify the mechanism of pain and to find novel drugs that can treat or manage peripheral neuropathies and injuries (Dowdall et al., 2005). These models can help to understand the mechanisms underlying pain and the interaction between neurons and other cell types in the CNS. Animal models of sciatic nerve injury have been used to assess the effect of spinal cord oligodendrocytes and myelination on pain. Following the nerve injury, injury-related signals are conveyed from the lesioned axons and non-neuronal cells retrogradely to their own injured neuronal cell body. Numerous factors in the spinal cord such as neurotrophic factors and neuropeptides have been identified to be up-regulated after nerve injury (Devor & Wall, 1978; Liu & Wang, 2020) and post-SCI interactions between neuronal and glial cells were shown to create maladaptive synaptic circuits and activate intracellular signaling events that permanently contribute to enhanced neuropathic pain (Gwak et al., 2017).

Echeverry et al. (2008) observed a significant increase in the co-localization of NG2 (neural/glial antigen 2; a marker for oligodendrocyte precursor cells (OPCs)) and BrdU⁺ (bromodeoxyuridine; a proliferation marker) cells on the spinal cord ipsilateral, but not contralateral to the sciatic nerve injury in rats. This proliferation, evident from day 3 to day 14 post-injury, correlates with an increased sensitivity to mechanical and heat pain, suggesting that OPC proliferation may be a reactive mechanism in response to injury. In this study, changes in the myelinating oligodendrocyte population were not shown. However, a previous study reported that following the decline of co-localized NG2 and BrdU cells, an increase in the number of oligodendrocytes is observed in the spinal cord (Horky et al., 2006), suggesting that the increase of NG2 cells may be to compensate for the loss of mature oligodendrocytes caused by peripheral injury. Although in the study of Echeverry et al. most of the proliferated glial cells were microglia (Iba-1), NG2-positive cells were also prevalent, indicating that injury to the peripheral nerve stimulates glial cells and may contribute to healing. The number of NG2 cells decreased compared to Iba-1 cells on day 29, indicating that microglia are more persistently active in rats with common sciatic nerve transections. Notably, they reported that following peripheral nerve injury, spinal neuronal cell death was not affected as NeuN and BrdU co-localization did not change, supporting previous observations that, compared to the direct injury of the spinal cord,

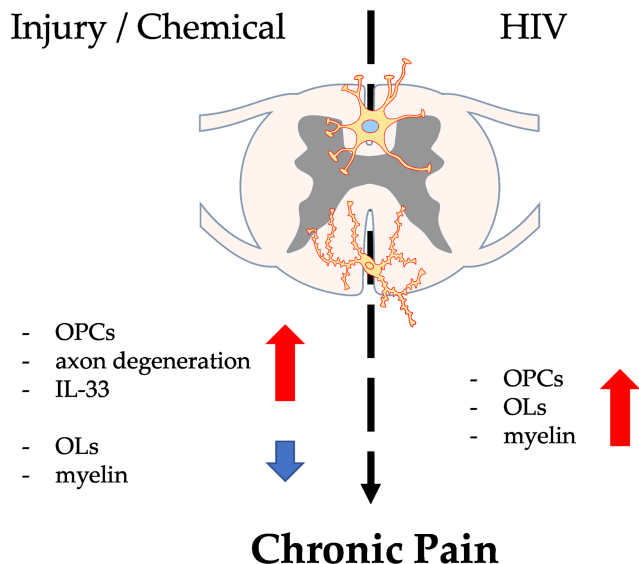


FIGURE 2 The role of spinal oligodendrocytes (OLs) in chronic pain. Chronic pain is induced by injury (e.g., peripheral nerve or spinal cord injury), chemicals (e.g., paclitaxel or diphtheria toxin), or human immunodeficiency virus (HIV). Both the injury and chemical-induced pain models decrease OLs and myelin in the spinal cord, whereas HIV-induced pain increases oligodendrocyte precursor cells (OPCs), OLs, and myelin. An increase in interleukin-33 (IL-33) and spinothalamic tract axonal degeneration are also associated with pain.

peripheral injury induces almost no cell loss but proliferative responses of glial cells (Gordh et al., 2006).

Zarpelon et al. (2016) reported that oligodendrocyte lineage cells marked by immunostainings against Olig2, a transcription factor expressed by the entire lineage, are major producers of interleukin (IL)-33 in the spinal cord following chronic constriction injury (CCI) of the sciatic nerve. IL-33 is a multifunctional IL-1 superfamily known for its various roles (Haraldsen et al., 2009). Zarpelon et al. linked oligodendroglia to the inflammatory processes associated with neuropathic pain and highlighted a novel aspect of glial involvement in pain pathways. They discovered via immunofluorescence assay, that in mice experiencing neuropathic pain, IL-33 is produced by oligodendroglia in the spinal cord, rather than by neurons, microglia, or astrocytes. A systematic use of multiple markers for oligodendrocyte lineage cells at different developmental stages would have been valuable in this study for effectively differentiating IL-33 expression in OPCs and mature oligodendrocytes. Nevertheless, a subsequent study by Sung et al. (2019) reported that this interleukin is expressed in both the nuclei of CC1-positive oligodendrocytes and NG2-positive OPCs under healthy conditions. Although this study focused on the brain, it further stated that IL-33 was expressed at higher levels during the OPC stage. Using IL-33 knockout mice, they demonstrated a reduced differentiation of OPCs into mature oligodendrocytes, along with a down-regulation of myelin-related genes such as MBP and PLP and abnormalities in the myelin structure. In addition, IL-33 has also been reported to be released from damaged post-mitotic oligodendrocytes, acting as an alarmin and impacting astrocytes and

