

Polydendrocytes in development and myelin repair

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Polydendrocytes (NG2 cells) are a distinct type of glia that populate the developing and adult central nervous systems (CNS). In the adult CNS, they retain mitotic activity and represent the largest proliferating cell population. Genetic and epigenetic mechanisms regulate the fate of polydendrocytes, which give rise to both oligodendrocytes and astrocytes. In addition, polydendrocytes actively differentiate into myelin-forming oligodendrocytes in response to demyelination. This review summarizes the current knowledge regarding polydendrocyte development, which provides an important basis for understanding the mechanisms that lead to the remyelination of demyelinated lesions.

Keywords: polydendrocytes; NG2 cells; oligodendrocytes; myelin; cell fate

Introduction

Myelin is composed of layers of membrane wrapping axons and it functions mainly to facilitate the propagation of action potentials. In demyelinating diseases such as multiple sclerosis (MS), the loss of myelin results in the ineffective conduction of electrical signals that can eventually create neurological disability. In the central nervous system (CNS), myelin is formed exclusively by oligodendrocytes, which differentiate from a type of glial progenitor known as NG2 cells that express the NG2 proteoglycan on the cell surface. Hence, NG2 cells are also commonly called oligodendrocyte precursor cells. In this paper, we will use the term “polydendrocytes”, referring to NG2 cells and recognizing them as one of the major resident glial populations in the CNS, as described in our previous publications^[1,2]. This nomenclature reflects their multi-processed morphology throughout development, from embryonic to adult CNS, and their close lineage relationship to oligodendrocytes.

Polydendrocytes are distributed throughout CNS in both white and gray matter. It is now widely accepted that polydendrocytes are distinct from astrocytes, oligodendrocytes and microglia both morphologically and functionally, and thus represent the fourth major type of glia in the CNS.

In addition, polydendrocytes persistently undergo cell division in the adult CNS and participate in the remyelination process^[1–3]. In this paper, we first introduce recent findings on the specification and proliferation of polydendrocytes *in vivo*. Next, we discuss the fate of polydendrocytes *in vivo* and the factors that contribute to their fate decision. The role of polydendrocytes in myelin repair is highlighted in the final section.

Origin and Specification of Polydendrocytes

In the mouse spinal cord, the first population of oligodendrocyte-lineage cells arise around embryonic day 12.5 (E12.5) from the pMN domain (motor neuron progenitor domain) in the ventral region, which generates motor neurons and oligodendrocytes. They are marked by the expression of the basic helix-loop-helix (bHLH) transcription factors Olig1 and Olig2^[4–6]. Together with cells from the p3 domain that express the homeodomain transcription factor Nkx2.2, they form the majority of oligodendrocyte-lineage cells in the spinal cord^[7]. These cells in the germinal zones do not express NG2 but instead are marked first by the expression of the oligodendrocyte-lineage transcription factor Sox10, followed shortly thereafter by the appearance of the alpha

receptor for platelet-derived growth factor (PDGFR α)^[8]. The onset of NG2 expression immediately follows the onset of PDGFR α expression on cells that have exited the germinal zone and populate the CNS parenchyma. A subpopulation of oligodendrocyte-lineage cells also arises from the dorsal ventricular zone of the spinal cord^[9–11].

In the mouse forebrain, PDGFR α -positive cells are first observed at E11.5–E12.5 in the medial ganglionic eminence and anterior entopeduncular area, followed by the generation of PDGFR α -positive cells from the lateral and caudal ganglionic eminences, as well as from the dorsal germinal zone in the postnatal cortex^[12]. The earliest NG2-positive polydendrocytes appear in the ventral forebrain shortly after the first appearance of PDGFR α on cells that have exited the germinal zone. They are readily detectable at E16.5 in the rat and E14.5 in the mouse in the posterior ventral regions of the forebrain^[8].

