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·Review·

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 (PDGFRα)[8]. The onset of NG2 expression immediately follows the onset of PDGFRα 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, PDGFRα-positive cells are first observed at E11.5–E12.5 in the medial ganglionic eminence and anterior entopeduncular area, followed by the generation of PDGFRα-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 PDGFRα 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 oligodendrogliogenesis 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 oligodendrogliogenesis by repressing Dlx1/2, which are transcriptional repressors of Olig2[25]. The prerequisites of oligodendrogliogenesis 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 PDGFRα, 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 PDGFRα-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

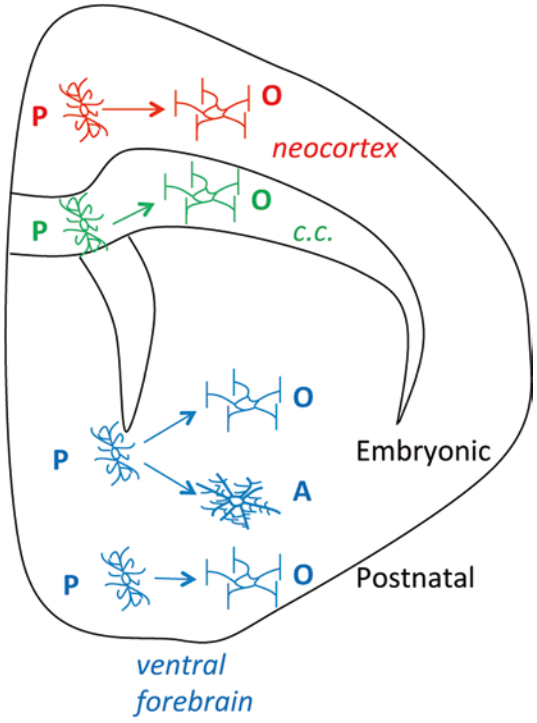

Fig. 1. The fate of polydendrocytes in different regions of the forebrain. The progeny of polydendrocytes in the neocortex and white matter only consists of oligodendrocyte-lineage cells. In the ventral forebrain, polydendrocytes in the embryonic brain differentiate into both astrocytes and oligodendrocytes, 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'-phophodiesterase 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 PDGFRα-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 PDGFRα-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,