microglia immediately after spinal cord injury (Gadani et al., 2015). Therefore, OPCs and oligodendrocytes appear to be the major source of IL-33 in both healthy conditions and after injury, making IL-33 from oligodendroglia a potential candidate for playing a role in pain. Indeed, IL-33 activates ST2 receptors on spinal microglia and astrocytes (Yasuoka et al., 2011), leading to neuropathic pain through signaling pathways like phosphatidylinositol 3-kinase (Xu et al., 2007). Intrathecal injection of IL-33 increased nociceptive behaviors in naïve mice, and injections of inhibitors of microglia and astrocytes (i.e., minocycline and fluorocitrate, respectively) significantly attenuated the pain (Zarpelon et al., 2016). This suggests that IL-33 released from oligodendrocyte lineage cells affects microglia and astrocytes, which express ST2 receptors, to further release pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF- α) and interleukin 1-beta (IL-1 β), thereby enhancing neuropathic pain. TNF- α (Leung & Cahill, 2010) and IL-1 β (Rutkowski & DeLeo, 2002) are known to play an important role in pain by initiating and enhancing the pain pathways. Overall, these findings point to a previously unappreciated role of IL-33 from oligodendrocyte lineage cells in mediating pain through a subsequent activation of microglia and astrocytes.

3.1.2 | Spinal cord injury and OPC transplantation

Spinal cord injury (SCI) represents a significant clinical challenge due to its complex pathophysiology and the profound impact it has on patient quality of life. SCI often results in a constellation of motor, sensory, and autonomic deficits, with neuropathic pain being one of the most debilitating and persistent symptoms experienced by patients (Zheng & Tuszynski, 2023). Neuropathic pain following SCI is attributed to both primary mechanical damage and secondary biological processes that alter neural function, at and beyond the injury site. The etiology of neuropathic pain in SCI is multifaceted, involving inflammatory responses, glial activation, neuronal excitability alterations, and changes in neurotransmitter levels (Dib-Hajj et al., 2010; McDonald & Sadowsky, 2002). Additionally, damage to the myelin sheath, along with neuronal and oligodendrocyte death, may lead to the abnormal signal transduction associated with pain. Moreover, spinal cord injuries are reported to result in the death of about 50% of the astrocytes and oligodendrocytes in the intact white matter near the damaged site (Grossman et al., 2001). Therapeutic approaches for treating neuropathic pain related to spinal cord injuries are continually developing, focusing on neuroprotection, preventing neurodegeneration, and managing neuroinflammatory pathways (Baroncini et al., 2021). Although there have been significant strides in understanding the pathophysiological factors that contribute to neuropathic pain, finding effective clinical treatments remains challenging, emphasizing the need for continued research into new therapies that can alleviate pain and promote neural recovery. OPC transplantation is a strategy under investigation for treating SCI and associated chronic neuropathic pain (Chanoumidou et al., 2020; Xu et al., 2022). However, its effect on pain has not

been clearly assessed and could be useful to investigate the biology of transplanted human oligodendroglia (Mozafari et al., 2020) in this disorder as well as its therapeutic potential. Studies conducted by Tao et al. (2013), and Yang et al. (2018) demonstrated that the transplantation of OPCs post-injury not only alleviates pain but also enhances myelination in animal models of SCI.

Tao et al. (2013) employed rat contusion injury models to demonstrate that neuropathic pain began as early as day 7 post-SCI and persisted throughout a 56-day observation period. The transplantation of mouse embryonic stem cell derived OPCs into the spinal cord on day 29 post-SCI significantly alleviated chronic neuropathic pain up to day 56 post-injury. Among the transplanted OPCs, 10% survived for 4 weeks in the injured spinal cord, and half of these surviving OPCs differentiated into mature oligodendrocytes. Only a small fraction of the transplanted cells differentiated into astrocytes (4.4%). Furthermore, the ratio of the myelinated white matter area to the total spinal cord area significantly increased following OPC transplantation. This therapeutic effect is partly attributed to the restoration of neuregulin-1 and its receptor, ErbB4 protein, which are known to be important for myelination. The levels of these proteins decreased after contusion injury but increased following OPC transplantation. The neuregulin-1 (NRG1) family encompasses over 15 different proteins, both membrane-bound and freely circulating (Falls, 2003). These NRG1 variants function by binding to ErbB receptors, which are part of the larger *epidermal growth factor* (EGF) receptor superfamily (Citri et al., 2003). Specifically, NRG1 interacts with either ErbB3, which lacks an active kinase domain, or ErbB4, which includes one. Both of these receptors can form complexes with ErbB2, which itself does not bind NRG1 directly but does possess an active kinase domain (Burgess et al., 2003; Nave & Salzer, 2006). Oligodendrocytes are known to express all three ErbB receptors in a developmentally regulated manner (Canoll et al., 1996). A study conducted by Lundgaard et al. (2013) demonstrated that neuregulin can accelerate and enhance myelination by shifting the myelination process from a program independent of neuronal activity (Rosenberg et al., 2008) to one that depends on the activation of acidic *N*-methyl-D-aspartate (NMDA) receptors. Additionally, Tao et al. (2013) showed that disrupting neuregulin-1 signaling through intrathecal injections of its interfering ribonucleic acid (RNA) reverses the benefits of OPC transplantation, highlighting the critical role of this pathway in the repair process.