It has been well documented that sonic hedgehog (Shh) and its downstream signaling pathway are required for the specification of oligodendrocyte-lineage cells in the developing spinal cord and forebrain^[13–17]. Subsequent studies revealed that the effect of Shh signaling on oligodendroglialogenesis is region-dependent, as the generation of oligodendrocyte-lineage cells in the dorsal spinal cord does not require the participation of Shh and the homeodomain transcription factors Nkx6.1 and Nkx6.2^[10], which regulate the expression of Olig2, a downstream target of Shh, in the ventral spinal cord^[10, 18]. In the embryonic spinal cord, oligodendrocyte production from embryonic neural precursors is nearly completely abolished in Olig2-null mice^[19–21]. Subsequent development of oligodendrocyte-lineage cells is also severely impaired in Olig2-null mice, and this can be rescued by overexpression of Olig2^[23]. In addition, mis-expression of Olig2 from E8.5 to E12.5 in the spinal cord is sufficient to promote ectopic oligodendrocyte generation^[22]. Thus, Olig2 appears to be required for oligodendrocyte specification and development. Ascl1 (Mash1) is another bHLH transcription factor that plays an important role in oligodendrocyte specification, as it has been shown to be required for the generation of a subpopulation of oligodendrocyte-lineage cells in the early embryonic ventral forebrain^[24]. Ascl1 promotes oligodendroglialogenesis by repressing Dlx1/2, which are transcriptional repressors of Olig2^[25]. The prerequisites of oligodendroglialogenesis also

include SoxE proteins, such as Sox8, Sox9 and Sox10. Sox9 functions as a key switch for activating gliogenesis in the embryonic spinal cord^[26]. It cooperates with Sox8 and/or Sox10 to specify oligodendrocyte-lineage cells^[26, 27]. Collectively, they have functions opposite to SoxD proteins including Sox5 and Sox6, which inhibit oligodendrocyte specification^[28]. Large-scale genomic analysis should be performed in the future to reveal additional factors that direct neural progenitors to commit to polydendrocytes.

Proliferation of Polydendrocytes

One of the important properties of polydendrocytes is the persistence of their ability to proliferate in the adult brain. Previous experiments showed that ~70% of 5-bromo-2'-deoxyuridine (BrdU)-incorporated cells in the adult rat brain and spinal cord co-expressed NG2^[29–31], indicating that polydendrocytes are the most abundant proliferating cell population in the adult brain. Several studies focusing on the cell-cycle properties of polydendrocytes demonstrated that the cell-cycle time in the cortex was 48 h at postnatal day 6 (P6) and 78 h at P9^[32, 33], whereas the cell-cycle time extended up to 18–37 days at P60, and 170 days at P540^[33, 34]. The increase in the cell-cycle time that occurs with age is likely caused by an increase in the length of the G1 phase^[34]. Interestingly, in spite of the prolonged cell cycle time and the decreased density in the adult brain compared to the density in the perinatal brain^[8], it was reported that the fraction of polydendrocytes that incorporated BrdU after cumulative labeling remained constant from neonate to adult. Reported numbers varied in different regions with ~40% in the cortex and 50% in the corpus callosum^[33, 35]. Using 5-ethynyl-2'-deoxyuridine, which can be detected with greater efficiency, intriguing results were obtained that all polydendrocytes in the adult brain are cycling^[36]. Together, these observations indicate that polydendrocytes continue to be mitotically active in the adult brain, albeit at a reduced rate.