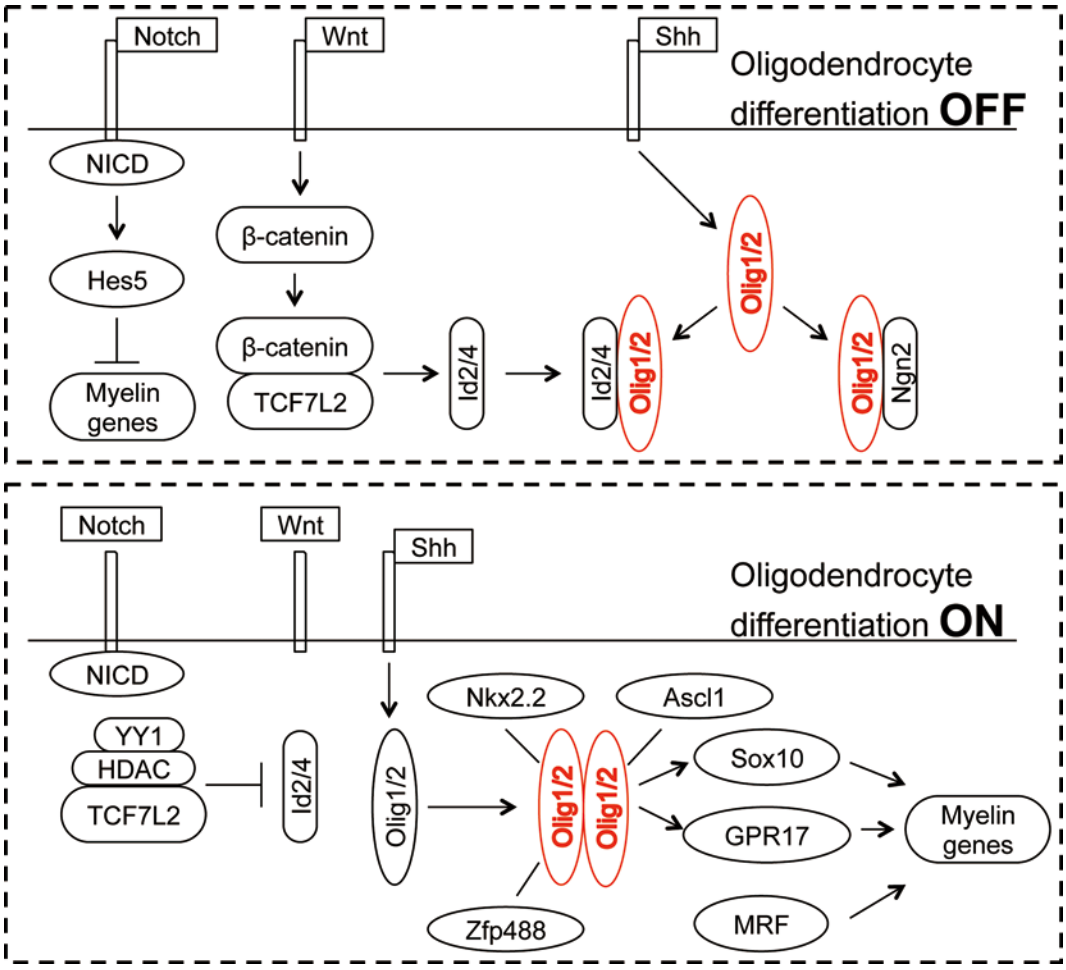

Fig. 2. Model of the transcriptional network regulating oligodendrocyte differentiation from polydendrocytes. Top: pathways that are activated when oligodendrocyte differentiation is limited. Notch actives the expression of Hes5 through NICD and thereby inhibits the expression of myelin genes. In addition, 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 its 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 inhibitors 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 PDGFRα, 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 PDGFRα-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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REFERENCES

[1] Nishiyama A, Watanabe M, Yang Z, Bu J. Identity, distribution, and development of polydendrocytes: NG2-expressing glial cells. J Neurocytol 2002, 31: 437–455.

[2] Nishiyama A, Komitova M, Suzuki R, Zhu X. Polydendrocytes (NG2 cells): multifunctional cells with lineage plasticity. Nat Rev Neurosci 2009, 10: 9–22.

[3] Dawson MR, Levine JM, Reynolds R. NG2-expressing cells in the central nervous system: are they oligodendroglial progenitors? J Neurosci Res 2000, 61: 471–479.

[4] Lu QR, Yuk D, Alberta JA, Zhu Z, Pawlitzky I, Chan J*, et al*. Sonic hedgehog--regulated oligodendrocyte lineage genes encoding bHLH proteins in the mammalian central nervous system. Neuron 2000, 25: 317–329.

[5] Zhou Q, Wang S, Anderson DJ. Identification of a novel family of oligodendrocyte lineage-specific basic helix-loop-helix transcription factors. Neuron 2000, 25: 331–343.

[6] Takebayashi H, Yoshida S, Sugimori M, Kosako H, Kominami R, Nakafuku M*, et al*. Dynamic expression of basic helix-loop-helix Olig family members: implication of Olig2 in neuron and oligodendrocyte differentiation and identification of a new member, Olig3. Mech Dev 2000, 99: 143–148.

[7] Fu H, Qi Y, Tan M, Cai J, Takebayashi H, Nakafuku M*, et al*. Dual origin of spinal oligodendrocyte progenitors and evidence for the cooperative role of Olig2 and Nkx2.2 in the control of oligodendrocyte differentiation. Development 2002, 129: 681–693.

[8] Nishiyama A, Lin XH, Giese N, Heldin CH, Stallcup WB. Co-localization of NG2 proteoglycan and PDGF alpha-receptor on O2A progenitor cells in the developing rat brain. J Neurosci Res 1996, 43: 299–314.