Yang et al. (2018) further investigated OPC transplantation using the Basso, Beattie, and Bresnahan (BBB) scoring system to assess motor and sensory recovery in rats with SCI. Seven days after surgery, 5 μ L cell suspensions were transplanted into each rat at two different sites: the rostral and the tail end of the injury. Mechanical pain was assessed on days 1, 3, 7, 14, 21, and 28 following the surgery. The transplantation significantly alleviated mechanical allodynia starting from day 7 and lasting until day 28. A notable aspect of the research involves studying microRNA (miRNA) expression post-OPC transplantation. A miRNA assay identified 45 differentially expressed miRNAs in the spinal cords of transplanted rats compared to controls. Among these, miR-375 and miR-1, known to primarily

inhibit cell proliferation and apoptosis through the regulation of transcription and translation, were significantly up-regulated (Ding et al., 2010; Xu et al., 2017). Conversely, miR-363, miR-449a, and miR-3074, which are known to inhibit cell proliferation and neuronal differentiation through the regulation of transcription, were down-regulated (Yao et al., 2018). Bioinformatics analysis suggests that these miRNAs regulated by OPC transplantation may modulate cell proliferation and apoptosis, playing a role in neuronal differentiation and the healing process post-SCI.

The clinical application of OPC transplantation is advancing, although it remains in the experimental and trial stages. Innovations such as the use of human-induced pluripotent stem cells (hiPSCs) to generate OPCs have shown potential for functional recovery after spinal cord injuries, particularly when these cells are combined with human umbilical vein endothelial cells (Li et al., 2024). This research is propelling the field towards potential clinical trials and applications in treating conditions like chronic progressive multiple sclerosis and other CNS disorders. In the context of neuropathic pain and SCI, transplantation of OPCs has been shown to mitigate pain and foster remyelination (Tao et al., 2013), partly through the restoration of key pathways such as neuregulin-1 and ErbB4. Advancements in understanding the changes in miRNA expression following OPC transplantation also provide a deeper understanding of the molecular mechanisms at play and have identified new molecular targets for enhancing therapeutic strategies (Yang et al., 2018). Emerging research points to improved cell survival rates, integration into host tissues, and functional outcomes. This is facilitated by advanced delivery techniques and the exploration of combinatorial approaches involving both OPC transplantation and pharmacological treatments (Nori et al., 2017). Furthermore, manipulating the spinal cord's extracellular matrix to create a conducive environment for cell integration is an exciting avenue that may improve therapeutic outcomes (Guo et al., 2021).

3.1.3 | Chemotherapy-induced neuropathic pain

The contribution of oligodendrocytes to the pathogenesis and persistence of chemotherapy-induced neuropathic pain remains obscure. Research by Lee and Hur (2020) has shown that agents based on taxol, such as paclitaxel, which specifically target microtubules, decrease the length of oligodendrocyte branches as well as the complexity of their processes. Furthermore, it was also reported that taxol can significantly inhibit the differentiation of oligodendrocytes even at concentrations that do not significantly affect the viability of neuronal cells (Xie et al., 2016). These observations suggest that these agents disrupt oligodendrocyte maturation and myelin formation and maintenance. In the study conducted by Yuan et al. (2014), an increase in the G-ratio, indicative of myelin sheath thinning—which is determined by the ratio of the axonal diameter to the total outer diameter of the nerve fiber—was observed in the spinal cords of rats following the administration of 8 mg/kg paclitaxel. This change in the G-ratio was associated with prolonged mechanical and

thermal hyperalgesia extending from the 7 to the 28 days following treatment. After the fourth day of injection of paclitaxel, histological examination of the sciatic nerves, dorsal root ganglia (DRG), and the dorsal horn of the spinal cord revealed axonal irregularities and signs of myelin degradation. However, by 56 days, when pain persisted, the change in the G-ratio was no longer statistically significant and signs of remyelination appeared. Notably, in the spinal dorsal horn, damage was exclusively observed in the myelin sheath without any detectable mitochondrial abnormalities. These findings provide further evidence for the hypothesis that structural myelin alterations could contribute to the modulation of pain perception, highlighting the critical role of oligodendrocytes in maintaining the integrity of neuronal networks.

3.1.4 | HIV-gp120

Data from the Joint United Nations Programme on human immunodeficiency virus (HIV) and AIDS (UNAIDS) showed that in 2016 approximately 36.7 million people worldwide were living with HIV (Nygren-Krug, 2018). HIV-associated sensory neuropathy is a common and potentially disabling complication seen in HIV patients (Aziz-Donnelly & Harrison, 2017). Clinical manifestations of HIV-induced sensory neuropathy vary, but often present as distal symmetric polyneuropathy often accompanied by autonomic neuropathy (Iyagba & Onwuchekwa, 2016).