Fate of Polydendrocytes

Polydendrocytes as Oligodendrocyte Progenitor Cells

Since the discovery in 1987 that confirmed that the so-called bipotential glial precursor cells were indeed NG2-

expressing polydendrocytes^[37,38], it had been predicted that they are capable of differentiating into oligodendrocytes *in vivo*. However, fate analysis of polydendrocytes *in vivo* was hindered by the observation that NG2 expression disappears before terminal differentiation, and that the progeny of polydendrocytes could not be directly detected by immunolabeling for NG2. Recent technological advances have enabled us to use transgenesis to study the fate of polydendrocytes. In particular, we have used NG2creBAC:ZEG transgenic mice to trace the fate of polydendrocytes. In this double-transgenic mouse line, Cre recombinase is permanently activated by the regulatory elements of the NG2 (Cspg4) gene throughout all stages of development. The activation of Cre triggers the expression of the reporter enhanced green fluorescence protein in polydendrocytes as well as all their progeny. Our results provided the first direct evidence that polydendrocytes differentiate into oligodendrocytes in the forebrain and spinal cord^[39,40]. We further used a tamoxifen-inducible creER transgene under the control of the Cspg4 gene to study the fate of polydendrocytes in the postnatal and adult CNS^[41]. The results confirmed that polydendrocytes in the mature brain are still capable of generating oligodendrocytes, which is consistent with other cre-lox fate-mapping studies that have used different promoters active in polydendrocytes such as PDGFR α , Olig2 and proteolipid protein (PLP), to drive the expression of creER^[35,42,43].

Similar to proliferation, the rate of oligodendrocyte differentiation from polydendrocytes declines with age^[41]. When Cre was induced on P2, 66% of the induced cells had become oligodendrocytes by 60 days after Cre induction (60 dpi). By contrast, when Cre was induced at P60, only 39% of the induced cells in the gray matter differentiated into oligodendrocytes by 60 dpi, and the remaining cells were polydendrocytes. The age-dependent decline in oligodendrocyte differentiation from polydendrocytes was also observed in the corpus callosum, although a greater proportion of polydendrocytes differentiated into oligodendrocytes in the white matter than in gray matter.

Time-lapse investigation of cultured brain slices showed that polydendrocytes initially undergo symmetrical division to give birth to two daughter polydendrocytes before differentiating into oligodendrocytes several days later^[41]. Furthermore, an independent study suggested that

the NG2 molecule redistributes asymmetrically during the cell division, which results in the asymmetric localization of epidermal growth factor receptor (EGFR). The loss of NG2 and EGFR in daughter polydendrocytes is positively correlated to oligodendrocyte differentiation^[44]. These observations strongly suggest a coupling between polydendrocyte division and differentiation, and that the cell cycle time is a critical determinant of the rate of oligodendrocyte differentiation from polydendrocytes.

Astroglial and Neuronal Fate of Polydendrocytes

The astroglial fate of polydendrocytes was proposed in the 1980s when cultured polydendrocytes were found to differentiate into type-2 astrocytes in the presence of fetal bovine serum^[45] or cytokines such as bone morphogenic proteins^[46]. However, there was a lack of evidence supporting the astroglial fate of polydendrocytes *in vivo* because of the failure to detect the co-expression of NG2 and astrocyte markers^[47,48], which led to the widely-accepted view that astrocyte differentiation of polydendrocytes is an artifact of the *in vitro* environment and that polydendrocytes are incapable of differentiating into astrocytes *in vivo*^[1,49,50]. Recently, we used NG2creBAC:ZEG transgenic mice to trace the progeny of polydendrocytes and found that polydendrocytes in the embryonic CNS give rise to protoplasmic astrocytes in the ventral forebrain but not in the neocortex or white matter^[39] (Fig. 1). Such regional differences in the astroglial fate of polydendrocytes have also been reported in other studies^[42,43]. These observations suggest that dorsal and ventral polydendrocytes are heterogeneous in their astroglial potential, possibly reflecting their different sites of origin^[12]. In a subsequent study focusing on the fate of polydendrocytes in the mature CNS, we found that the progeny of polydendrocytes in the postnatal brain consist of exclusively oligodendrocyte-lineage cells but not astrocytes^[41]. This result is consistent with other studies that examined the fate of PDGFR α -positive and Olig2-positive cells^[35,42,51], but differed from the report that postnatal PLP-positive cells are capable of generating a subset of protoplasmic astrocytes^[43], possibly due to the activation of the Plp1 promoter in a subset of neural stem cells which are not yet committed to polydendrocytes^[52].

