Received: 16 March 2023 | Revised: 19 May 2023 | Accepted: 23 May 2023

DOI: 10.1002/glia.24426

GLIA

WILEY

REVIEW ARTICLE

The committed oligodendrocyte precursor cell, a newly-defined intermediate progenitor cell type in oligodendroglial lineage

Minxi Fang[1,2] | Lixia Chen[1] | Tao Tang[3] | Mengsheng Qiu[1,2,4] | Xiaofeng Xu[1]

[1]Zhejiang Key Laboratory of Organ Development and Regeneration, Institute of Life Sciences, College of Life and Environmental Sciences, Hangzhou Normal University, Hangzhou, China

[2]College of Life Sciences, Zhejiang University, Hangzhou, China

[3]Department of Anatomy, Cell Biology & Physiology, Indiana University School of Medicine, Indianapolis, Indiana, USA

[4]School of Basic Medical Science, Hangzhou Normal University, Hangzhou, China

Correspondence
Mengsheng Qiu and Xiaofeng Xu, Zhejiang Key Laboratory of Organ Development and Regeneration, Institute of Life Sciences, College of Life and Environmental Sciences, Hangzhou Normal University, Hangzhou 311121, China.
Email: m0qiu001@yahoo.com; xuxf1988@gmail.com

Funding information
Ministry of Science and Technology China Brain Initiative Grant, Grant/Award Number: 2022ZD0204701; National Natural Science Foundation of China, Grant/Award Numbers: 32170969, 82101244

Abstract

In the central nervous system, oligodendrocytes (OLs) produce myelin sheaths that provide trophic support to neuronal axons and increase the propagation speed of action potential. OLs are constantly generated from OL precursor cells (OPCs) throughout life span. The production of myelinating OLs consists of three canonical stages: OPCs, newly-formed OLs (NFOs), and mature myelinating OLs. Recently, single-cell RNA transcriptomic analyses identified a new population of oligodendroglial cells, namely differentiation committed OPCs (COPs). COPs represent a critical intermediate population between OPCs and NFOs, as revealed by specific expression of G-protein coupled receptor 17 (GPR17). The dysregulation of COPs leads to the remyelination failure in demyelinating diseases and impairs the replacement of lost myelin sheaths due to aging. Hence, understanding the development of COPs and their underlying regulatory network will be helpful in establishing new strategies for promoting myelin repair in demyelinating diseases. This review summarizes the current knowledge on the development and functions of COPs under both physiological and pathological conditions. Overall, COPs function as "checkpoints" to prevent inappropriate precocious OL differentiation and myelination through expressing distinct regulatory factors. Deepening our understanding of COPs may not only advance our knowledge of how OL lineage progresses during development, but also open the door to new treatments for demyelinating diseases.

KEYWORDS
COPs, GPR17, myelination, oligodendrocytes, remyelination

1 | INTRODUCTION

In the central nervous system (CNS), oligodendrocytes (OLs) produce myelin sheaths that provide trophic support to neuronal axons and increase the propagation speed of action potentials (Bergles & Richardson, 2015). OLs are constantly generated from OL precursor cells (OPCs) throughout life span. OPCs are distributed throughout the CNS and characterized by the high expression of platelet-derived growth factor-alpha receptor (PDGFRα) and chondroitin sulfate proteoglycan 4 (CSPG4, also referred to as NG2) (Rivers et al., 2008; Zhu et al., 2008). The formation of myelinating OLs is a stepwise differentiation process consisting of three canonical stages: OPCs, newly-formed OLs (NFOs) and mature myelinating OLs (MOLs) (Zhang et al., 2014). Very recently, single-cell RNA sequencing (scRNA-seq) analyses have identified multiple intermediate cell populations belonging to the OL lineage. Notably, one cluster of oligodendroglial cells, defined as "differentiation committed OPCs" (COPs) was identified with specific enriched expression of G-protein coupled receptor 17 (GPR17) (Artegiani et al., 2017; Marques et al., 2016). COPs constitute a population of post-mitotic OPCs, but have not yet

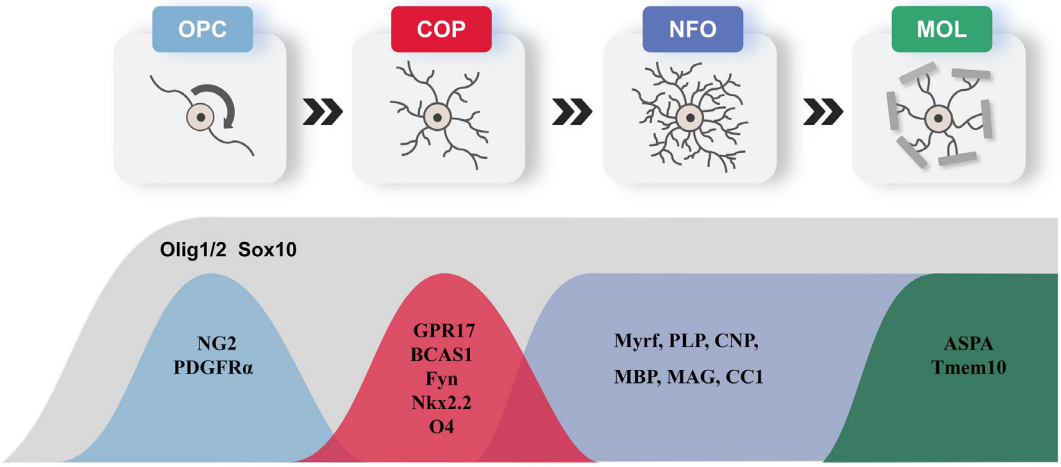

FIGURE 1 Diagram of oligodendroglial development and stage-specific markers.

initiated terminal differentiation. The newly classified COPs are probably equivalent to the so-called but ill-defined "late OPCs" (Rivera et al., 2021). Thus, the developmental trajectory of oligodendroglial lineage cells is OPCs-COPs-NFOs-MOLs. Multiple markers for distinct stages of OL development have been well documented (Huang et al., 2023) (Figure 1). Although significant research has been conducted on the characterization and function of OPCs as well as differentiated OLs (Bergles & Richardson, 2015; Elbaz & Popko, 2019; Fernandez-Castaneda & Gaultier, 2016), the molecular and functional features of COPs remain to be determined.

Proper myelination is crucial for normal functions of CNS, while demyelination impairs the integrity of myelin sheaths and disrupts saltatory conduction (Fancy et al., 2011). Remyelination is necessary for the restoration of proper nerve conduction after demyelination, which involves the recruitment and proliferation of adult OPCs, as well as their differentiation into MOLs (Franklin & Ffrench-Constant, 2008). Multiple sclerosis (MS) is an autoimmune disease causing a chronic demyelination in the CNS (Karussis, 2014). At present, the primary focus of MS treatment has been to prevent disease recurrence by modulating the immune system. Considering that remyelination is very limited in the majority of MS lesion, new approaches to promote remyelination have been studied and are currently underway. OPC deficiency and differentiation obstacles are major causes of inefficient remyelination. Moreover, a significant decrease in the number of OPCs and COPs has been reported in the aging brain, probably due to the reduced self-renewal of OPCs (Neumann et al., 2019; Rivera et al., 2021). Hence, understanding the development of COPs and their underlying regulatory network will be helpful in establishing new strategies for promoting myelin repair in demyelinating diseases and aging. This review summarizes the current knowledge on the development and functions of COPs under both physiological and pathological conditions, aiming to elucidate the regulatory network of oligodendroglial development and search for novel therapeutic targets for the treatment of demyelinating diseases.

2 | IDENTIFICATION OF COPS THROUGH SINGLE-CELL RNA TRANSCRIPTOMIC ANALYSES

A pioneering study from Ben Barres and Jianqian Wu labs has used RNA-sequencing (RNA-seq) technology to expand the analyses of COPs, NFOs, and MOLs in the postnatal brain (Zhang et al., 2014). Later on, microarray analyses were employed to investigate the expression profiles of OPCs during demyelination and remyelination (Moyon et al., 2015). Although these bulk RNA-seq datasets of OL-lineage cells have become very informative resources and been extensively used by the neuroscience community, they are restricted in quantifying the average signal of a bulk cell population. Recent development and application of single-cell transcriptomic technologies have advanced the characterization of oligodendroglial transcriptomic signatures, and proposed novel intermediate states between OPCs and mature OLs (Artegiani et al., 2017; Marques et al., 2016; van Bruggen et al., 2017). Marques et al., 2016 performed scRNA-seq on 5072 cells of OL-lineage from 10 regions of mouse juvenile and adult CNS. They identified COPs, an intermediate population between OPCs and NFOs. Distinct from OPCs, COPs lack *PDGFRα* and *NG2*, but express *Neu4* and other genes that prevent OLs from undergoing differentiation (*Gpr17*, *Sox6*, and *Bmp4*) (Marques et al., 2016). Furthermore, in order to characterize oligodendroglial cells in hippocampal niches, Artegiani et al., 2017 performed a subclustering analysis. Apart from OPCs and MOLs, they also identified a small number of COPs, characterized by specific expression *Gpr17*, *Bmp4*, and *Fyn* (Artegiani et al., 2017). Overall, COPs are OPC-like progenitor cells that express genes responsible for maintaining the undifferentiated states. However, they are different from OPCs, as they do not express *PDGFRα* and *NG2*. Besides, COPs exhibit low levels of cell cycle markers but express genes involved in cell migration.