Despite its prevalence, the molecular and cellular mechanisms underpinning neuropathic pain in this context remain insufficiently elucidated. An investigation conducted by Shi et al. (2016) explored the involvement of oligodendrocytes in the pathogenesis of neuropathic pain associated with HIV. This study specifically analyzed the expression levels of oligodendrocyte lineage markers including NG2 and platelet-derived growth factor receptor alpha (PDGFR α) for OPCs, Olig2 for the oligodendrocyte lineage, and PLP alongside MBP as indicators of myelination status. The analysis was performed on postmortem spinal cord samples from human subjects having HIV and pain, as well as in a murine model induced by the intrathecal administration of the HIV envelope protein gp120. In mice, the pain was assessed by measuring the changes in the threshold to mechanical stimuli. In human postmortem tissue, PLP significantly decreased, whereas in the murine spinal cord, PLP increased along with the other markers. According to the literature, PLP plays an important role in maintaining myelin, and myelin lacking PLP is shown to be more prone to degeneration (Rosenbluth et al., 1996). However, it has also been suggested that PLP may have an important myelin-independent role in the CNS (Nave, 2010) and studies have shown that, except for minor ultrastructural abnormalities of myelin and reduced physical stability, PLP-null mutants develop normally and are long-lived (Rosenbluth et al., 2006). Although the discrepancy in PLP expression between species needs to be resolved, the results demonstrated significant up-regulation of NG2, PDGFR α , Olig2, and MBP in the spinal dorsal horn of both human subjects and murine models. In the mouse model, a significant increase in oligodendroglia

protein levels was observed soon after the gp120 injection and peaked between 2 and 3 hours. These changes in protein expression coincided with the pain behavior tests; pain was observable at 1 hour post-gp120 injection and fully developed between 2 and 5 hours. However, siRNA-mediated MBP knock-down approaches did not affect the pain behavior induced by gp120. Contrary to other studies, this study found that oligodendrocyte and myelin-related markers were significantly increased in both human and mouse spinal cords. The authors suggest that this increase represents an attempt to remyelinate axons following the damage caused by gp120 injection, but further investigation is required to clarify this point.

3.1.5 | Oligodendrocytes depletion induce pain

Gritsch et al. (2014) created a double transgenic mouse model (DTR^{fl/fl}; MOG-Cre^{+ve}) and specifically ablated oligodendrocytes by injecting diphtheria toxin (DTX). Shortly after DTX injection, mice developed cold and mechanical, but not heat, allodynia. In the spinal cord, the immunoreactivity for MBP remained unchanged and the count of unmyelinated axons did not rise significantly up to 24 days after DTX administration. However, MBP staining significantly declined by 42 days post-injection. Nevertheless, compared to the late changes in myelin, oligodendrocyte-related markers (i.e., mRNA expressions of *Plp* and *Mag*) showed significant decreases prior to the onset of sensory dysfunction. Although the number of Iba-1 positive microglia increased significantly at day 6 after DTX treatment, blocking microglial activation did not inhibit the development of pain induced by DTX treatment, suggesting that microgliosis is not involved in the pain induced by oligodendrocyte ablation. However, accumulation of amyloid precursor protein (APP), a protein that has been demonstrated to be a marker for acute axonal pathology as well as disruption of axonal transport (Vohra et al., 2010), showed a significant increase at day 6 post-DTX. Moreover, ablation of oligodendrocytes induced axonal degeneration in the spinothalamic tract, a key pathway for transmitting pain signals from the spinal cord to the brain (Steeds, 2009), suggesting that axonopathy is involved in the development of pain. However, this paper does not explore how oligodendrocyte depletion induces axonopathy, and no direct quantification of protein expression levels of MBP, PLP, or myelin-associated glycoprotein (MAG), or electron microscopy analyses were performed to examine potential early changes in myelination. Overall, Gritsch et al. suggest that the loss of oligodendrocytes, even without substantial demyelination, can trigger pain, underscoring the critical role of these cells in maintaining homeostasis and functional signaling in the spinal cord.

In line with these results, using cuprizone-induced demyelinated mice, Sen et al. (2020) reported that demyelination in some areas such as the cerebrum, hippocampus, basal ganglia, and diencephalon of the CNS is not related to pain. The cuprizone model is widely used for studying demyelinating diseases such as multiple sclerosis (MS), and serves as a valuable tool for research on myelination (Torkildsen et al., 2008). In the study of Sen et al., mechanical and thermal pain

were assessed from day 0 to day 36 in mice fed with 0.2% cuprizone mixed with chow for 37 days. In their study, myelination in the pain pathways of the CNS, such as the spinal cord dorsal horn, thalamus, and somatosensory cortex, was not affected. In the spinal cord, although oligodendrocytes did not change, astrocytes and microglia increased compared to the control. The absence of demyelination in these key pain pathways (Colloca et al., 2017) suggests that demyelination in other brain areas does not necessarily affect pain perception.

3.2 | The role of oligodendrocytes and pain in the brain

Emerging evidence suggests a complex involvement of oligodendrocytes and myelination in the modulation of pain in the brain. In this section, we aim to elucidate the function of oligodendrocytes and myelination in pain perception and modulation, drawing on findings from three recently published studies that explore these relationships within different contexts of pain (Figure 3).