The hypothesis that polydendrocytes can differentiate into neurons has always been in the center of the debate regarding the fate of polydendrocytes. Kondo and Raff

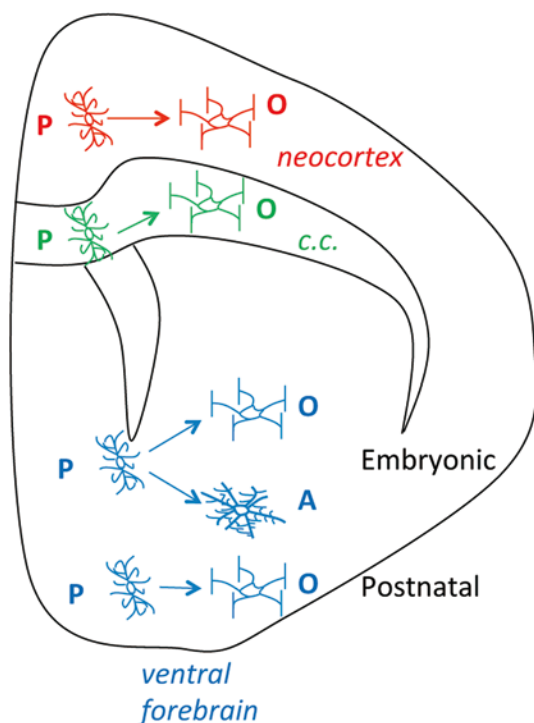


Fig. 1. The fate of polydendrocytes in different regions of the forebrain. The progeny of polydendrocytes in the neocortex and white matter only consists of oligodendrocyte-lineage cells. In the ventral forebrain, polydendrocytes in the embryonic brain differentiate into both astrocytes and oligodendrocytes, whereas polydendrocytes in the postnatal brain only give rise to oligodendrocytes. P, polydendrocytes; O, oligodendrocytes; A, astrocytes; c.c., corpus callosum.

first discovered that the neuronal fate potential of polydendrocytes *in vitro* can be realized by prolonged exposure to basic fibroblast growth factor^[53], which is dependent on the epigenetic modification and reactivation of the Sox2 gene^[54]. Subsequently, other attempts were made to support this hypothesis by showing that purified cells expressing the oligodendrocyte-lineage cell marker 2'3'-cyclic-nucleotide 3'-phosphodiesterase differentiate into neurons in culture and in the host brain after transplantation^[55-57]. However, our studies showed contrasting results that purified NG2-positive polydendrocytes from NG2DsRed transgenic mice do not give rise to any neurons in culture^[39]. Such a discrepancy could be caused by the different starting populations used for the fate analyses, which used different antigens to isolate oligodendrocyte-lineage cells.

Contrary to the prevailing view that supports the notion that polydendrocytes are capable of producing neurons *in vitro*, there is little direct evidence from recent *in vivo* fate-mapping studies to suggest that this occurs. Rivers *et al.* first detected polydendrocyte-derived neurons in the piriform cortex using a PDGFR α -creER transgenic mouse line^[35], but this discovery was challenged by a subsequent study from the same group and another study that used an independently-generated PDGFR α -creER line and showed that postnatal polydendrocytes do not generate neurons in any region of the forebrain^[36,51]. Another positive report came from Guo and colleagues, who showed that Plp-positive cells differentiate into neurons in the piriform cortex^[43], which is confounded by the fact that PLP is expressed in cells other than polydendrocytes and oligodendrocytes, as discussed above. Together with the negative observations from other groups using different oligodendrocyte-lineage-specific Cre driver mouse lines^[39,41,42,51], the consensus seems to be that the lineage potential of polydendrocytes is restricted to glial cells.