In addition to the initial identification from murine single-cell studies, the COP cluster has been identified based on scRNA-seq

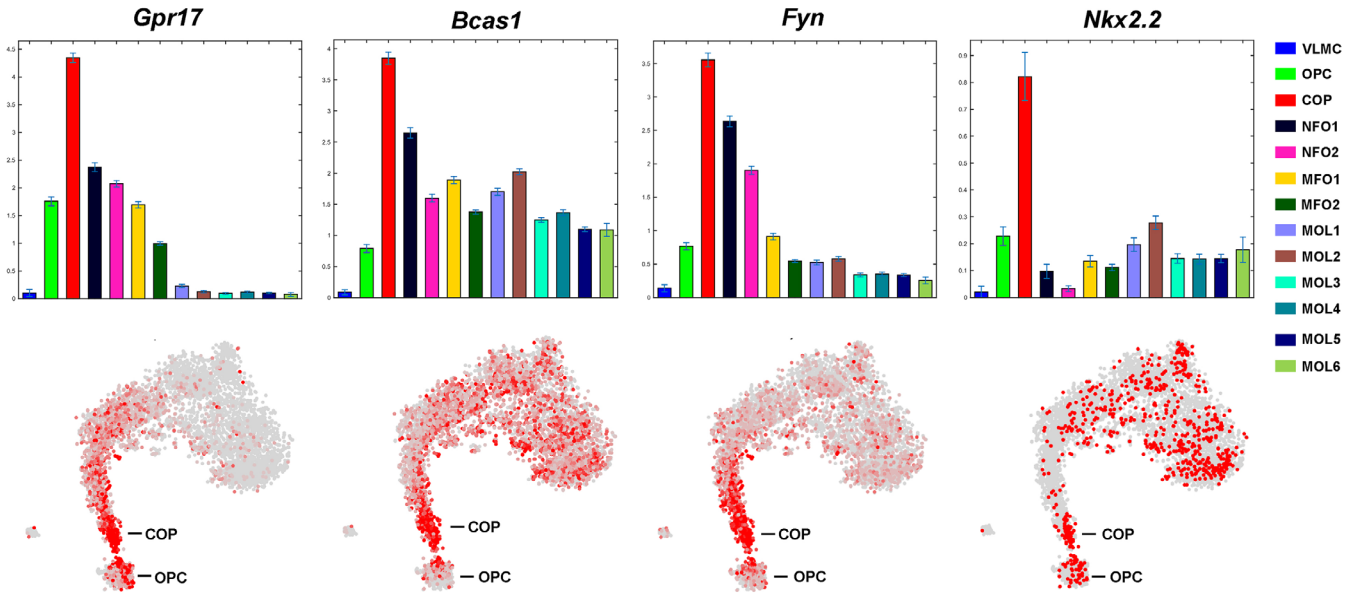

FIGURE 2 Relative expression levels of COP-enriched genes in distinct oligodendroglial populations clustered by scRNA-seq (from Marques et al., 2016). The figure panels are retrieved from the scRNA-seq datasets (http://linnarssonlab.org/oligodendrocytes/). VLMC, vascular and leptomeningeal cells; NFO, newly-formed oligodendrocytes; MFO, myelin-forming oligodendrocytes; MOL: mature oligodendrocytes.

analyses in the human brain (Fernandes et al., 2021; Jakel et al., 2019). However, this finding could not be replicated by two other groups (Lake et al., 2018; Tran et al., 2021). A recent paper discovered that neuronal ambient RNA contamination might lead to misinterpretation and masking of rare cell types (such as COPs) (Caglayan et al., 2022). In this study, they showed that COPs, despite their low abundance, represent an intermediate population between OPCs and differentiated OLs. After ambient RNA removal, they indeed singled out the COP population in all human brain scRNA-seq datasets and highlighted some previously undescribed markers for COPs.

3 | TRANSCRIPTOMIC SIGNATURES OF COPS

According to the scRNA-seq analyses, COPs have a transcriptomic signature that distinguishes them from OPCs or mature OLs (Marques et al., 2016; Tasic et al., 2016). Gene ontology analyses demonstrated that COPs are enriched with genes involved in cell fate determination and cell adhension. Identification of COP-enriched genes is highly beneficial for the characterization of novel and important functional players. Of note, Caglayan et al., 2022 found the most specific COP markers in human brains: BCAS1, GPR17, Fyn, TNS3, SH3RE3, EPHB1, CRB1, SIRT2, and ARHGAP5. Through comparison between murine and human scRNA-seq datasets, we focus on several critical factors that exhibit peak expression in COPs and participate in the regulation of OL development and myelination (Figure 2).

3.1 | G-protein coupled receptor 17

Previous studies have demonstrated that GPR17 is an orphan receptor involved in the process of OL differentiation and myelination. This identification and cloning of GPR17 was firstly reported in human and rat (Ciana et al., 2006). It could be activated in several cell lines in response to uracile nucleotides and cysteinyl leukotrienes (cysLTs). After 2 years, detailed characterization of mouse GPR17 demonstrated its specific expression in OPCs (Lecca et al., 2008). During development, the expression of GPR17 is restricted in OL-lineage cells and rapidly downregulated at the peak of myelination (Chen et al., 2009). It was later found that GPR17 is mainly expressed in the late ramified OPCs, characterized by NG2 downregulation (Fumagalli et al., 2011), reminiscent of the COPs. Indeed, GPR17 expression is induced in NG2+ glia cells at the end of cell cycle and its upregulation defines a stage when OPCs start to exit cell cycle (Boda et al., 2011). Consistently, analysis of spinal cord development in zebrafish indicates that GPR17 is strictly expressed in a subset of OPCs that produce myelinating OLs, while it is virtually absent in OPCs that never differentiate (Marisca et al., 2020). Due to these findings, GPR17 has been recognized as an important marker to label COPs.

Studies have been performed by several groups to determine the function of GPR17 in OL development (Capelli et al., 2020; Chen et al., 2009; Fumagalli et al., 2011). In primary cultured OPCs, *Gpr17* knockdown through specific small-interfering RNAs (siRNAs) profoundly impaired their capability to produce mature OLs, implying the potential role of GPR17 in the initiation of differentiation (Fumagalli et al., 2011). Conversely, continuous exposure to either endogenous or synthetic GPR17 agonist promoted OPC differentiation and

accelerated myelination in OPC-DRG co-cultures (Capelli et al., 2020). However, contrary to these in vitro studies, genetic analysis revealed that GPR17 functions to prevent OPCs from maturing into OLs. *Gpr17* knockout mice display an earlier onset of myelination in the spinal cord. Consistently, transgenic mice with sustained GPR17 expression in OLs display typical features of myelination disorders in the CNS, with absence of myelin or reduction in myelin thickness (Chen et al., 2009). It has been proposed that the inhibitory effects of GPR17 on OPC maturation are, at least partially, due to the upregulation and nuclear translocation of ID2/ID4, the potent OL differentiation inhibitors (Chen et al., 2009; Wang et al., 2001). However, a recent study demonstrated that ID2/ID4 are not expressed in OPCs during normal CNS development, and genetic disruption of both ID2 and ID4 has no or little effect on OPC generation and differentiation (Huang et al., 2022). Therefore, the precise function of GPR17 in OPC lineage progression and its working mechanism are still somewhat controversial and remain to be further clarified.

3.2 | Breast carcinoma amplified sequence 1

Breast carcinoma amplified sequence 1 (BCAS1) was originally identified as mRNA amplified in human cancer cell lines (Collins et al., 1998), but recent transcriptomic and proteomic studies have revealed its abundant expression in oligodendroglial cells (Sharma et al., 2015; Zeisel et al., 2015; Zhang et al., 2014). Immunostaining of the mouse brain revealed that BCAS1 is co-labeled with the pan OL-lineage markers (Sox10, Olig1, and Olig2), but not with the OPC marker NG2, and its expression is later downregulated in myelinating OLs (Fard et al., 2017). Thus, BCAS1+ cells represent an intermediate oligodendroglial cell population, segregating from OPCs and mature OLs, indicative of COP cluster. In primary cultured OPCs, BCAS1 is expressed in majority of O4+ OLs with arborized morphology. However, when OLs form sheets and express MBP, its expression is reduced. In OLs generated from induced pluripotent human stem cells (iPSCs), BCAS1 is also expressed in majority of O4+ OLs at 24 days in vitro. At later time points of differentiation, BCAS1 is hardly detected in MBP+ mature OLs. Together, these findings verify the enrichment of BCAS1 in COPs during early differentiation in both mouse and human cells (Fard et al., 2017).

The function of BCAS1 in OL development has remained elusive, although there is evidence that BCAS1 is required for normal myelination and brain functions in vivo. *Bcas1* knockout mice exhibit schizophrenia-like abnormal behaviors and a tendency towards anxiety-like behaviors. Moreover, its absence results in hypomyelination and upregulation of inflammatory genes in the brain (Ishimoto et al., 2017). At present, it is not known what causes the schizophrenia-like symptom in *Bcas1*-deficient mice. It was previously proposed that a change in BCAS1 splicing is associated with the alternative splicing of quaking (QKI), an RNA-binding protein (Lauriat et al., 2008). A deficiency in QKI also induced myelination defects and schizophrenia-like behaviors (Aberg et al., 2006; Haroutunian et al., 2006; Zhao et al., 2010). Thus, BCAS1 mutation appears to cause schizophrenia-like symptom by influencing QKI splicing and myelin development.