Opioid-induced hyperalgesia (OIH) is a critical issue in chronic pain management, where prolonged opioid usage paradoxically leads to increased pain sensitivity (Roedel et al., 2016). A pivotal study

examining this topic investigated the function of oligodendrocytes in the prelimbic medial prefrontal cortex (PI-mPFC), a brain area implicated in pain regulation. This region is notable for its connections to various cortical regions involved in modulating pain, including the periaqueductal gray (PAG) and the ventral tegmental area (VTA) (Roedel et al., 2016). Additionally, the mPFC is known to have a high concentration of opioid receptors (Giacchino & Henriksen, 1996), and it is also established that oligodendrocytes express opioid receptors (Butt, 2006). This research demonstrated that oligodendrocyte apoptosis, detected by an increase in cleaved-caspase 3 and a reduction in myelin-related proteins such as MBP, PLP1, MOG, MAG, and myelin-associated oligodendrocytic basic protein (MOBP)—observed 6.5 h post-injection—plays a crucial role in OIH. Notably, preventive measures to inhibit oligodendrocyte apoptosis in the PI-mPFC effectively alleviated mechanical and thermal hyperalgesia triggered by fentanyl (Wang et al., 2022). Interestingly, while the OPC were unaffected by fentanyl—as indicated by stable NG2 expression levels—the decrease in MBP was initially observed at 6.5 h but fully recovered 12 h post-injection. These findings suggest that oligodendrocyte apoptosis rather than demyelination is directly associated with OIH-induced pain and highlight a new dimension of opioid pharmacodynamics, proposing that maintaining oligodendrocyte integrity could be essential in reducing opioid-related adverse effects (Figure 4).

Building on the importance of oligodendrocytes in pain modulation, another crucial pathway involved in oligodendrocytes dynamics is the Notch signaling pathway, particularly involving Notch receptor 1 in OPCs. This pathway plays a crucial role in oligodendrocytes formation and myelin regeneration (Wang et al., 1998, 2017) and its activation led to suppressed differentiation of OPCs in culture (Wang et al., 1998). In the dorsolateral prefrontal cortex (dl-PFC) after SCI, OPC differentiation was revealed by a decrease in OLIG2 and 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNPase) levels, as well as reduced MBP and PLP protein density, while notch1/NG2 cells significantly increased (Li et al., 2022). Based on these observations, Li et al. explored whether targeting the Notch signaling pathway can alleviate the hypomyelination caused by SCI in the dl-PFC. Targeting this pathway with DAPT, a gamma secretase inhibitor, showed promise in improving pain thresholds and significantly enhancing the number of OLIG2 and CNPase cells and the expression of MBP and PLP, although not to baseline levels. These changes appeared specific to oligodendrocytes, as no major alterations were observed in astrocytes and microglia, also known to modulate pain in the CNS. This specificity strengthens the link between SCI and oligodendrocyte changes in the brain during pain.

Expanding on the signaling pathways involved in pain modulation, a recent study by Chen et al. (2023) investigated the role of bone morphogenetic protein 7 (BMP7) in treating trigeminal neuralgia (TN), a condition marked by severe facial pain. The research employed an infraorbital nerve chronic-constriction injury model to induce TN in rats and manipulated BMP7 expression using adeno-associated viruses (AAV). Known also as osteogenic protein-1 (OP-1),

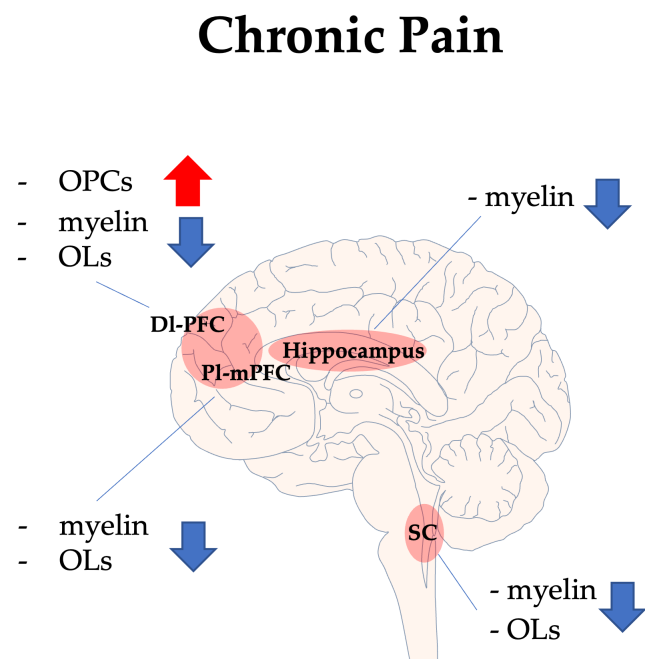


FIGURE 3 The changes in oligodendrocytes (OLs) and myelin in the brain in chronic pain. Surgery (e.g., peripheral nerve or spinal cord injury) or fentanyl-induced chronic pain in rodents. Spinal cord injury induced a decrease in myelin and OLs but an increase in oligodendrocyte precursor cells (OPCs) in the dorsolateral prefrontal cortex (DI-PFC). Fentanyl induced a decrease in myelin and OLs in the prelimbic medial prefrontal cortex (PI-mPFC). Trigeminal neuralgia induced a decrease in myelin and OLs in the subnucleus caudalis (SC). Finally, peripheral nerve injury induced a decrease in myelin in the hippocampus.