Factors That Regulate the Fate of Polydendrocytes

Transcription Factors

Transcriptional control has been well characterized in the differentiation process of polydendrocytes^[58-60]. Among the transcription factors, Olig2 is crucial for polydendrocytes to undergo oligodendrocyte differentiation in addition to its role in polydendrocyte specification^[61]. Our recent study showed that deletion of Olig2 in polydendrocytes severely impaired their oligodendrocyte differentiation and converted them into protoplasmic astrocytes in the embryonic and postnatal neocortex, where polydendrocytes normally do not give rise to astrocytes. Olig1, which is a close relative of Olig2, regulates the development of polydendrocytes mainly at the stage of terminal differentiation by promoting the expression of several myelin genes including Plp, myelin basic protein and myelin-associated glycoprotein^[62,63].

Together with Olig1/2, various other transcription factors form a complex network and regulate the fate of polydendrocytes (Fig. 2). Olig2 binds to the E-box element at the promoter of its target genes as homodimers^[64,65]. The inhibitor of differentiation family members Id2 and Id4,

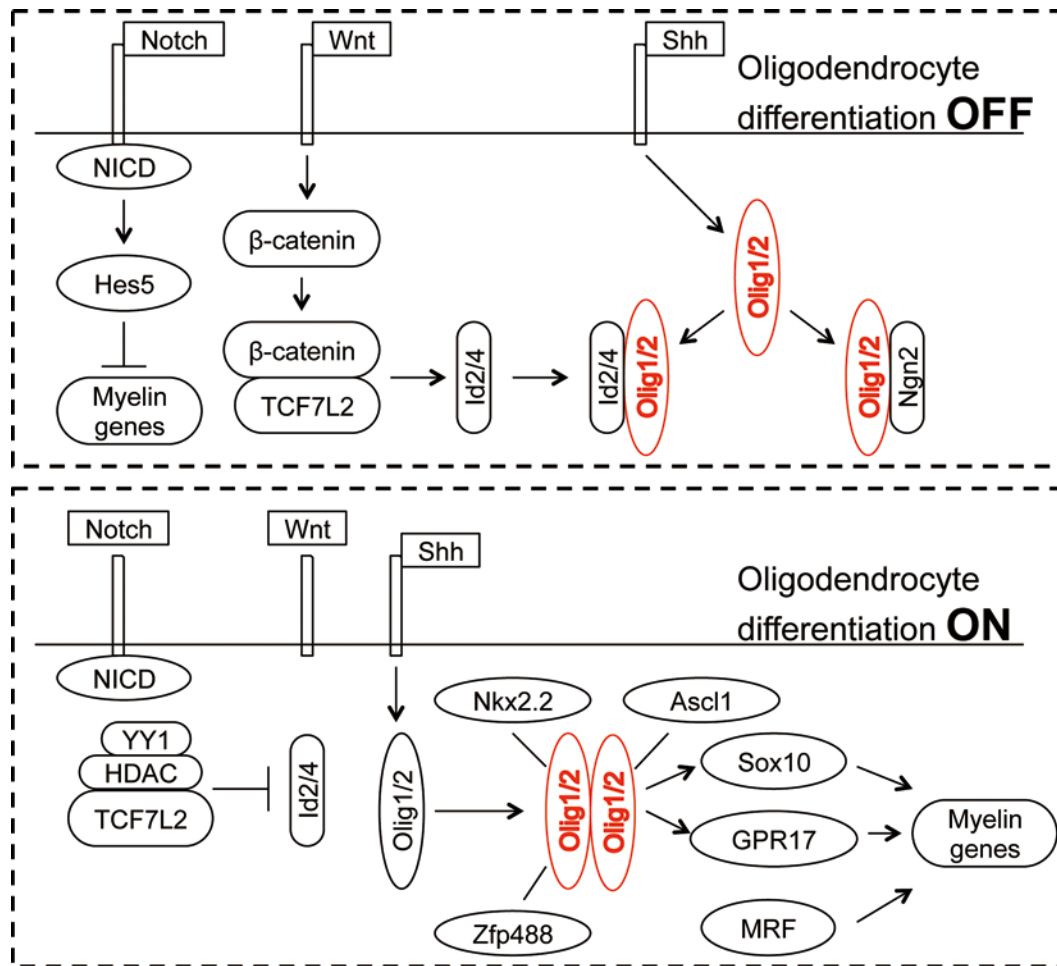


Fig. 2. Model of the transcriptional network regulating oligodendrocyte differentiation from polydendrocytes. Top: pathways that are activated when oligodendrocyte differentiation is limited. Notch activates the expression of Hes5 through NICD and thereby inhibits the expression of myelin genes. In addition, activation of the Wnt signaling pathway causes nuclear translocation of active β-catenin, which binds to TCF7L2 and activates the transcription of Id2/4. Id2/4 or Ngn2 forms a heterodimer with Olig1/2 and shuts down Olig1/2-dependent activation of genes that are required for oligodendrocyte differentiation. Bottom: pathways that are activated during oligodendrocyte differentiation. The complex of HDAC, YY1 and TCF7L2 represses the transcription of Id2/4. As homodimers, Olig1/2 function together with Nkx2.2, Ascl1 and Zfp488 to activate the expression of Sox10 and Gpr17, which in turn lead to the activation of myelin genes and oligodendrocyte differentiation.