[9] Fogarty M, Richardson WD, Kessaris N. A subset of oligodendrocytes generated from radial glia in the dorsal spinal cord. Development 2005, 132: 1951–1959.

[10] Cai J, Qi Y, Hu X, Tan M, Liu Z, Zhang J*, et al*. Generation of oligodendrocyte precursor cells from mouse dorsal spinal cord independent of Nkx6 regulation and Shh signaling. Neuron 2005, 45: 41–53.

[11] Vallstedt A, Klos JM, Ericson J. Multiple dorsoventral origins of oligodendrocyte generation in the spinal cord and hindbrain. Neuron 2005, 45: 55–67.

[12] Kessaris N, Fogarty M, Iannarelli P, Grist M, Wegner M, Richardson WD. Competing waves of oligodendrocytes in the forebrain and postnatal elimination of an embryonic lineage. Nat Neurosci 2006, 9: 173–179.

[13] Orentas DM, Hayes JE, Dyer KL, Miller RH. Sonic hedgehog signaling is required during the appearance of spinal cord oligodendrocyte precursors. Development 1999, 126: 2419–2429.

[14] Alberta JA, Park SK, Mora J, Yuk D, Pawlitzky I, Iannarelli P*, et al*. Sonic hedgehog is required during an early phase of oligodendrocyte development in mammalian brain. Mol Cell Neurosci 2001, 18: 434–441.

[15] Nery S, Wichterle H, Fishell G. Sonic hedgehog contributes to oligodendrocyte specification in the mammalian forebrain. Development 2001, 128: 527–540.

[16] Sussman CR, Davies JE, Miller RH. Extracellular and intracellular regulation of oligodendrocyte development: roles of Sonic hedgehog and expression of E proteins. Glia 2002, 40: 55–64.

[17] Tekki-Kessaris N, Woodruff R, Hall AC, Gaffield W, Kimura S, Stiles CD*, et al*. Hedgehog-dependent oligodendrocyte lineage specification in the telencephalon. Development 2001, 128: 2545–2554.

[18] Liu R, Cai J, Hu X, Tan M, Qi Y, German M*, et al*. Region-specific and stage-dependent regulation of Olig gene expression and oligodendrogenesis by Nkx6.1 homeodomain transcription factor. Development 2003, 130: 6221–6231.

[19] Lu QR, Sun T, Zhu Z, Ma N, Garcia M, Stiles CD*, et al*. Common developmental requirement for Olig function indicates a motor neuron/oligodendrocyte connection. Cell 2002, 109: 75–86.

[20] Zhou Q, Anderson DJ. The bHLH transcription factors OLIG2 and OLIG1 couple neuronal and glial subtype specification. Cell 2002, 109: 61–73.

[21] Takebayashi H, Nabeshima Y, Yoshida S, Chisaka O, Ikenaka K, Nabeshima Y. The basic helix-loop-helix factor olig2 is essential for the development of motoneuron and oligodendrocyte lineages. Curr Biol 2002, 12: 1157–1163.

[22] Maire CL, Wegener A, Kerninon C, Nait Oumesmar B. Gain-of-function of Olig transcription factors enhances oligodendrogenesis and myelination. Stem Cells 2010, 28: 1611–1622.

[23] Ligon KL, Kesari S, Kitada M, Sun T, Arnett HA, Alberta JA*, et al*. Development of NG2 neural progenitor cells requires Olig gene function. Proc Natl Acad Sci U S A 2006, 103: 7853–7858.

[24] Parras CM, Hunt C, Sugimori M, Nakafuku M, Rowitch D, Guillemot F. The proneural gene Mash1 specifies an early population of telencephalic oligodendrocytes. J Neurosci 2007, 27: 4233–4242.

[25] Petryniak MA, Potter GB, Rowitch DH, Rubenstein JL. Dlx1 and Dlx2 control neuronal versus oligodendroglial cell fate acquisition in the developing forebrain. Neuron 2007, 55: 417–433.

[26] Stolt CC, Lommes P, Sock E, Chaboissier MC, Schedl A, Wegner M. The Sox9 transcription factor determines glial fate choice in the developing spinal cord. Genes Dev 2003, 17: 1677–1689.