3.3 | Fyn

Fyn is a non-receptor tyrosine kinase belonging to the Src family of kinases (SFKs). The peak of Fyn expression corresponds to the peak of myelination in the brain (Bare et al., 1993). Genetic evidences showed that *Fyn*-deficient mice exhibit hypomyelination in the brain, further confirming the role of Fyn in developmental myelination (Umemori et al., 1994). In the past decades, the contribution of Fyn to stimulating OPC differentiation and enhancing myelin formation has been studied in-depth, as reviewed by Guglietti et al (Guglietti et al., 2021). During differentiation, upon binding to OPCs, ECM integrins interact with and activate Fyn kinase. In turn, the activated Fyn phosphorylates RhoGTPase, increases the expression of RhoGDP, and inactivates RhoA, allowing hyperextension of oligodendroglial processes and promoting OL differentiation and maturation (Liang et al., 2004; Wolf et al., 2001). In support of this, inhibition of Fyn activity blocks morphological changes from OPCs into mature OLs (Osterhout et al., 1999). Fyn also promotes OL maturation through interacting with Tau, regulating the assembly of microtubules necessary for the formation of OL cytoskeletons (White & Krämer-Albers, 2014). Additionally, Fyn activity is required for the production and maintenance of MBP through phosphorylation of MBP mRNA binding protein QKI (Wake et al., 2011; Zhang et al., 2003). Finally, it was reported that growth factor BDNF stimulates the phosphorylation of Fyn and activates Erk1/2, which promotes rapid myelin growth (Peckham et al., 2016). Given that the failure of remyelination in MS is strongly linked to defective OPC differentiation and subsequent myelination, modulation of Fyn activity may thus represent a novel therapeutic strategy to facilitate the differentiation and maturation of OLs.

3.4 | Nkx2.2

Homeodomain proteins are closely linked to oligodendroglial development, ranging from the initial stage of fate specification to the late stage of terminal differentiation and myelination. Among them, Nkx2.2 transcription factor has been shown to be involved in both early and late oligodendroglial development stages. Nkx2.2 plays a critical role in the initial patterning of the ventral spinal cord by defining the p3 progenitor domain, which is essential for the generation of V3 interneurons (Briscoe et al., 1999). Then Nkx2.2 expression is excluded from the pMN domain due to the antagonistic actions of Pax6 to allow specification of OPCs (Sun et al., 2001; Sun et al., 2003). Later in the spinal cord, the expression of Nkx2.2 is upregulated in OPCs, immediately before the initiation of their differentiation and rapidly downregulated following their differentiation (Fu et al., 2002; Soula et al., 2001; Xu et al., 2000; Zhou et al., 2001). Therefore, the expression of Nkx2.2 in COPs is strongly associated with the onset of OL differentiation.

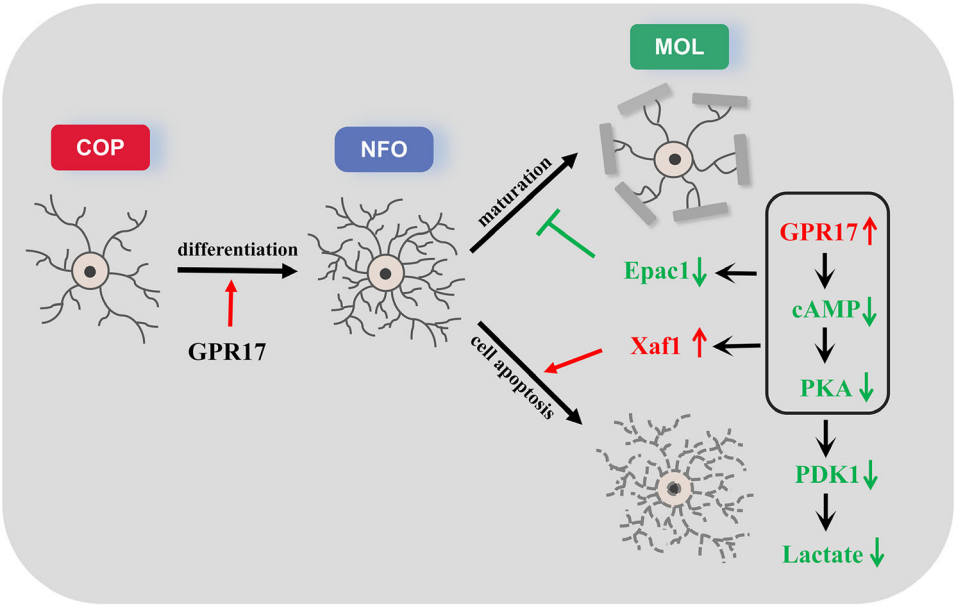

FIGURE 3 Simplified diagram of the regulation of oligodendroglial development by GPR17. High expression of GPR17 in COPs is required for the initiation of terminal differentiation. Sustained overexpression of GPR17 in NFOs results in a decrease in intracellular cAMP levels, deactivates PKA signaling pathway, and inhibits the expression of Epac1, leading to blockade in OL differentiation. Meanwhile, deactivation of PKA signaling pathway upregulates the expression of Xaf1, resulting in cell apoptosis. Deactivation of PKA signaling in OLs further inhibits the activity of PDK1, which reduces lactate production.

Molecular and genetic analyses of mouse and chicken embryos demonstrate that Nkx2.2 plays an essential role in controlling the timing of OL terminal differentiation. Conventional (Qi et al., 2001) or conditional knockout of *Nkx2.2* in OPCs (Zhu, Zhao, et al., 2014b) can lead to a significant but transient delay of OPC maturation and myelin gene expression, although the delayed differentiation is completely overcome later in young adults. Conversely, conditional overexpression of Nkx2.2 in OPCs results in precocious OL differentiation, accompanied by reduced proliferation and migration of OPCs (Zhu, Zhao, et al., 2014b). Thus, Nkx2.2 does not appear to be an essential factor for OL differentiation, but rather it modulates the timing of OL differentiation during development. Additional studies suggest that Nkx2.2 directly represses the expression of PDGFRα, which promotes OPC division but inhibits its differentiation, thus controlling the timing of OPC differentiation (Zhu, Zhao, et al., 2014b). By repressing PDGFRα expression, Nkx2.2+ COPs become unresponsive to the external mitogen PDGF-A, which prompts them to exit the cell cycle and leads to the activation of the intrinsic differentiation program.

4 | MULTIPLE FUNCTIONS OF COPS IN OLIGODENDROGLIAL DEVELOPMENT

4.1 | COP-related mechanisms control the timing of OL terminal differentiation

As mentioned above, COPs represent an intermediate population between proliferating OPCs and differentiated OLs. Notably, many factors enriched in COPs regulate OPC differentiation and maturation in a stage-specific manner. In general, these factors exhibit peak expression in COPs, but are downregulated upon initiation of differentiation. Disturbance of their expression frequently results in myelination defects. However, the molecular mechanisms by which COP-derived factors facilitate the transition between OPCs and differentiated OLs remain elusive.

The amount of intracellular cyclic AMP (cAMP) is crucial to assess the rate of OL differentiation (Malone et al., 2013), and is fine-tuned by GPR17 (Fumagalli et al., 2016). A high level of cAMP suppresses the expression of PDGFRα, thereby promoting the expression of myelin genes (Clark Jr et al., 2002), and inhibiting the proliferation of OPCs (Li & Wang, 2011). Consistently, endogenous activation of GPR17 or exogenous agonist MDL29951 has been reported to suppress OPC maturation by decreasing cAMP levels (Hennen et al., 2013). Besides, treatment with cAMP promotes the phosphorylation of protein kinase A (PKA) in OPCs, which subsequently promotes OL differentiation through downstream effector Epac1 (Simon et al., 2016). Accordingly, overexpression of GPR17 in vitro could reduce the levels of Epac1 and impair OL differentiation (Simon et al., 2016), whereas deletion of Gpr17 in vivo could increase Epac1 expression and enhance OL differentiation (Ou et al., 2016). Together, these results imply that GPR17 activation reduces the level of intracellular cAMP, deactivates PKA signaling pathway, and inhibits the expression of Epac1, leading to a blockade of OPC maturation (Figure 3).

On the other hand, downregulation of PDGFRα in COPs may contribute to the initiation of the intrinsic differentiation program. PDGF modulates the proliferation, migration and surivial of OPCs through PDGFRα, the only PDGF receptor isoform expressed in OPCs (McKinnon et al., 1990; Pringle et al., 1989). As OPCs differentiate into mature OLs, the expression of PDGFRα is gradually reduced and ultimately extinguished in mature OLs. Conditional ablation of PDGFRα in OPCs can lead to precocious OPC differentiation, accompanied by the suppression of cell proliferation and migration, resembling the phenotype observed in transgenic mice overexpressing Nkx2.2 (Zhu, Zhao, et al., 2014b). Thus, PDGFRα is a negative modulator of OPC maturation. In COPs, Nkx2.2 has been shown to directly

repress the transcription of PDGFRα through its specific binding to the upstream regulatory elements (Zhu, Zhao, et al., 2014b).

4.2 | COPs maintain intrinsic OL homeostasis through regulating cell survival

A previous study on the developing optic nerve demonstrated that over 50% of NFOs undergo programmed cell death, reaching a peak shortly after their initial appearance. Excess production and subsequent culling of OLs serve to ensure that OL population is appropriately matched to the number of axons required to be myelinated (Burne et al., 1996; Raff et al., 1993). This hints the presence of a homeostatic mechanism that regulates the number of OLs to meet the demands of neural plasticity, and COPs are reported to participate in the maintenance of this intrinsic homeostasis through regulating the survival of NFOs. The transcription factor EB (TFEB) is another critical transcription factor that exhibits the highest expression level in COPs. Recently, Sun et al., 2018 demonstrated that TFEB functions cell-autonomously to induce the apoptosis of premyelinating OLs by activating the PUMA-Bax-Bak axis, leading to the targeted elimination of OLs in normally unmyelinated brain regions. The loss of TFEB causes precocious and ectopic myelination in several regions of the murine brain (Sun et al., 2018), further confirming the importance of COPs in OL sculpting to ensure proper myelination.