which are helix-loop-helix proteins that lack a DNA-binding domain, inhibit the function of Olig2 by competitively binding to it and sequestering it from activating downstream myelin genes^[66]. Consequently, the levels of Id2 and Id4 are critical for the initiation and correct timing of oligodendrocyte differentiation from polydendrocytes^[53,67,68]. Similarly, the neuron-specifying bHLH transcription factor Neurogenin 2 (Ngn2) antagonizes the function of Olig2 by forming heterodimers with it^[64,65]. Upstream of Olig2, downstream targets of the Wnt signaling pathway TCF7L2 and β-catenin

negatively regulate Olig2 expression by activating Id2 and Id4. Conversely, the transcription factor Ying Yang 1 (YY1) represses Id2 and Id4^[69,70]. Working cooperatively with Olig2, Nkx2.2 and Ascl1 were found to promote oligodendrocyte differentiation in the developing spinal cord^[7,71]. The loss of Nkx2.2 or Ascl1 leads to defects in oligodendrocyte production but not specification^[72,73]. Zfp488 is a newly-identified positive regulator of oligodendrocyte differentiation that cooperates with Olig2, and knockdown of Zfp488 by RNA interference causes a deficiency in myelin gene ex-

pression^[74]. Sox10 lies downstream of the Olig genes, and Olig2 activates Sox10 transcription by binding to the U2 enhancer in the Sox10 gene^[63,75]. Thus, Sox10, which has been shown to directly activate myelin genes, might function as a bridge between Olig2 and myelin genes and promote oligodendrocyte differentiation^[76]. A recent study using microarray analysis demonstrated Gpr17 as a downstream target of Olig1 and a negative regulator of oligodendrocyte differentiation^[77]. The results also showed that Gpr17 inhibits oligodendrocyte differentiation by activating the expression of Id2 and Id4, indicating a negative feedback in the transcriptional regulation of oligodendrocyte differentiation.

Independently of Olig2, oligodendrocyte differentiation from polydendrocytes is also under the control of the Notch signaling pathway^[78,79]. Genetic deletion of Notch1 or inhibiting γ -secretase, which is responsible for the cleavage of Notch1 and producing the Notch intracellular domain (NICD), promotes oligodendrocyte differentiation^[79-81]. The bHLH transcription factor Hes5 mediates the effect of Notch1 and inhibits the expression of Ascl1 and Sox10^[82]. Furthermore, myelin gene regulatory factor has been implicated as a transcriptional activator critical for myelin gene expression^[83]. Identification of additional transcription factors and their functions over the next few years should bring us closer to understanding the network of key players in polydendrocyte differentiation.