[27] Stolt CC, Schmitt S, Lommes P, Sock E, Wegner M. Impact of transcription factor Sox8 on oligodendrocyte specification in the mouse embryonic spinal cord. Dev Biol 2005, 281: 309–317.

[28] Stolt CC, Schlierf A, Lommes P, Hillgartner S, Werner T, Kosian T*, et al*. SoxD proteins influence multiple stages of oligodendrocyte development and modulate SoxE protein function. Dev Cell 2006, 11: 697–709.

[29] Horner PJ, Power AE, Kempermann G, Kuhn HG, Palmer TD, Winkler J*, et al*. Proliferation and differentiation of progenitor cells throughout the intact adult rat spinal cord. J Neurosci 2000, 20: 2218–2228.

[30] Dawson MR, Polito A, Levine JM, Reynolds R. NG2-expressing glial progenitor cells: an abundant and widespread population of cycling cells in the adult rat CNS. Mol Cell Neurosci 2003, 24: 476–488.

[31] Lasiene J, Matsui A, Sawa Y, Wong F Horner PJ. Age-related myelin dynamics revealed by increased oligodendrogenesis and short internodes. Aging Cell 2009, 8: 201–213.

[32] Kukley M, Kiladze M, Tognatta R, Hans M, Swandulla D, Schramm J*, et al*. Glial cells are born with synapses. FASEB J 2008, 22: 2957–2969.

[33] Psachoulia K, Jamen F, Young KM, Richardson WD. Cell cycle dynamics of NG2 cells in the postnatal and ageing brain. Neuron Glia Biol 2009, 5: 57–67.

[34] Simon C, Gotz M, Dimou L. Progenitors in the adult cerebral cortex: cell cycle properties and regulation by physiological stimuli and injury. Glia 2011, 59: 869–881.

[35] Rivers LE, Young KM, Rizzi M, Jamen F, Psachoulia K, Wade A*, et al*. PDGFRA/NG2 glia generate myelinating oligodendrocytes and piriform projection neurons in adult mice. Nat Neurosci 2008, 11: 1392–1401.

[36] Clarke LE, Young KM, Hamilton NB, Li H, Richardson WD, Attwell D. Properties and fate of oligodendrocyte progenitor cells in the corpus callosum, motor cortex, and piriform cortex of the mouse. J Neurosci 2012, 32: 8173–8185.

[37] Levine JM, Stallcup WB. Plasticity of developing cerebellar cells *in vitro* studied with antibodies against the NG2 antigen. J Neurosci 1987, 7: 2721–2731.

[38] Stallcup WB, Beasley L. Bipotential glial precursor cells of the optic nerve express the NG2 proteoglycan. J Neurosci 1987, 7: 2737–2744.

[39] Zhu X, Bergles DE, Nishiyama A. NG2 cells generate both oligodendrocytes and gray matter astrocytes. Development 2008, 135: 145–157.

[40] Zhu X, Hill RA, Nishiyama A. NG2 cells generate oligodendrocytes and gray matter astrocytes in the spinal cord. Neuron Glia Biol 2008, 4: 19–26.

[41] Zhu X, Hill RA, Dietrich D, Komitova M, Suzuki R, Nishiyama A. Age-dependent fate and lineage restriction of single NG2 cells. Development 2011, 138: 745–753.

[42] Dimou L, Simon C, Kirchhoff F, Takebayashi H, Gotz M. Progeny of Olig2-expressing progenitors in the gray and white matter of the adult mouse cerebral cortex. J Neurosci 2008, 28: 10434–10442.

[43] Guo F, Ma J, McCauley E, Bannerman P, Pleasure D. Early postnatal proteolipid promoter-expressing progenitors produce multilineage cells *in vivo*. J Neurosci 2009, 29: 7256–7270.

[44] Sugiarto S, Persson AI, Munoz EG, Waldhuber M, Lamagna C, Andor N*, et al*. Asymmetry-defective oligodendrocyte progenitors are glioma precursors. Cancer Cell 2011, 20: 328–340.