Overexpression or activation of GPR17 with MDL29951 also inhibits the survival of OLs via promoting cell apoptosis (Ou et al., 2016). XIAP-associated factor 1 (Xaf1) is a well-characterized tumor suppressor involved in the apoptosis of various cell types (Zhu, Shi, et al., 2014a). Activation of GPR17 was reproted to decrease the level of intracellular cAMP, inhibit PKA activation and upregulate Xaf1 expression, eventually resulting in OL apoptosis. Thus, ectopic activation of GPR17-cAMP-PKA axis in OLs inhibits both the maturation and survival of oligodendroglial lineage cells (Figure 3).

4.3 | GPR17 regulates body metabolism through intermediate COPs

Accumulating evidences suggest that GPR17 is involved in the regulation of energy homeostasis. Administration of GPR17 antagonist Cangrelor to mice reduces food intake, while GPR17 agonist LTD induces food intake (Ren et al., 2012). Genetics evidence showed that both *Gpr17*-null and OL-specific knockout mice exhibit lean phenotypes on a high-fat diet, demonstrating that GPR17 regulates whole-body metabolism through COPs (Ou et al., 2019). Mechanistically, loss of GPR17 in COPs results in activation of PKA signaling and elevated expression of pyruvate dehydrogenase kinase 1 (PDK1), which promotes lactate production (Figure 3). Elevated lactate production in OLs enhances its transfer to nearby hypothalamic neurons, which activates the AKT/STAT3 signaling pathways, increases synthesis of anorexigenic POMC peptides and reduces synthesis of orexigenic AgRP peptides, eventually inhibiting food intake (Ou et al., 2019). This finding unveils a significant role of GPR17 in metabolic control, where GPR17/cAMP/lactate signaling axis regulates the activity of hypothalamic neurons to maintain energy homeostasis, raising the possibility that modulation of this signaling might be beneficial for treating obesity.

Recently, Marangon et al., 2022 tried to investigate how physiological downregulation of GPR17 in differentiated OLs facilitates cell metabolism through transcriptomics, metabolomics and lipidomics. After GPR17 silencing, they found a significant increase in the expression of mature OL markers, as well as alteration of genes involved in glucose metabolism and lipid synthesis. Metabolomic analysis further revealed that, after GPR17 downregulation, OLs rewrite their metabolism and increase lactate release, which could directly affect OL differentiation program. Concomitantly, GPR17 depletion alters the abundance of myelin-specific lipids (Marangon et al., 2022). Thus, this study unveils a functional link between GPR17 expression, lactate production and myelin composition.

5 | THE INVOLVEMENT AND REGULATION OF COPS DURING REMYELINATION AND REMYELINATION

5.1 | COPs accumulate in MS patients and respond rapidly to brain insults

Several independent studies have been performed to confirm the accumulation of COPs in MS patients. Chen et al., 2009 firstly reported that the number of COPs, as identified by GPR17 expression, is markedly higher in MS patients than in healthy conditions, despite its gradual decline along with disease progression. In human MS lesions, the density of BCAS1+ cells is higher at the lesion border and within the remyelination areas, but low in the core of lesion sites, suggesting that remyelination starts at the lesion borders and COPs are actively engaged in remyelination (Fard et al., 2017). Recently, Angelini et al., 2021 examined the expression GPR17 in MS brain and discovered a marked accumulation of GPR17+ COPs in the normal appearing white matter (NAWM) of MS patients. NAWM is characterized by relevant and diffuse ongoing inflammation, but absence of demyelination (Angelini et al., 2021). The abundance of COPs in NAWM suggests that COP accumulation might not be related to demyelination lesion, but rather to inflammatory states.

In addition to the marked accumulation of COPs in MS patients, pathologically increased GPR17 expression has been found in several animal models of diseases, including traumatic brain injury (Boda et al., 2011), ischemia (Ciana et al., 2006; Lecca et al., 2008) and ALS (Bonfanti et al., 2020). In particular, GPR17+ COPs are specifically associated to rapid response to myelin injury, regardless of the insult type (e.g Cuprizone-, EAE- or LPC-induced demyeliantion) (Chen et al., 2009; Coppolino et al., 2018; Nyamoya et al., 2019; Ou et al., 2016). Thus, COPs serve as a "reserve pool" after injury. In the adult brain, they are maintained in an immature state as a population of cells surveying and rapidly responding to damage.

5.2 | The final density of COPs varies in different models of myelin injury

The GPR17 reporter line (*GPR17-iCre*^{ERT2}; *CAG-eGFP*) has been widely used to determine the final fate of COPs under different pathological conditions. Vigano et al., 2016 performed acute brain injury through stab wound in this reporter line. After challenging the cortical environment by inducing acute brain injury, there is an increase, albeit not statistically significant, of recombined GPR17+ cells. More interestingly, the majority of recombined GPR17+ COPs proceed with differentiation and expression of mature OL marker genes (Vigano et al., 2016). Thus, despite their quiescence under physiological conditions, GPR17+ COPs resumed their differentiation program after acute brain insults, further validating that COPs represent an intermediate progenitor pool in the brain parenchyma for a rapid and efficient regenerative process.

Contradictorily, when Bonfanti et al., 2017 induced ischemia by middle cerebral artery occlusion (MCAO) in GPR17 reporter mice, they found that quiescent COPs are activated to proliferate and migrate towards the lesion shortly after ischemia. However, the majority of COPs are kept at a precursor state and remain undifferentiated even at 8 weeks after MCAO (Bonfanti et al., 2017). Coppolino et al., 2018 employed the GPR17 reporter line to trace the fate of COPs in two demyelinated models, EAE- and Cuprizone-induced models. In both models, the pool of COPs responds rapidly as an increasing number of GPR17+ cells accumulate at the demyelinated sites. In Cuprizone model, GPR17+ COPs differentiate into mature OLs, which is crucial for remyelination. However, in EAE model, GPR17+ cells are arrested at an immature state and fail to differentiate into myelinating OLs (Coppolino et al., 2018). Given that EAE model is characterized by prominent activation of immune cells and inflammation, while Cuprizone model bypasses the autoimmune components, it is postulated that the inflammatory environments in ischemia and EAE model could account for the remyelination failure of COPs.

5.3 | Chronic inflammatory environment accounts for the remyelination failure of COPs

As mentioned above, evidences from different demyelinating models suggest that sustained GPR17 overexpression might be induced by pro-inflammatory chemokines or cytokines accumulating around the lesion sites (Coppolino et al., 2018). In support of this, the stromal-derived factor 1 (SDF1) could specifically activate GPR17, leading to aberrant signaling transduction (Calderon et al., 2006; Parravicini et al., 2016). Chronic inflammation might cause aberrant GPR17 upregulation in COPs, as observed in severe or chronic MS patients, and "freeze" these cells at an immature state. Due to the differentiation blockade and continuous inflammation, COPs are then committed to programmed cell death (Ou et al., 2016). Thus, combinatory treatments with pro-remyelination agents and anti-inflammatory drugs may provide a new therapeutic strategy to halt disease progression and enhance myelin recovery. Recently, Raffaele et al., 2021 investigated the contribution of immune cells (microglia/macrophages) to the response of GPR17+ COPs after ischemic stroke. They found that microglia/macrophages exhibit a beneficial action on COPs during early injury phase after MCAO, whereas their action becomes detrimental at later stages. More importantly, infusion of extracellular vesicles (EVs) derived from early pro-regenerative microglia favors a pro-resolving phenotype and rescues the dystrophic "senescent-like" traits of resident immune cells, leading to COP differentiation and increasing functional recovery (Raffaele et al., 2021). This exciting finding not only advances out knowledge of the complex relationship between immune cells and COPs under pathological conditions, but also lays a foundation for developing EV-based strategy to promote myelin repair.

5.4 | Modulation of GPR17 enhances remyeliantion

Considering GPR17 overexpression in MS patients, its strong correlation with inflammatory milieu and direct involvement in myelin genesis and repair, GPR17 has been recognized as a promising target for pro-myelinating therapies. In contrast to the remyelination failure upon GPR17 overexpression, *Gpr17*-deficient mice exhibit an improved ability to regenerate myelin sheaths in LPC-induced demyelinating models (Lu et al., 2018; Ou et al., 2016). Several intracellular pathways have been found to be involved. Ou et al., 2016 suggested inactivation of GPR17 stimulates OL differentiation through activating cAMP/PKA/Epac1 pathway. Lu et al., 2018 further demonstrated that the enhanced remyelination in the absence of GPR17 is correlated with activation of Erk1/2.

Due to its localization on the extracellular membrane, GPR17 could be a suitable target for pharmacological interventions (Boda et al., 2011; Lecca et al., 2008; Lecca et al., 2020). Recently, Parravicini et al., 2020 proposed and validated an iterative drug discovery pipeline through which novel putative GPR17 modulators have been designed and then validated using screening paradigms from in silico simulations to in vivo disease models. For the first time, they found that a selective GPR17 agonist (Galinex) is able to significantly delay the symptomatic onset of EAE (Parravicini et al., 2020). Thus, modulation of GPR17 activity provides a promising strategy in the prevention and treatment of demyelinating diseases.