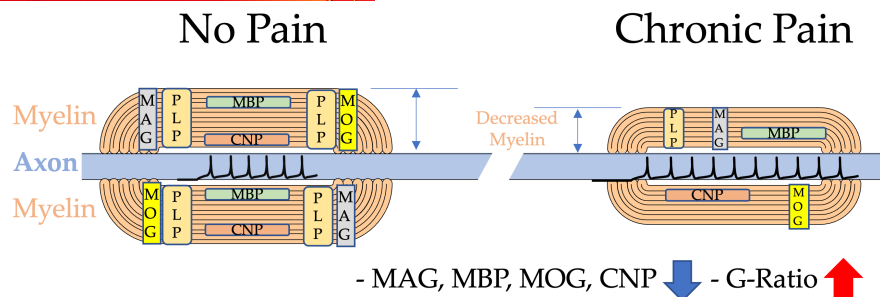


FIGURE 4 Changes in myelin-related proteins in chronic pain state. In the chronic pain state, transmembrane proteins such as myelin-associated glycoprotein (MAG), myelin oligodendrocyte glycoprotein (MOG), proteolipid protein (PLP), as well as the membrane-associated and cytoplasmic proteins myelin basic protein (MBP) and 2',3'-cyclic-nucleotide 3'-phosphodiesterase (CNP), all show a decrease. However, in HIV-induced pain, MBP is observed to increase, whereas PLP decreased. This reduction in myelin-related proteins correlates with an increase in the G-ratio, which indicates a thinner myelin sheath relative to the axon diameter, observed both in the spinal cord and brain axons.

BMP7 is part of the bone morphogenetic protein family within the transforming growth factor-beta (TGF- β) superfamily (Obradovic Wagner et al., 2010), which are cytokines recognized for their role in bone and cartilage formation. BMP7 operates by binding to specific cellular receptors, initiating a signal cascade that promotes the differentiation of progenitor cells into bone or cartilage-forming cells (Sakou, 1998).

It was previously noted that BMP7 up-regulation significantly increases oligodendrocyte numbers in vitro (Tsai et al., 2007) and stimulates oligodendrogenesis in rats with SCI (Park et al., 2013). Chen et al. (2023) examined alterations in myelination within the trigeminal spinal subnucleus caudalis (Vc) of CCI group rats. The Vc plays a crucial role in pain transmission from craniofacial tissues as it houses the second-order neurons (Bereiter et al., 2008). Previous research shows that nociceptive neurons in the Vc project to CNS regions like the periaqueductal gray (PAG), parabrachial nuclei (PBN), and various thalamic and hypothalamic areas (Saito et al., 2017). In Chen et al., mechanical pain was reported in rats from day 7 to day 28 post-surgery, with transmission electron microscopy revealing that some myelin sheaths were thin, loose, or even fractured in the CCI group, and the G-ratio indicated thinner, disproportionate myelin sheaths. A decrease in the mRNA levels of CNPase and BMP7 was observed from day 1 and persisted until day 28 post-CCI. Notably, although significant pain commenced on day seven, CNPase mRNA levels began declining on day 1, with protein expression changes following day 7. BMP7 shRNA treatment led to increased pain, oligodendrocyte apoptosis, and demyelination, as evidenced by reduced MBP levels. Conversely, AAV-BMP7 treatment enhanced mechanical thresholds and both the mRNA and protein levels of CNPase and MBP. These results suggest that BMP7 can alleviate pain behaviors, reduce oligodendrocyte apoptosis, and mitigate demyelination, effects likely mediated through the modulation of the STAT3 and NF- κ B/p65 signaling pathways crucial for cell survival. Although this study did not specify the targets within oligodendrocytes, it not only highlights the therapeutic potential of BMP7 but also deepens our understanding of the molecular dynamics involved in managing pain through myelin and oligodendrocyte modulation.

In another brain region, Zhu et al. (2024) focused on the relationship between chronic pain and memory impairment using an animal model of CCI in mice. CCI of the sciatic nerve induced myelin degradation in the hippocampus, resulting in both mechanical allodynia and memory deficits, as assessed by the Y maze test, open field test, and novel object recognition tests. Both the expression and the number of MBP significantly decreased, along with the myelin sheath thickness and the number of myelinated axons. The G-ratio significantly increased. However, intraperitoneal injection of clemastine (10 mg/kg/day for 3 weeks), known to promote remyelination in demyelinating injury models (Mei et al., 2016; Wang et al., 2018), failed to reverse the CCI-induced paw withdrawal threshold. Nonetheless, clemastine improved the memory impairment.

4 | OVERVIEW

Myelination, carried out by oligodendrocytes in the CNS, is critical for the efficient transmission of neural information. This review elucidates how the death of oligodendrocytes, demyelination, and dysmyelination, often resulting from diseases or injuries, disrupt signal transmission, leading to neuropathic pain conditions like hyperalgesia and allodynia (Table 1). By preventing oligodendrocyte apoptosis and restoring myelin integrity or promoting remyelination, as shown in the included studies, there is potential to decrease pain perception, highlighting the therapeutic value of enhancing oligodendrocytes and myelination in managing neuropathic pain.

This review addresses various models of pain, such as SCI (Tao et al., 2013) and peripheral nerve injury (Echeverry et al., 2008; Zarpelon et al., 2016), where the behavior of oligodendrocytes correlates with pain outcomes. In most of the included studies, with the exception of Shi et al. (2016), where pain was associated with an increase in oligodendrocyte markers, pain was related to a decrease in oligodendrocyte-related gene expression or cell density (Chen et al., 2023; Gritsch et al., 2014; Wang et al., 2022; Zhu et al., 2024) and an increase in OPCs (Echeverry et al., 2008; Li et al., 2022). This could be interpreted as a mechanism to repair



TABLE 1 Summary of studies on oligodendrocytes and myelin in chronic pain.