[45] Raff MC, Miller RH, Noble M. A glial progenitor cell that develops in vitro into an astrocyte or an oligodendrocyte depending on culture medium. Nature 1983, 303: 390–396.

[46] Mabie PC, Mehler MF, Marmur R, Papavasiliou A, Song Q, Kessler JA. Bone morphogenetic proteins induce astroglial differentiation of oligodendroglial-astroglial progenitor cells. J Neurosci 1997, 17: 4112–4120.

[47] Reynolds R, Dawson M, Papadopoulos D, Polito A, Di Bello IC, Pham-Dinh D*, et al*. The response of NG2-expressing oligodendrocyte progenitors to demyelination in MOG-EAE and MS. J Neurocytol 2002, 31: 523–536.

[48] Nishiyama A, Yang Z, Butt A. Astrocytes and NG2-glia: what's in a name? J Anat 2005, 207: 687–693.

[49] Liu Y, Wu Y, Lee JC, Xue H, Pevny LH, Kaprielian Z*, et al*. Oligodendrocyte and astrocyte development in rodents: an in situ and immunohistological analysis during embryonic development. Glia 2002, 40: 25–43.

[50] Cahoy JD, Emery B, Kaushal A, Foo LC, Zamanian JL, Christopherson KS*, et al*. A transcriptome database for astrocytes, neurons, and oligodendrocytes: a new resource for understanding brain development and function. J Neurosci 2008, 28: 264–278.

[51] Kang SH, Fukaya M, Yang JK, Rothstein JD, Bergles DE. NG2+ CNS glial progenitors remain committed to the oligodendrocyte lineage in postnatal life and following neurode-

generation. Neuron 2010, 68: 668–681.

[52] Mallon BS, Shick HE, Kidd GJ, Macklin WB. Proteolipid promoter activity distinguishes two populations of NG2-positive cells throughout neonatal cortical development. J Neurosci 2002, 22: 876–885.

[53] Kondo T, Raff M. Oligodendrocyte precursor cells reprogrammed to become multipotential CNS stem cells. Science 2000, 289: 1754–1757.

[54] Kondo T, Raff M. Chromatin remodeling and histone modification in the conversion of oligodendrocyte precursors to neural stem cells. Genes Dev 2004, 18: 2963–2972.

[55] Belachew S, Chittajallu R, Aguirre AA, Yuan X, Kirby M, Anderson S*, et al*. Postnatal NG2 proteoglycan-expressing progenitor cells are intrinsically multipotent and generate functional neurons. J Cell Biol 2003, 161: 169–186.

[56] Aguirre AA, Chittajallu R, Belachew S, Gallo V. NG2-expressing cells in the subventricular zone are type C-like cells and contribute to interneuron generation in the postnatal hippocampus. J Cell Biol 2004, 165: 575–589.

[57] Aguirre A, Gallo V. Postnatal neurogenesis and gliogenesis in the olfactory bulb from NG2-expressing progenitors of the subventricular zone. J Neurosci 2004, 24: 10530–10541.

[58] Li H, Richardson WD. Genetics meets epigenetics: HDACs and Wnt signaling in myelin development and regeneration. Nat Neurosci 2009, 12: 815–817.

[59] Chong SY, Chan JR. Tapping into the glial reservoir: cells committed to remaining uncommitted. J Cell Biol 2010, 188: 305–312.

[60] Emery B. Transcriptional and post-transcriptional control of CNS myelination. Curr Opin Neurobiol 2010, 20: 601–607.

[61] Zhu X, Zuo H, Maher BJ, Serwanski DR, LoTurco JJ, Lu QR*, et al*. Olig2-dependent developmental fate switch of NG2 cells. Development 2012, 139: 2299–2307.

[62] Xin M, Yue T, Ma Z, Wu FF, Gow A, Lu QR. Myelinogenesis and axonal recognition by oligodendrocytes in brain are uncoupled in Olig1-null mice. J Neurosci 2005, 25: 1354–1365.