Epigenetic Factors

One striking finding from the past few years is that glial cell development is tightly regulated by epigenetic mechanisms^[84-86]. Post-translational modification of histones, especially deacetylation, has been proposed to promote oligodendrocyte-lineage progression from polydendrocytes in culture^[87]. Inhibition of class I histone deacetylases (HDACs) during the first two postnatal weeks but not in the third postnatal week results in a severe defect in oligodendrocyte differentiation from polydendrocytes^[88]. Another group independently showed that oligodendrocyte development was mostly abolished in HDAC1 and HDAC2 double knockout mice, which confirmed the critical role of HDAC in oligodendrocyte differentiation^[70]. Recent evidence suggests that HDAC forms a complex with the transcription factors YY1 and Tcf7L2 to repress the expression of differentiation inhibitors such as Id2 and Id4, thus promoting oligodendrocyte differentiation^[69,70]. In addition, it was also reported that HDAC is recruited to the promoters of differentiation inhibi-

tors including Sox2 and Hes5 in the corpus callosum that is undergoing remyelination, thus preventing them from inhibiting oligodendrocyte differentiation and myelination^[89].

Emerging evidence from the past few years has further expanded our knowledge of polydendrocyte fate determinants into the field of microRNA (miRNA). The function of miRNA in polydendrocyte development was investigated by independent groups, who used different transgenic mouse lines to delete Dicer, required for miRNA processing, in oligodendrocyte-lineage cells expressing Olig1^[90,91], Plp^[92], Olig2 or Cnp^[93]. It appears that Dicer is required for the specification of oligodendrocyte-lineage cells in the spinal cord^[91], whereas the deletion of Dicer in postnatal Plp-positive cells resulted in partial loss of myelin proteins^[92]. Two other reports further established a role for miRNA in oligodendrocyte differentiation from polydendrocytes^[90,93]. In both cases, Dicer-null mice exhibited greatly reduced oligodendrocyte differentiation and myelination *in vivo* and *in vitro*^[90,93], which suggests that a dynamic expression pattern of miRNA during different stages of oligodendrocyte development regulates polydendrocyte differentiation^[94,95]. Using microarray analysis of purified polydendrocytes or CNS tissues from Dicer-knockout mice, both studies showed that mir-219 and mir-338 are enriched at the time of oligodendrocyte differentiation. Functional analysis revealed that mir-219 and mir-338 are necessary and sufficient to induce differentiation of polydendrocytes by inhibiting genes that are required for maintaining the progenitor state, such as PDGFR α , Hes5 and Sox6^[90,93]. In other studies, additional miRNAs including mir17-92 cluster, mir-20a and mir-71 were identified as post-transcriptional modifiers that regulate oligodendrocyte differentiation^[96-98]. Together, these observations clearly suggest the important function of miRNA in oligodendrocyte development.

Role of Polydendrocytes in Restoring Myelin

Response of Polydendrocytes to Acute Demyelination

It has been well established that the demyelinating environment triggers a reactive response in grafted or endogenous polydendrocytes^[99,100], which is typically manifested by rapid proliferation of polydendrocytes surrounding and within the demyelinating regions^[47,101-104]. However, for decades, there had been a lack of direct evidence that polydendrocytes

differentiate into oligodendrocytes and contribute to remyelination. Recent cre recombinase-based fate-mapping studies confirmed that polydendrocytes do indeed give rise to oligodendrocytes in acute demyelinating lesions. In an experimental autoimmune encephalomyelitis (EAE) model that mimics the early inflammatory phase of MS^[47], Tripathi *et al.* demonstrated that PDGFR α -positive polydendrocytes underwent expansion and gave rise to myelinating oligodendrocytes in the spinal cord^[105]. Another study by Guo *et al.* supported this observation by showing that the progeny of Olig2-positive cells in the adult spinal cord underwent increased proliferation and differentiated into oligodendrocytes in response to EAE^[106]. Furthermore, a study using lysolecithin-induced acute demyelination in the CNS showed that in addition to generating oligodendrocytes, polydendrocytes could surprisingly generate Schwann cells which are the myelinating cells in peripheral nervous system (PNS) in the center of demyelinated lesions which were typically devoid of Schwann cells^[107].