6 | COPS MIGHT PROMOTE ADAPTIVE MYELINATION BY RESPONDING TO NEURONAL ACTIVITY

Overall, much of our understanding about COPs comes from studies on developmental myelination and pathological de/remyelination. Of note, the possible association between COPs and adaptive

myelination needs to be explored. Adaptive myelination is a process by which myelination continues through adulthood in an activity-dependent manner (Knowles et al., 2022; Mount & Monje, 2017). The direct involvement of COPs in adaptive myelination has not been reported. It has been found that OPCs in the adult mouse brain respond to changes in neural activity by increasing their proliferation and differentiation capacity (Hughes et al., 2018). Motor learning, the gradual acquisition of a specific novel motor skill, promotes adaptive myelination in the CNS. Xiao et al., 2016 traced OL differentiation in adult mice during motor learning (running a wheel with unevenly spaced rungs). Within just 2 hours of exposure to the complex wheel, production of OLs was accelerated in the subcortical white matter, suggesting a direct and active role of OPCs in motor learning (Xiao et al., 2016). Thus, it is plausible that the resident OPCs as well as COPs in the adult brain play a critical role in adaptive myelination, as they are able to respond quickly to changes in neuronal activity and promote myelin production accordingly. Moreover, it has been reported that neurons could promote OL differentiation through increasing cAMP levels of nearby OPCs (Mitew et al., 2018). As mentioned before, the level of cAMP is fine-tuned by GPR17 to facilitate the transition between OPCs and mature OLs. Finally, it has been demonstrated that increased neural activity in the visual cortex led to changes in ECM that prompted myelination of specific axons (Hughes et al., 2018). The ECM genes are among the most enriched genes in COPs. Together, these findings suggest that neuronal activity may induce changes in the composition and signaling transduction of COPs, which in turn influences myelination patterns. It will be of interest and importance in the future to investigate the functional role of COPs in adaptive myelination.

7 | CONCLUSIONS

As mentioned above, COPs represent a critical stage of oligodendrogenesis during which OL-lineage cells slow down proliferation and differentiation until they are ready to produce myelin sheaths around axons. COPs express distinct regulatory factors that act as "checkpoints" preventing inappropriate precocious OL differentiation and myelination under the physiological conditions, and these regulatory factors are specifically downregulated at later stages when cells are prepared for terminal differentiation. In the past decades, increasing studies have been performed with the aim of determining the roles of COPs in developmental myelination and myelin regeneration. GPR17 is identified and validated as a novel attractive target for remyelination treatment. Notably, aberrant GPR17 upregulation during chronic inflammation might be responsible for the impaired differentiation capacity of COPs. Thus, combined therapies or multimodal modulators that simultaneously target GPR17 and immune response, may serve as an effective strategy to promote myelin recovery and injury repair. Recent advances in high-throughput screening of GPR17 ligands, as well as EV-based strategy will pave the way for implementing myelin repair and functional recovery in demyelinating diseases.

AUTHOR CONTRIBUTIONS

Conceptualization, Mengsheng Qiu and Xiaofeng Xu; first draft preparation, Minxi Fang, Lixia Chen, Tao Tang, and Xiaofeng Xu; writing-review and editing, Mengsheng Qiu and Xiaofeng Xu; supervision, Mengsheng Qiu; funding acquisition, Mengsheng Qiu and Xiaofeng Xu. All authors have read and agreed to the published version of the manuscript.

ACKNOWLEDGMENTS

This work was supported by National Natural Sciences Foundation of China (82101244, 32170969) and Ministry of Science and Technology China Brain Initiative Grant (2022ZD0204701).

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

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

ORCID

Xiaofeng Xu https://orcid.org/0000-0001-7910-0407

REFERENCES

Aberg, K., Saetre, P., Jareborg, N., & Jazin, E. (2006). Human QKI, a potential regulator of mRNA expression of human oligodendrocyte-related genes involved in schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America*, *103*(19), 7482–7487. https://doi.org/10.1073/pnas.0601213103

Angelini, J., Marangon, D., Raffaele, S., Lecca, D., & Abbracchio, M. P. (2021). The distribution of GPR17-expressing cells correlates with White matter inflammation status in brain tissues of multiple sclerosis patients. *International Journal of Molecular Sciences*, *22*(9), 4574. https://doi.org/10.3390/ijms22094574

Artegiani, B., Lyubimova, A., Muraro, M., van Es, J. H., van Oudenaarden, A., & Clevers, H. (2017). A single-cell RNA sequencing study reveals cellular and molecular dynamics of the hippocampal neurogenic nich. *Cell Reports*, *21*(11), 3271–3284. https://doi.org/10.1016/j.celrep.2017.11.050

Bare, D. J., Lauder, J. M., Wilkie, M. B., & Maness, P. F. (1993). p59fyn in rat brain is localized in developing axonal tracts and subpopulations of adult neurons and glia. *Oncogene*, *8*(6), 1429–1436.

Bergles, D. E., & Richardson, W. D. (2015). Oligodendrocyte development and plasticity. *Cold Spring Harbors Perspectives in Biology*, *8*(2), a20453. https://doi.org/10.1101/cshperspect.a020453

Boda, E., Vigano, F., Rosa, P., Fumagalli, M., Labat-Gest, V., Tempia, F., Abbracchio, M. P., Dimou, L., & Buffo, A. (2011). The GPR17 receptor in NG2 expressing cells: Focus on in vivo cell maturation and participation in acute trauma and chronic damage. *Glia*, *59*(12), 1958–1973. https://doi.org/10.1002/glia.21237

Bonfanti, E., Bonifacino, T., Raffaele, S., Milanese, M., Morgante, E., Bonanno, G., Abbracchio, M. P., & Fumagalli, M. (2020). Abnormal upregulation of GPR17 receptor contributes to oligodendrocyte dysfunction in SOD1 G93A mice. *International Journal of Molecular Sciences*, *21*(7), 2395. https://doi.org/10.3390/ijms21072395

Bonfanti, E., Gelosa, P., Fumagalli, M., Dimou, L., Vigano, F., Tremoli, E., Cimino, M., Sironi, L., & Abbracchio, M. P. (2017). The role of oligodendrocyte precursor cells expressing the GPR17 receptor in brain remodeling after stroke. *Cell Death & Disease*, *8*(6), e2871. https://doi.org/10.1038/cddis.2017.256

Briscoe, J., Sussel, L., Serup, P., Hartigan-O'Connor, D., Jessell, T. M., Rubenstein, J. L., & Ericson, J. (1999). Homeobox gene Nkx2.2 and specification of neuronal identity by graded sonic hedgehog signalling. *Nature*, *398*(6728), 622–627. https://doi.org/10.1038/19315

Burne, J. F., Staple, J. K., & Raff, M. C. (1996). Glial cells are increased proportionally in transgenic optic nerves with increased numbers of axons. *Journal of Neuroscience*, *16*(6), 2064–2073. https://doi.org/10.1523/JNEUROSCI.16-06-02064.1996

Caglayan, E., Liu, Y., & Konopka, G. (2022). Neuronal ambient RNA contamination causes misinterpreted and masked cell types in brain single-nuclei datasets. *Neuron*, *110*(24), 4043–4056.e5. https://doi.org/10.1016/j.neuron.2022.09.010

Calderon, T. M., Eugenin, E. A., Lopez, L., Kumar, S. S., Hesselgesser, J., Raine, C. S., & Berman, J. W. (2006). A role for CXCL12 (SDF-1alpha) in the pathogenesis of multiple sclerosis: Regulation of CXCL12 expression in astrocytes by soluble myelin basic protein. *Journal of Neuroimmunology*, *177*(1–2), 27–39. https://doi.org/10.1016/j.jneuroim.2006.05.003

Capelli, D., Parravicini, C., Pochetti, G., Montanari, R., Temporini, C., Rabuffetti, M., Trincavelli, M. L., Daniele, S., Fumagalli, M., Saporiti, S., Bonfanti, E., Abbracchio, M. P., Eberini, I., Ceruti, S., Calleri, E., & Capaldi, S. (2020). Surface plasmon resonance as a tool for ligand binding investigation of engineered GPR17 receptor, a G protein coupled receptor involved in myelination. *Frontiers in Chemistry*, *7*, 910. https://doi.org/10.3389/fchem.2019.00910

Chen, Y., Wu, H., Wang, S., Koito, H., Li, J., Ye, F., Hoang, J., Escobar, S. S., Gow, A., Arnett, H. A., Trapp, B. D., Karandikar, N. J., Hsieh, J., & Lu, Q. R. (2009). The oligodendrocyte-specific G protein-coupled receptor GPR17 is a cell-intrinsic timer of myelination. *Nature Neuroscience*, *12*(11), 1398–1406. https://doi.org/10.1038/nn.2410

Ciana, P., Fumagalli, M., Trincavelli, M. L., Verderio, C., Rosa, P., Lecca, D., Ferrario, S., Parravicini, C., Capra, V., Gelosa, P., Guerrini, U., Belcredito, S., Cimino, M., Sironi, L., Tremoli, E., Rovati, G. E., Martini, C., & Abbracchio, M. P. (2006). The orphan receptor GPR17 identified as a new dual uracil nucleotides/cysteinyl-leukotrienes receptor. *The EMBO Journal*, *25*(19), 4615–4627. https://doi.org/10.1038/sj.emboj.7601341

Clark, R. E., Jr., Miskimins, W. K., & Miskimins, R. (2002). Cyclic AMP inducibility of the myelin basic protein gene promoter requires the NF1 site. *International Journal of Developmental Neuroscience: The Official Journal of the International Society for Developmental Neuroscience*, *20*(2), 103–111. https://doi.org/10.1016/s0736-5748(02)00013-8

Collins, C., Rommens, J. M., Kowbel, D., Godfrey, T., Tanner, M., Hwang, S. I., Polikoff, D., Nonet, G., Cochran, J., Myambo, K., Jay, K. E., Froula, J., Cloutier, T., Kuo, W. L., Yaswen, P., Dairkee, S., Giovanola, J., Hutchinson, G. B., Isola, J., … Gray, J. W. (1998). Positional cloning of ZNF217 and NABC1: Genes amplified at 20q13.2 and overexpressed in breast carcinoma. *Proceedings of the National Academy of Sciences of the United States of America*, *95*(15), 8703–8708. https://doi.org/10.1073/pnas.95.15.8703