Author/publication year	Animal	Pain inducement method	Site	Assessed pain (duration)	Marker	Method	Oligodendrocytes & myelin-related results
Echeverry et al. (2008)	Male SD rats	Sciatic nerve injury	Spinal cord	Heat & Mechanical (D4–D14)	NG2/BrdU co-localization	IHC	Increased at D3 Peaked at D14 Reduced at D29
Tao et al. (2013)	Female Long-evans Rats	Contusion (10g, T9) SCI Model	Spinal cord	Mechanical (D7–D56)	Toluidine blue staining	TEM	OPC transplantation (i.t.) decrease pain & enhance remyelination
Yuan et al. (2014)	Male SD rats	Paclitaxel 8 mg/kg (i.p.)	Spinal cord	Heat & Mechanical (D7–D56)	Toluidine blue staining	TEM	G-ratio Increased at D7–D28 Reduced at D56
Gritsch et al. (2014)	MOG-Cre ^{+/ve} DTR ^{fl/fl}	DTX	Spinal cord	Cold & Mechanical (D6–D30)	MBP, Olig2, PLP, MAG, ASPA, APC	IHC, TEM, qRT-PCR	Decreased: PLP, MAG (D3 – D27) Increased: degenerated axons in the STT (D6 –)
Zarpelon et al. (2016)	BALB/c mice	Sciatic nerve—CCI	Spinal cord	Mechanical (D1–D24)	Olig2 / IL-33 co-localization	IHC	Olig2 ⁺ cells are the major IL-33 producer in the spinal cord (~82%) Increased: D3–D21
Shi et al. (2016)	Human postmortem tissue /C57BL/6 mice	HIV-gp120 7 μL of 15 ng/μL (i.t.; L5–L6)	Spinal cord	Mechanical (Acute: 2 h–4 h, Chronic: D1–D24)	NG2, PDGFR α , Olig2, MBP, PLP	Western blot	Human: increased: NG2, PDGFR α , Olig2, MBP decreased: PLP Mice: all increased (acute & chronic)
Yang et al. (2018)	Male SD Rats	Contusion (10g, T10) SCI Model	Spinal Cord	Mechanical (D1–D28)	miRNA microarray assay	GO ontology, KEGG	OPC transplantation decrease pain (D7 – D28) & induce changes in miRNA
Sen et al. (2020)	Male C57BL/6 Mice	0.2% cuprizone fed for 37 D	Brain & spinal cord	No pain (D0–D36)	Silver myelin intensity	Bright field microscopy	S1HL, TH, & Spinal Cord (DH); no significant demyelination
Wang et al. (2022)	Male SD Rats	Fentanyl (s.c., 60 μg, 15 min intervals, total 240 μg)	Pl-mPFC	Mechanical & Heat (6.5 h–D4)	MBP, PLP1, MOG, MAG, MOBP, NG2	LC-MS/MS, Western blot, IHC	Decreased: MBP, PLP1, MOG, MAG, MOBP Unchanged: NG2 Increased: Caspase3 ⁺ oligodendrocytes
Li et al. (2022)	Male C57BL/6J	Contusion (70g, T10) SCI Model	DI-PFC	Mechanical & Heat (D3–D14)	NG2, CNPase, Olig2, MBP, PLP	Western blot, IHC	Increased: NG2, Notch1 Decreased: Olig2, MBP, PLP (D14)

(Continues)



TABLE 1 (Continued)

Author/publication year	Animal	Pain induction method	Site	Assessed pain (duration)	Marker	Method	Oligodendrocytes & myelin-related results
Chen et al. (2023)	Male SD Rats	ION-CCI-induced trigeminal neuralgia	Subnucleus caudalis	Mechanical (D7-D28)	APC MBP, CNPase G ratio	IHC Western blot, qPCR TEM	Decreased: APC, CNPase, MBP Increased: G-ratio
Zhu et al. (2024)	Male C57BL/6J	Sciatic nerve-CCI	Hippocampus	Mechanical (D7-D21)	MBP Myelin thickness/G-ratio	Western blot, IHC TEM	Decreased MBP, myelin thickness, & myelinated axon Increased: G-ratio

Abbreviations: APC, adenomatous polyposis coli; ASPA, aspartoacylase; BrdU, bromodeoxyuridine; CNPase, cyclic nucleotide 3'-phosphodiesterase; DH, dorsal horn; DL-PFC, dorsolateral prefrontal cortex; DTX, diphtheria toxin; GO ontology, gene ontology; HIV-gp120, Human Immunodeficiency Virus-gp120; IHC, immunohistochemistry; ION-CCI, infraorbital nerve chronic-constriction injury model; iPSC, induced pluripotent stem cell; KEGG, Kyoto Encyclopedia of Genes and Genomes; LC-MS/MS, Liquid Chromatography with tandem mass spectrometry; MAG, myelin-associated glycoprotein; MBP, myelin basic protein; miRNA, microRNA; MOBP, myelin-associated oligodendrocytic basic protein; NG2, neural/glia antigen 2; Olig2, Oligodendrocyte lineage transcription factor 2; IL-33, interleukin-33; PDGFR α , Platelet-derived growth factor receptor α ; Pl-mPFC, prelimbic medial prefrontal cortex; PLP, myelin proteolipid protein; qRT-PCR, quantitative reverse transcription polymerase chain reaction; S1HL, somatosensory cortex 1 hind limb area; SCI, spinal cord injury; STT, spinothalamic tract; TEM, transmission electron microscopy; TH, thalamus.