A BrdU pulse-chase study by Alonso raised the possibility that polydendrocytes could also generate reactive astrocytes in response to pathological stimuli^[108]. However, a subsequent study using *in vivo* fate mapping analysis demonstrated that no reactive astrocytes were observed among the progeny of polydendrocytes after cortical stab injury^[109], which was consistent with another report that showed that cortical injury did not induce BrdU-positive polydendrocytes to become reactive astrocytes^[34]. Similarly, demyelination did not induce polydendrocytes to differentiate into reactive astrocytes^[105-107]. These observations indicate that polydendrocytes are not a source of reactive astrocytes.

Inefficient Remyelination from Polydendrocytes in Chronic Demyelination and in the Aged CNS

Experimental rodents with induced acute demyelination often undergo efficient remyelination, whereas demyelinated lesions in progressive demyelinating diseases such as chronic MS are not successfully remyelinated^[110]. Despite the observation that premyelinating oligodendrocytes were still present in demyelinating lesions in human MS patients which led to the popular theory that myelination from oligodendrocytes is the critical stage for remyelination of demyelinated axons^[111], the lack of oligodendrocytes is still considered as one of the major reasons that contribute to the inefficient remyelination in mouse chronic demyelination

models^[110]. The loss of oligodendrocytes in demyelinated lesions could be explained by (1) the failure to adequately recruit polydendrocytes or (2) the failure of polydendrocytes to differentiate into oligodendrocytes. The first possibility was supported by the observations that polydendrocytes were progressively depleted and the number of oligodendrocytes did not return to normal in a chronic demyelination model created by cuprizone feeding^[112]. However, contradictory results were also reported that polydendrocytes accumulate during the recovery time in the same chronic demyelination model, but in a mouse line with a different genetic background^[113]. In addition, polydendrocytes were shown to be present in the lesion and to proliferate in response to chronic demyelination^[113], which supports the second hypothesis that polydendrocytes fail to differentiate into oligodendrocytes. Further studies are still needed to clarify the behavior of polydendrocytes in chronic demyelinating diseases.

Aging is another factor that affects the efficiency of remyelination^[114,115]. In old rats, the recruitment and differentiation of polydendrocytes is largely impaired in acute demyelination compared with young rats^[116], which is likely caused by the inefficient recruitment of HDAC to the promoter of differentiation inhibitors as described above^[89]. The decline in the proliferative rate of polydendrocytes that occurs with age could also be responsible for the inefficiency of remyelination in aged animals (see discussion above).

Concluding Remarks

Recent research progress has greatly expanded our knowledge of the role of polydendrocytes in the normal and diseased CNS. Appearing in the mid-embryonic stage, polydendrocytes actively undergo cell division and spread throughout the entire CNS. Recent findings have confirmed that polydendrocytes are primarily oligodendrocyte precursor cells in the CNS that also possess lineage plasticity early in life, mostly before birth, when they generate astrocytes as well as oligodendrocytes in the ventral forebrain, and that polydendrocyte differentiation is under the control of various genetic and epigenetic factors. Importantly, the proliferation of polydendrocytes persists into the adult stage and contributes to myelin repair. Therefore, polydendrocytes have been considered a promising therapeutic target for cell-based treatment for demyelinating diseases such as

MS, and further studies on the molecular mechanisms that orchestrate the recruitment and differentiation of polydendrocytes are necessary to exploit this large endogenous progenitor cell population for therapy.

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