Coppolino, G. T., Marangon, D., Negri, C., Menichetti, G., Fumagalli, M., Gelosa, P., Dimou, L., Furlan, R., Lecca, D., & Abbracchio, M. P. (2018). Differential local tissue permissiveness influences the final fate of GPR17-expressing oligodendrocyte precursors in two distinct models of demyelination. *Glia*, *66*(5), 1118–1130. https://doi.org/10.1002/glia.23305

Elbaz, B., & Popko, B. (2019). Molecular control of oligodendrocyte development. *Trends in Neurosciences*, *42*(4), 263–277. https://doi.org/10.1016/j.tins.2019.01.002

Fancy, S. P., Chan, J. R., Baranzini, S. E., Franklin, R. J., & Rowitch, D. H. (2011). Myelin regeneration: A recapitulation of development? *Annual Review of Neuroscience*, *34*, 21–43. https://doi.org/10.1146/annurev-neuro-061010-113629

Fard, M. K., van der Meer, F., Sánchez, P., Cantuti-Castelvetri, L., Mandad, S., Jäkel, S., Fornasiero, E. F., Schmitt, S., Ehrlich, M., Starost, L., Kuhlmann, T., Sergiou, C., Schultz, V., Wrzos, C., Brück, W., Urlaub, H., Dimou, L., Stadelmann, C., & Simons, M. (2017). BCAS1 expression defines a population of early myelinating oligodendrocytes in multiple sclerosis lesions. *Science Translational Medicine*, *9*(419), eaam7816. https://doi.org/10.1126/scitranslmed.aam7816

Fernandes, M. G. F., Luo, J. X. X., Cui, Q. L., Perlman, K., Pernin, F., Yaqubi, M., Hall, J. A., Dudley, R., Srour, M., Couturier, C. P., Petrecca, K., Larochelle, C., Healy, L. M., Stratton, J. A., Kennedy, T. E., & Antel, J. P. (2021). Age-related injury responses of human oligodendrocytes to metabolic insults: Link to BCL-2 and autophagy pathways. *Communications Biology*, *4*(1), 20. https://doi.org/10.1038/s42003-020-01557-1

Fernandez-Castaneda, A., & Gaultier, A. (2016). Adult oligodendrocyte progenitor cells-multifaceted regulators of the CNS in health and disease. *Brain, Behavior, and Immunity*, *57*, 1–7. https://doi.org/10.1016/j.bbi.2016.01.005

Franklin, R. J., & Ffrench-Constant, C. (2008). Remyelination in the CNS: From biology to therapy. *Nature Reviews Neuroscience*, *9*(11), 839–855. https://doi.org/10.1038/nrn2480

Fu, H., Qi, Y., Tan, M., Cai, J., Takebayashi, H., Nakafuku, M., Richardson, W., & Qiu, M. (2002). Dual origin of spinal oligodendrocyte progenitors and evidence for the cooperative role of Olig2 and Nkx2.2 in the control of oligodendrocyte differentiation. *Development*, *129*(3), 681–693. https://doi.org/10.1242/dev.129.3.681

Fumagalli, M., Daniele, S., Lecca, D., Lee, P. R., Parravicini, C., Fields, R. D., Rosa, P., Antonucci, F., Verderio, C., Trincavelli, M. L., Bramanti, P., Martini, C., & Abbracchio, M. P. (2011). Phenotypic changes, signaling pathway, and functional correlates of GPR17-expressing neural precursor cells during oligodendrocyte differentiation. *Journal of Biological Chemistry*, *286*(12), 10593–10604. https://doi.org/10.1074/jbc.M110.162867

Fumagalli, M., Lecca, D., & Abbracchio, M. P. (2016). CNS remyelination as a novel reparative approach to neurodegenerative diseases: The roles of purinergic signaling and the P2Y-like receptor GPR17. *Neuropharmacology*, *104*, 82–93. https://doi.org/10.1016/j.neuropharm.2015.10.005

Guglietti, B., Sivasankar, S., Mustafa, S., Corrigan, F., & Collins-Praino, L. E. (2021). Fyn kinase activity and its role in neurodegenerative disease pathology: A potential universal target? *Molecular Neurobiology*, *58*(11), 5986–6005. https://doi.org/10.1007/s12035-021-02518-3

Haroutunian, V., Katsel, P., Dracheva, S., & Davis, K. L. (2006). The human homolog of the QKI gene affected in the severe dysmyelination "quaking" mouse phenotype: Downregulated in multiple brain regions in schizophrenia. *The American Journal of Psychiatry*, *163*(10), 1834–1837. https://doi.org/10.1176/ajp.2006.163.10.1834

Hennen, S., Wang, H., Peters, L., Merten, N., Simon, K., Spinrath, A., Blättermann, S., Akkari, R., Schrage, R., Schröder, R., Schulz, D., Vermeiren, C., Zimmermann, K., Kehraus, S., Drewke, C., Pfeifer, A., König, G. M., Mohr, K., Gillard, M., … Kostenis, E. (2013). Decoding signaling and function of the orphan G protein-coupled receptor GPR17 with a small-molecule agonist. *Science Signaling*, *6*(298), ra93. https://doi.org/10.1126/scisignal.2004350

Huang, H., He, W., Tang, T., & Qiu, M. (2023). Immunological markers for central nervous system glia. *Neuroscience Bulletin*, *39*(3), 379–392. https://doi.org/10.1007/s12264-022-00938-2

Huang, H., Wu, H., He, W., Zhou, F., Yu, X., Yi, M., Du, J., Xie, B., & Qiu, M. (2022). Id2 and Id4 are not the major negative regulators of oligodendrocyte differentiation during early central nervous system development. *Glia*, *70*(3), 590–601. http://doi.org/10.1002/glia.24126

Hughes, E. G., Orthmann-Murphy, J. L., Langseth, A. J., & Bergles, D. E. (2018). Myelin remodeling through experience-dependent oligodendrogenesis in the adult somatosensory cortex. *Nature Neuroscience*, *21*(5), 696–706. https://doi.org/10.1038/s41593-018-0121-5

Ishimoto, T., Ninomiya, K., Inoue, R., Koike, M., Uchiyama, Y., & Mori, H. (2017). Mice lacking BCAS1, a novel myelin-associated protein, display

hypomyelination, schizophrenia-like abnormal behaviors, and upregulation of inflammatory genes in the brain. *Glia*, *65*(5), 727–739. https://doi.org/10.1002/glia.23129

Jakel, S., Agirre, E., Mendanha, F. A., van Bruggen, D., Lee, K. W., Knuesel, I., Malhotra, D., Ffrench-Constant, C., Williams, A., & Castelo-Branco, G. (2019). Altered human oligodendrocyte heterogeneity in multiple sclerosis. *Nature*, *566*(7745), 543–547. https://doi.org/10.1038/s41586-019-0903-2

Karussis, D. (2014). The diagnosis of multiple sclerosis and the various related demyelinating syndromes: A critical review. *Journal of Autoimmunity*, *48-49*, 134–142. https://doi.org/10.1016/j.jaut.2014.01.022

Knowles, J. K., Batra, A., Xu, H., & Monje, M. (2022). Adaptive and maladaptive myelination in health and disease. *Nature Reviews. Neurology*, *18*(12), 735–746. https://doi.org/10.1038/s41582-022-00737-3

Lake, B. B., Chen, S., Sos, B. C., Fan, J., Kaeser, G. E., Yung, Y. C., Duong, T. E., Gao, D., Chun, J., Kharchenko, P. V., & Zhang, K. (2018). Integrative single-cell analysis of transcriptional and epigenetic states in the human adult brain. *Nature Biotechnology*, *36*(1), 70–80. https://doi.org/10.1038/nbt.4038

Lauriat, T. L., Shiue, L., Haroutunian, V., Verbitsky, M., Ares, M., Jr., Ospina, L., & McInnes, L. A. (2008). Developmental expression profile of quaking, a candidate gene for schizophrenia, and its target genes in human prefrontal cortex and hippocampus shows regional specificity. *Journal of Neuroscience Research*, *86*(4), 785–796. https://doi.org/10.1002/jnr.21534

Lecca, D., Raffaele, S., Abbracchio, M. P., & Fumagalli, M. (2020). Regulation and signaling of the GPR17 receptor in oligodendroglial cells. *Glia*, *68*(10), 1957–1967. https://doi.org/10.1002/glia.23807

Lecca, D., Trincavelli, M. L., Gelosa, P., Sironi, L., Ciana, P., Fumagalli, M., Villa, G., Verderio, C., Grumelli, C., Guerrini, U., Tremoli, E., Rosa, P., Cuboni, S., Martini, C., Buffo, A., Cimino, M., & Abbracchio, M. P. (2008). The recently identified P2Y-like receptor GPR17 is a sensor of brain damage and a new target for brain repair. *PLoS One*, *3*(10), e3579. https://doi.org/10.1371/journal.pone.0003579

Li, H., & Wang, C. (2011). Post-transcriptional regulation of PDGFalpha-receptor in O-2A progenitor cells. *International Journal of Clinical and Experimental Medicine*, *4*(4), 241–251.