[63] Li H, Lu Y, Smith HK, Richardson WD. Olig1 and Sox10 interact synergistically to drive myelin basic protein transcription in oligodendrocytes. J Neurosci 2007, 27: 14375–14382.

[64] Lee SK, Lee B, Ruiz EC, Pfaff SL. Olig2 and Ngn2 function in opposition to modulate gene expression in motor neuron progenitor cells. Genes Dev 2005, 19: 282–294.

[65] Li H, de Faria JP, Andrew P, Nitarska J, Richardson WD. Phosphorylation regulates OLIG2 cofactor choice and the motor neuron-oligodendrocyte fate switch. Neuron 2011, 69: 918–929.

[66] Samanta J, Kessler JA. Interactions between ID and OLIG proteins mediate the inhibitory effects of BMP4 on oligodendroglial differentiation. Development 2004, 131: 4131–4142.

[67] Wang S, Sdrulla A, Johnson JE, Yokota Y Barres BA. A role for the helix-loop-helix protein Id2 in the control of oligodendrocyte development. Neuron 2001, 29: 603–614.

[68] Chen XS, Zhang YH, Cai QY, Yao ZX. ID2: A negative transcription factor regulating oligodendroglia differentiation. J Neurosci Res 2012, 90: 925–932.

[69] He Y, Dupree J, Wang J, Sandoval J, Li J, Liu H*, et al*. The transcription factor Yin Yang 1 is essential for oligodendrocyte progenitor differentiation. Neuron 2007, 55: 217–230.

[70] Ye F, Chen Y, Hoang T, Montgomery RL, Zhao XH, Bu H*, et al*. HDAC1 and HDAC2 regulate oligodendrocyte differentiation by disrupting the beta-catenin-TCF interaction. Nat Neurosci 2009, 12: 829–838.

[71] Zhou Q, Choi G, Anderson DJ. The bHLH transcription factor Olig2 promotes oligodendrocyte differentiation in collaboration with Nkx2.2. Neuron 2001, 31: 791–807.

[72] Qi Y, Cai J, Wu Y, Wu R, Lee J, Fu H*, et al*. Control of oligodendrocyte differentiation by the Nkx2.2 homeodomain transcription factor. Development 2001, 128: 2723–2733.

[73] Sugimori M, Nagao M, Parras CM, Nakatani H, Lebel M, Guillemot F*, et al*. Ascl1 is required for oligodendrocyte development in the spinal cord. Development 2008, 135: 1271–1281.

[74] Wang SZ, Dulin J, Wu H, Hurlock E, Lee SE, Jansson K*, et al*. An oligodendrocyte-specific zinc-finger transcription regulator cooperates with Olig2 to promote oligodendrocyte differentiation. Development 2006, 133: 3389–3398.

[75] Kuspert M, Hammer A, Bosl MR, Wegner M. Olig2 regulates Sox10 expression in oligodendrocyte precursors through an evolutionary conserved distal enhancer. Nucleic Acids Res 2011, 39: 1280–1293.

[76] Stolt CC, Rehberg S, Ader M, Lommes P, Riethmacher D, Schachner M*, et al*. Terminal differentiation of myelin-forming oligodendrocytes depends on the transcription factor Sox10. Genes Dev 2002, 16: 165–170.

[77] Chen Y, Wu H, Wang S, Koito H, Li J, Ye F*, et al*. The oligodendrocyte-specific G protein-coupled receptor GPR17 is a cell-intrinsic timer of myelination. Nat Neurosci 2009, 12: 1398–1406.

[78] Wang S, Sdrulla AD, diSibio G, Bush G, Nofziger D, Hicks C*, et al*. Notch receptor activation inhibits oligodendrocyte differentiation. Neuron 1998, 21: 63–75.

[79] Genoud S, Lappe-Siefke C, Goebbels S, Radtke F, Aguet M, Scherer SS*, et al*. Notch1 control of oligodendrocyte differentiation in the spinal cord. J Cell Biol 2002, 158: 709–718.

[80] Watkins TA, Emery B, Mulinyawe S, Barres BA. Distinct stages of myelination regulated by gamma-secretase and astrocytes in a rapidly myelinating CNS coculture system. Neuron 2008, 60: 555–569.