the damaged cells or to differentiate additional oligodendrocytes to compensate for the loss caused by pain. Thus, given the dual roles of oligodendrocytes in both structural integrity and functional modulation of neural circuits (Pepper et al., 2018), targeting these cells should be a good option to alleviate pain. For instance, direct OPC transplantation to the injured spinal cord shows potential not only in enhancing remyelination but also in alleviating pain associated with spinal cord injuries (Tao et al., 2013; Yang et al., 2018). However, discussion over the survival, long-term effects, and benefits of OPC transplantation persists (Jenkins et al., 2014; Ogawa et al., 2020), and it should also be noted that OPC transplantation can carry risks such as immune rejection (Plemel et al., 2014), incorrect differentiation, and local inflammation (Keirstead et al., 2005). Therefore, while targeting oligodendroglia presents a promising strategy for alleviating pain, careful consideration of the potential risks and long-term outcomes of this strategy is essential for its successful application.

Focusing on the imbalance of oligodendrocytes may also be beneficial, as both hypermyelination and hypomyelination can disrupt neural processing (Franklin et al., 2024; Narine & Colognato, 2022; Stadelmann et al., 2019). Hypermyelination can lead to an increased duration of the action potential, which, if prolonged, might excite the axon tract (Devor, 1984). Demyelination can cause a delay in nerve transmission, resulting in a progressive increase in sodium channels along the axons as compensation, which could result in pathological hyperexcitability of the neuron (Balzani et al., 2021). The findings by Shi et al. (2016), which showed significant increases in oligodendrocytes, myelin, and OPCs in both acute and chronic pain conditions, further support the idea that imbalances in oligodendrocyte function can contribute to pain. This imbalance could lead to either hypermyelination or hypomyelination, both of which are detrimental to neural processing and may exacerbate pain.

Furthermore, targeting the gut microbiota could also be a therapeutic option, as some studies suggest that gut microbiota could play a significant role in pain regulation by affecting myelination in the CNS (Lynch et al., 2021). For example, microbial metabolites like p-cresol and short-chain fatty acids (SCFAs), such as butyrate, produced by gut bacteria, have been reported to influence the differentiation and maturation of oligodendrocytes. These effects can also modulate microglia (Bar & Barak, 2019) and astrocytes (Gao et al., 2022) thereby possibly affecting pain perception. However, a direct causal link between gut microbiota and pain regulation has not yet been definitively demonstrated.

As the limitation of this study, only research on oligodendrocytes and myelin in the CNS has been included, whereas the role of myelin and myelin-generating Schwann cells in the peripheral nervous system has not been assessed. However, several studies have also observed changes in myelination in peripheral nerves, such as the sciatic nerve, in relation to pain (Campana, 2007; Ueda, 2008; Wei et al., 2019). Thus, in future studies, it will be helpful to also focus on and compare the roles of Schwann cells and oligodendrocytes in pain development and maintenance.



This review highlights significant gaps in our understanding of how oligodendrocytes precisely affect various pain states. There is an urgent need for further research to elucidate the detailed mechanisms by which oligodendrocytes and myelin dynamics impact pain pathways. These insights could lead to innovative treatments that specifically target these mechanisms, potentially improving the management of chronic pain.

AUTHOR CONTRIBUTIONS

Woojin Kim: Writing – review and editing; writing – original draft; funding acquisition; conceptualization. **María Cecilia Angulo:** Conceptualization; writing – review and editing; funding acquisition.

ACKNOWLEDGEMENTS

I acknowledge the use of ChatGPT (Open AI, <https://chat.openai.com>) to proofread my draft and make grammatical corrections. After using this tool, the authors reviewed and edited the content as needed, and take full responsibility for the content of the publication.

FUNDING INFORMATION

MCA was supported by grants from Fondation pour la Recherche Médicale (FRM, EQU202103012626), ANR CoLD (ANR, ANR-20-CE16-0001-01), and ANR Myelex (ANR, ANR-21-CE37-0020-01). She is a CNRS (Centre National de la Recherche Scientifique) investigator. Woojin Kim was supported by the National Research Foundation of Korea (NRF) grants funded by the Korean government (MSIT): No. 2020R1A5A2019413 and RS-2023-00258816. María Cecilia Angulo and Woojin Kim acknowledge the support from the bilateral French-Korean exchange program STAR-PHC (N° 50149UH and RS-2023-00258816).

[Correction added on 2 October 2024, after first online publication: funding information has been updated in this version].

CONFLICT OF INTEREST STATEMENT

None of the authors has a financial conflict of interest to declare.

PEER REVIEW

The peer review history for this article is available at <https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/jnc.16205>.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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How to cite this article: Kim, W., & Angulo, M. C. (2024). Unraveling the role of oligodendrocytes and myelin in pain. *Journal of Neurochemistry*, 00, 1–14. <https://doi.org/10.1111/jnc.16206>