Liang, X., Draghi, N. A., & Resh, M. D. (2004). Signaling from integrins to Fyn to rho family GTPases regulates morphologic differentiation of oligodendrocytes. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *24*(32), 7140–7149. https://doi.org/10.1523/JNEUROSCI.5319-03.2004

Lu, C., Dong, L., Zhou, H., Li, Q., Huang, G., Bai, S. J., & Liao, L. (2018). G-protein-coupled receptor Gpr17 regulates oligodendrocyte differentiation in response to lysolecithin-induced demyelination. *Scientific Reports*, *8*(1), 4502. https://doi.org/10.1038/s41598-018-22452-0

Malone, M., Gary, D., Yang, I. H., Miglioretti, A., Houdayer, T., Thakor, N., & McDonald, J. (2013). Neuronal activity promotes myelination via a cAMP pathway. *Glia*, *61*(6), 843–854. https://doi.org/10.1002/glia.22476

Marangon, D., Audano, M., Pedretti, S., Fumagalli, M., Mitro, N., Lecca, D., Caruso, D., & Abbracchio, M. P. (2022). Rewiring of glucose and lipid metabolism induced by G protein-coupled receptor 17 silencing enables the transition of oligodendrocyte progenitors to myelinating cells. *Cells*, *11*(15), 2369. https://doi.org/10.3390/cells11152369

Marisca, R., Hoche, T., Agirre, E., Hoodless, L. J., Barkey, W., Auer, F., Castelo-Branco, G., & Czopka, T. (2020). Functionally distinct subgroups of oligodendrocyte precursor cells integrate neural activity and execute myelin formation. *Nature Neuroscience*, *23*(3), 363–374. https://doi.org/10.1038/s41593-019-0581-2

Marques, S., Zeisel, A., Codeluppi, S., van Bruggen, D., Mendanha Falcão, A., Xiao, L., Li, H., Häring, M., Hochgerner, H., Romanov, R. A., Gyllborg, D., Muñoz Manchado, A., La Manno, G., Lönnerberg, P., Floriddia, E. M., Rezayee, F., Ernfors, P., Arenas, E., Hjerling-Leffler, J., … Castelo-Branco, G. (2016). Oligodendrocyte heterogeneity in the mouse juvenile and adult central nervous system. *Science*, *352*(6291), 1326–1329. https://doi.org/10.1126/science.aaf6463

McKinnon, R. D., Matsui, T., Dubois-Dalcq, M., & Aaronson, S. A. (1990). FGF modulates the PDGF-driven pathway of oligodendrocyte development. *Neuron*, *5*(5), 603–614. https://doi.org/10.1016/0896-6273(90)90215-2

Mitew, S., Gobius, I., Fenlon, L. R., McDougall, S. J., Hawkes, D., Xing, Y. L., Bujalka, H., Gundlach, A. L., Richards, L. J., Kilpatrick, T. J., Merson, T. D., & Emery, B. (2018). Pharmacogenetic stimulation of neuronal activity increases myelination in an axon-specific manner. *Nature Communications*, *9*(1), 306. https://doi.org/10.1038/s41467-017-02719-2

Mount, C. W., & Monje, M. (2017). Wrapped to adapt: Experience-dependent myelination. *Neuron*, *95*(4), 743–756. https://doi.org/10.1016/j.neuron.2017.07.009

Moyon, S., Dubessy, A. L., Aigrot, M. S., Trotter, M., Huang, J. K., Dauphinot, L., Potier, M. C., Kerninon, C., Parsadaniantz, S. M., Franklin, R. J., & Lubetzki, C. (2015). Demyelination causes adult CNS progenitors to revert to an immature state and express immune cues that support their migration. *Journal of Neuroscience*, *35*(1), 4–20. https://doi.org/10.1523/JNEUROSCI.0849-14.2015

Neumann, B., Baror, R., Zhao, C., Segel, M., Dietmann, S., Rawji, K. S., Foerster, S., McClain, C. R., Chalut, K., van Wijngaarden, P., & Franklin, R. (2019). Metformin restores CNS remyelination capacity by rejuvenating aged stem cells. *Cell Stem Cell*, *25*(4), 473–485. https://doi.org/10.1016/j.stem.2019.08.015

Nyamoya, S., Leopold, P., Becker, B., Beyer, C., Hustadt, F., Schmitz, C., Michel, A., & Kipp, M. (2019). G-protein-coupled receptor Gpr17 expression in two multiple sclerosis remyelination models. *Molecular Neurobiology*, *56*(2), 1109–1123. https://doi.org/10.1007/s12035-018-1146-1

Osterhout, D. J., Wolven, A., Wolf, R. M., Resh, M. D., & Chao, M. V. (1999). Morphological differentiation of oligodendrocytes requires activation of Fyn tyrosine kinase. *The Journal of Cell Biology*, *145*(6), 1209–1218. https://doi.org/10.1083/jcb.145.6.1209

Ou, Z., Ma, Y., Sun, Y., Zheng, G., Wang, S., Xing, R., Chen, X., Han, Y., Wang, J., Lu, Q. R., Zhao, T. J., & Chen, Y. (2019). A GPR17-cAMP-lactate signaling axis in oligodendrocytes regulates whole-body metabolism. *Cell Reports*, *26*(11), 2984–2997.e4. https://doi.org/10.1016/j.celrep.2019.02.060

Ou, Z., Sun, Y., Lin, L., You, N., Liu, X., Li, H., Ma, Y., Cao, L., Han, Y., Liu, M., Deng, Y., Yao, L., Lu, Q. R., & Chen, Y. (2016). Olig2-targeted G-protein-coupled receptor Gpr17 regulates oligodendrocyte survival in response to lysolecithin-induced demyelination. *Journal of Neuroscience*, *36*(41), 10560–10573. https://doi.org/10.1523/JNEUROSCI.0898-16.2016

Parravicini, C., Daniele, S., Palazzolo, L., Trincavelli, M. L., Martini, C., Zaratin, P., Primi, R., Coppolino, G., Gianazza, E., Abbracchio, M. P., & Eberini, I. (2016). A promiscuous recognition mechanism between GPR17 and SDF-1: Molecular insights. *Cellular Signalling*, *28*(6), 631–642. https://doi.org/10.1016/j.cellsig.2016.03.001

Parravicini, C., Lecca, D., Marangon, D., Coppolino, G. T., Daniele, S., Bonfanti, E., Fumagalli, M., Raveglia, L., Martini, C., Gianazza, E., Trincavelli, M. L., Abbracchio, M. P., & Eberini, I. (2020). Development of the first in vivo GPR17 ligand through an iterative drug discovery pipeline: A novel disease-modifying strategy for multiple sclerosis. *PLoS One*, *15*(4), e0231483. https://doi.org/10.1371/journal.pone.0231483

Peckham, H., Giuffrida, L., Wood, R., Gonsalvez, D., Ferner, A., Kilpatrick, T. J., Murray, S. S., & Xiao, J. (2016). Fyn is an intermediate kinase that BDNF utilizes to promote oligodendrocyte myelination. *Glia*, *64*(2), 255–269. https://doi.org/10.1002/glia.22927

Pringle, N., Collarini, E. J., Mosley, M. J., Heldin, C. H., Westermark, B., & Richardson, W. D. (1989). PDGF a chain homodimers drive proliferation of bipotential (O-2A) glial progenitor cells in the developing rat

optic nerve. *EMBO Journal*, *8*(4), 1049–1056. https://doi.org/10.1002/j.1460-2075.1989.tb03472.x

Qi, Y., Cai, J., Wu, Y., Wu, R., Lee, J., Fu, H., Rao, M., Sussel, L., Rubenstein, J., & Qiu, M. (2001). Control of oligodendrocyte differentiation by the Nkx2.2 homeodomain transcription factor. *Development*, *128*(14), 2723–2733. https://doi.org/10.1242/dev.128.14.2723

Raff, M. C., Barres, B. A., Burne, J. F., Coles, H. S., Ishizaki, Y., & Jacobson, M. D. (1993). Programmed cell death and the control of cell survival: Lessons from the nervous system. *Science*, *262*(5134), 695–700. https://doi.org/10.1126/science.8235590

Raffaele, S., Gelosa, P., Bonfanti, E., Lombardi, M., Castiglioni, L., Cimino, M., Sironi, L., Abbracchio, M. P., Verderio, C., & Fumagalli, M. (2021). Microglial vesicles improve post-stroke recovery by preventing immune cell senescence and favoring oligodendrogenesis. *Molecular Therapy: The Journal of the American Society of Gene Therapy*, *29*(4), 1439–1458. https://doi.org/10.1016/j.ymthe.2020.12.009

Ren, H., Orozco, I. J., Su, Y., Suyama, S., Gutiérrez-Juárez, R., Horvath, T. L., Wardlaw, S. L., Plum, L., Arancio, O., & Accili, D. (2012). FoxO1 target Gpr17 activates AgRP neurons to regulate food intake. *Cell*, *149*(6), 1314–1326. https://doi.org/10.1016/j.cell.2012.04.032

Rivera, A. D., Chacon-De-La-Rocha, I., Pieropan, F., Papanikolau, M., Azim, K., & Butt, A. M. (2021). Keeping the ageing brain wired: A role for purine signalling in regulating cellular metabolism in oligodendrocyte progenitors. *Pflügers Archiv-European Journal of Physiology*, *473*(5), 775–783. https://doi.org/10.1007/s00424-021-02544-z

Rivers, L. E., Young, K. M., Rizzi, M., Jamen, F., Psachoulia, K., Wade, A., Kessaris, N., & Richardson, W. D. (2008). PDGFRA/NG2 glia generate myelinating oligodendrocytes and piriform projection neurons in adult mice. *Nature Neuroscience*, *11*(12), 1392–1401. https://doi.org/10.1038/nn.2220