[81] Zhang Y, Argaw AT, Gurfein BT, Zameer A, Snyder BJ, Ge C*, et al*. Notch1 signaling plays a role in regulating precursor dif-

ferentiation during CNS remyelination. Proc Natl Acad Sci U S A 2009, 106: 19162–19167.

[82] Liu A, Li J, Marin-Husstege M, Kageyama R, Fan Y, Gelinas C*, et al*. A molecular insight of Hes5-dependent inhibition of myelin gene expression: old partners and new players. EMBO J 2006, 25: 4833–4842.

[83] Emery B, Agalliu D, Cahoy JD, Watkins TA, Dugas JC, Mulinyawe SB*, et al*. Myelin gene regulatory factor is a critical transcriptional regulator required for CNS myelination. Cell 2009, 138: 172–185.

[84] Copray S, Huynh JL, Sher F, Casaccia-Bonnefil P, Boddeke E. Epigenetic mechanisms facilitating oligodendrocyte development, maturation, and aging. Glia 2009, 57: 1579–1587.

[85] Yu Y, Casaccia P, Lu QR. Shaping the oligodendrocyte identity by epigenetic control. Epigenetics 2010, 5: 124–128.

[86] Liu J, Casaccia P. Epigenetic regulation of oligodendrocyte identity. Trends Neurosci 2010, 33: 193–201.

[87] Marin-Husstege M, Muggironi M, Liu A, Casaccia-Bonnefil P. Histone deacetylase activity is necessary for oligodendrocyte lineage progression. J Neurosci 2002, 22: 10333–10345.

[88] Shen S, Li J, Casaccia-Bonnefil P. Histone modifications affect timing of oligodendrocyte progenitor differentiation in the developing rat brain. J Cell Biol 2005, 169: 577–589.

[89] Shen S, Sandoval J, Swiss VA, Li J, Dupree J, Franklin RJ*, et al*. Age-dependent epigenetic control of differentiation inhibitors is critical for remyelination efficiency. Nat Neurosci 2008, 11: 1024–1034.

[90] Zhao X, He X, Han X, Yu Y, Ye F, Chen Y*, et al*. MicroRNA-mediated control of oligodendrocyte differentiation. Neuron 2010, 65: 612–626.

[91] Zheng K, Li H, Zhu Y, Zhu Q, Qiu M. MicroRNAs are essential for the developmental switch from neurogenesis to gliogenesis in the developing spinal cord. J Neurosci 2010, 30: 8245–8250.

[92] Shin D, Shin JY, McManus MT, Ptacek LJ, Fu YH. Dicer ablation in oligodendrocytes provokes neuronal impairment in mice. Ann Neurol 2009, 66: 843–857.

[93] Dugas JC, Cuellar TL, Scholze A, Ason B, Ibrahim A, Emery B*, et al*. Dicer1 and miR-219 Are required for normal oligodendrocyte differentiation and myelination. Neuron 2010, 65: 597–611.

[94] Lau P, Verrier JD, Nielsen JA, Johnson KR, Notterpek L, Hudson LD. Identification of dynamically regulated microRNA and mRNA networks in developing oligodendrocytes. J Neurosci 2008, 28: 11720–11730.

[95] Letzen BS, Liu C, Thakor NV, Gearhart JD, All AH, Kerr CL. MicroRNA expression profiling of oligodendrocyte differentiation from human embryonic stem cells. PLoS One 2010, 5: e10480.

[96] Budde H, Schmitt S, Fitzner D, Opitz L, Salinas-Riester G, Simons M. Control of oligodendroglial cell number by the miR-17-92 cluster. Development 2010, 137: 2127–2132.

[97] Wang E, Cambi F. MicroRNA expression in mouse oligodendrocytes and regulation of proteolipid protein gene expression. J Neurosci Res 2012, 90: 1701–1712.

[98] Zhao X, Wu J, Zheng M, Gao F, Ju G. Specification and maintenance of oligodendrocyte precursor cells from neural progenitor cells: involvement of microRNA-7a. Mol Biol Cell 2012, 23: 2867–2878.