Sharma, K., Schmitt, S., Bergner, C. G., Tyanova, S., Kannaiyan, N., Manrique-Hoyos, N., Kongi, K., Cantuti, L., Hanisch, U. K., Philips, M. A., Rossner, M. J., Mann, M., & Simons, M. (2015). Cell type- and brain region-resolved mouse brain proteome. *Nature Neuroscience*, *18*(12), 1819–1831. https://doi.org/10.1038/nn.4160

Simon, K., Hennen, S., Merten, N., Blattermann, S., Gillard, M., Kostenis, E., & Gomeza, J. (2016). The orphan G protein-coupled receptor GPR17 negatively regulates oligodendrocyte differentiation via Galphai/o and its downstream effector molecules. *Journal of Biological Chemistry*, *291*(2), 705–718. https://doi.org/10.1074/jbc.M115.683953

Soula, C., Danesin, C., Kan, P., Grob, M., Poncet, C., & Cochard, P. (2001). Distinct sites of origin of oligodendrocytes and somatic motoneurons in the chick spinal cord: Oligodendrocytes arise from Nkx2.2-expressing progenitors by a shh-dependent mechanism. *Development*, *128*(8), 1369–1379. https://doi.org/10.1242/dev.128.8.1369

Sun, L. O., Mulinyawe, S. B., Collins, H. Y., Ibrahim, A., Li, Q., Simon, D. J., Tessier-Lavigne, M., & Barres, B. A. (2018). Spatiotemporal control of CNS myelination by oligodendrocyte programmed cell death through the TFEB-PUMA axis. *Cell*, *175*(7), 1811–1826. https://doi.org/10.1016/j.cell.2018.10.044

Sun, T., Dong, H., Wu, L., Kane, M., Rowitch, D. H., & Stiles, C. D. (2003). Cross-repressive interaction of the Olig2 and Nkx2.2 transcription factors in developing neural tube associated with formation of a specific physical complex. *Journal of Neuroscience*, *23*(29), 9547–9556. https://doi.org/10.1523/JNEUROSCI.23-29-09547.2003

Sun, T., Echelard, Y., Lu, R., Yuk, D. I., Kaing, S., Stiles, C. D., & Rowitch, D. H. (2001). Olig bHLH proteins interact with homeodomain proteins to regulate cell fate acquisition in progenitors of the ventral neural tube. *Current Biology*, *11*(18), 1413–1420. https://doi.org/10.1016/s0960-9822(01)00441-9

Tasic, B., Menon, V., Nguyen, T. N., Kim, T. K., Jarsky, T., Yao, Z., Levi, B., Gray, L. T., Sorensen, S. A., Dolbeare, T., Bertagnolli, D., Goldy, J., Shapovalova, N., Parry, S., Lee, C., Smith, K., Bernard, A., Madisen, L., Sunkin, S. M., … Zeng, H. (2016). Adult mouse cortical cell taxonomy revealed by single cell transcriptomics. *Nature Neuroscience*, *19*(2), 335–346. https://doi.org/10.1038/nn.4216

Tran, M. N., Maynard, K. R., Spangler, A., Huuki, L. A., Montgomery, K. D., Sadashivaiah, V., Tippani, M., Barry, B. K., Hancock, D. B., Hicks, S. C., Kleinman, J. E., Hyde, T. M., Collado-Torres, L., Jaffe, A. E., & Martinowich, K. (2021). Single-nucleus transcriptome analysis reveals cell-type-specific molecular signatures across reward circuitry in the human brain. *Neuron*, *109*(19), 3088–3103.e5. https://doi.org/10.1016/j.neuron.2021.09.001

Umemori, H., Sato, S., Yagi, T., Aizawa, S., & Yamamoto, T. (1994). Initial events of myelination involve Fyn tyrosine kinase signalling. *Nature*, *367*(6463), 572–576. https://doi.org/10.1038/367572a0

van Bruggen, D., Agirre, E., & Castelo-Branco, G. (2017). Single-cell transcriptomic analysis of oligodendrocyte lineage cells. *Current Opinion in Neurobiology*, *47*, 168–175. https://doi.org/10.1016/j.conb.2017.10.005

Vigano, F., Schneider, S., Cimino, M., Bonfanti, E., Gelosa, P., Sironi, L., Abbracchio, M. P., & Dimou, L. (2016). GPR17 expressing NG2-glia: Oligodendrocyte progenitors serving as a reserve pool after injury. *Glia*, *64*(2), 287–299. https://doi.org/10.1002/glia.22929

Wake, H., Lee, P. R., & Fields, R. D. (2011). Control of local protein synthesis and initial events in myelination by action potentials. *Science*, *333*(6049), 1647–1651. https://doi.org/10.1126/science.1206998

Wang, S., Sdrulla, A., Johnson, J. E., Yokota, Y., & Barres, B. A. (2001). A role for the helix-loop-helix protein Id2 in the control of oligodendrocyte development. *Neuron*, *29*(3), 603–614. https://doi.org/10.1016/s0896-6273(01)00237-9

White, R., & Krämer-Albers, E. M. (2014). Axon-glia interaction and membrane traffic in myelin formation. *Frontiers in Cellular Neuroscience*, *7*, 284. https://doi.org/10.3389/fncel.2013.00284

Wolf, R. M., Wilkes, J. J., Chao, M. V., & Resh, M. D. (2001). Tyrosine phosphorylation of p190 RhoGAP by Fyn regulates oligodendrocyte differentiation. *Journal of Neurobiology*, *49*(1), 62–78. https://doi.org/10.1002/neu.1066

Xiao, L., Ohayon, D., McKenzie, I. A., Sinclair-Wilson, A., Wright, J. L., Fudge, A. D., Emery, B., Li, H., & Richardson, W. D. (2016). Rapid production of new oligodendrocytes is required in the earliest stages of motor-skill learning. *Nature Neuroscience*, *19*(9), 1210–1217. https://doi.org/10.1038/nn.4351

Xu, X., Cai, J., Fu, H., Wu, R., Qi, Y., Modderman, G., Liu, R., & Qiu, M. (2000). Selective expression of Nkx-2.2 transcription factor in chicken oligodendrocyte progenitors and implications for the embryonic origin of oligodendrocytes. *Molecular and Cellular Neuroscience*, *16*(6), 740–753. https://doi.org/10.1006/mcne.2000.0916

Zeisel, A., Muñoz-Manchado, A. B., Codeluppi, S., Lönnerberg, P., La Manno, G., Juréus, A., Marques, S., Munguba, H., He, L., Betsholtz, C., Rolny, C., Castelo-Branco, G., Hjerling-Leffler, J., & Linnarsson, S. (2015). Brain structure. Cell types in the mouse cortex and hippocampus revealed by single-cell RNA-seq. *Science*, *347*(6226), 1138–1142. https://doi.org/10.1126/science.aaa1934

Zhang, Y., Chen, K., Sloan, S. A., Bennett, M. L., Scholze, A. R., O'Keeffe, S., Phatnani, H. P., Guarnieri, P., Caneda, C., Ruderisch, N., Deng, S., Liddelow, S. A., Zhang, C., Daneman, R., Maniatis, T., Barres, B. A., & Wu, J. Q. (2014). An RNA-sequencing transcriptome and splicing database of glia, neurons, and vascular cells of the cerebral cortex. *Journal of Neuroscience*, *34*(36), 11929–11947. https://doi.org/10.1523/JNEUROSCI.1860-14.2014

Zhang, Y., Lu, Z., Ku, L., Chen, Y., Wang, H., & Feng, Y. (2003). Tyrosine phosphorylation of QKI mediates developmental signals to regulate mRNA metabolism. *The EMBO Journal*, *22*(8), 1801–1810. https://doi.org/10.1093/emboj/cdg171

Zhao, L., Mandler, M. D., Yi, H., & Feng, Y. (2010). Quaking I controls a unique cytoplasmic pathway that regulates alternative splicing of

myelin-associated glycoprotein. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(44), 19061–19066. https://doi.org/10.1073/pnas.1007487107

Zhou, Q., Choi, G., & Anderson, D. J. (2001). The bHLH transcription factor Olig2 promotes oligodendrocyte differentiation in collaboration with Nkx2.2. *Neuron*, *31*(5), 791–807. https://doi.org/10.1016/s0896-6273(01)00414-7

Zhu, L. M., Shi, D. M., Dai, Q., Cheng, X. J., Yao, W. Y., Sun, P. H., Ding, Y., Qiao, M. M., Wu, Y. L., Jiang, S. H., & Tu, S. P. (2014a). Tumor suppressor XAF1 induces apoptosis, inhibits angiogenesis and inhibits tumor growth in hepatocellular carcinoma. *Oncotarget*, *5*(14), 5403–5415. http://doi.org/10.18632/oncotarget.2114

Zhu, Q., Zhao, X., Zheng, K., Li, H., Huang, H., Zhang, Z., Mastracci, T., Wegner, M., Chen, Y., Sussel, L., & Qiu, M. (2014b). Genetic evidence that Nkx2.2 and Pdgfra are major determinants of the timing of oligodendrocyte differentiation in the developing CNS. *Development*, *141*(3), 548–555. https://doi.org/10.1242/dev.095323

Zhu, X., Bergles, D. E., & Nishiyama, A. (2008). NG2 cells generate both oligodendrocytes and gray matter astrocytes. *Development*, *135*(1), 145–157. https://doi.org/10.1242/dev.004895

How to cite this article: Fang, M., Chen, L., Tang, T., Qiu, M., & Xu, X. (2023). The committed oligodendrocyte precursor cell, a newly-defined intermediate progenitor cell type in oligodendroglial lineage. *Glia*, *71*(11), 2499–2510. https://doi.org/10.1002/glia.24426