[99] Franklin RJ, Blakemore WF. Transplanting oligodendrocyte progenitors into the adult CNS. J Anat 1997, 190 (Pt 1): 23–33.

[100] Levine JM, Reynolds R, Fawcett JW. The oligodendrocyte precursor cell in health and disease. Trends Neurosci 2001, 24: 39–47.

[101] Keirstead HS, Levine JM, Blakemore WF. Response of the oligodendrocyte progenitor cell population (defined by NG2 labelling) to demyelination of the adult spinal cord. Glia 1998, 22: 161–170.

[102] Di Bello IC, Dawson MR, Levine JM, Reynolds R. Generation of oligodendroglial progenitors in acute inflammatory demyelinating lesions of the rat brain stem is associated with demyelination rather than inflammation. J Neurocytol 1999, 28: 365–381.

[103] Levine JM, Reynolds R. Activation and proliferation of endogenous oligodendrocyte precursor cells during ethidium bromide-induced demyelination. Exp Neurol 1999, 160: 333–347.

[104] Watanabe M, Toyama Y Nishiyama A. Differentiation of proliferated NG2-positive glial progenitor cells in a remyelinating lesion. J Neurosci Res 2002, 69: 826–836.

[105] Tripathi RB, Rivers LE, Young KM, Jamen F, Richardson WD. NG2 glia generate new oligodendrocytes but few astrocytes in a murine experimental autoimmune encephalomyelitis model of demyelinating disease. J Neurosci 2010, 30: 16383–16390.

[106] Guo F, Maeda Y, Ma J, Delgado M, Sohn J, Miers L*, et al*. Macroglial plasticity and the origins of reactive astroglia in experimental autoimmune encephalomyelitis. J Neurosci 2011, 31: 11914–11928.

[107] Zawadzka M, Rivers LE, Fancy SP, Zhao C, Tripathi R, Jamen F*, et al*. CNS-resident glial progenitor/stem cells produce Schwann cells as well as oligodendrocytes during repair of CNS demyelination. Cell Stem Cell 2010, 6: 578–590.

[108] Alonso G. NG2 proteoglycan-expressing cells of the adult rat brain: possible involvement in the formation of glial scar astrocytes following stab wound. Glia 2005, 49: 318–338.

[109] Komitova M, Serwanski DR, Lu QR, Nishiyama A. NG2 cells are not a major source of reactive astrocytes after neocortical stab wound injury. Glia 2011, 59: 800–809.

[110] Franklin RJ. Why does remyelination fail in multiple sclerosis? Nat Rev Neurosci 2002, 3: 705–714.

[111] Chang A, Tourtellotte WW, Rudick R, Trapp BD. Premyelinating oligodendrocytes in chronic lesions of multiple sclerosis. N Engl J Med 2002, 346: 165–173.

[112] Mason JL, Toews A, Hostettler JD, Morell P, Suzuki K, Goldman JE*, et al*. Oligodendrocytes and progenitors become progressively depleted within chronically demyelinated lesions. Am J Pathol 2004, 164: 1673–1682.

[113] Armstrong RC, Le TQ, Flint NC, Vana AC, Zhou YX. Endogenous cell repair of chronic demyelination. J Neuropathol Exp Neurol 2006, 65: 245–256.

[114] Shields SA, Gilson JM, Blakemore WF, Franklin RJ. Remyelination occurs as extensively but more slowly in old rats compared to young rats following gliotoxin-induced CNS demyelination. Glia 1999, 28: 77–83.

[115] Li WW, Penderis J, Zhao C, Schumacher M, Franklin RJ. Females remyelinate more efficiently than males following demyelination in the aged but not young adult CNS. Exp Neurol 2006, 202: 250–254.

[116] Sim FJ, Zhao C, Penderis J, Franklin RJ. The age-related decrease in CNS remyelination efficiency is attributable to an impairment of both oligodendrocyte progenitor recruitment and differentiation. J Neurosci 2002, 22: 2451–2459.