HHS Public Access

Author manuscript

Neurosci Lett. Author manuscript; available in PMC 2021 January 10.

Published in final edited form as:

Neurosci Lett. 2020 January 10; 715: 134593. doi:10.1016/j.neulet.2019.134593.

The effects of developmental and current niches on oligodendrocyte precursor dynamics and fate

Linda L. Boshans[1], **Amin Sherafat**[1], **Akiko Nishiyama**[1,*,2,3]

[1]Department of Physiology and Neurobiology, University of Connecticut, Storrs, CT 06268

[2]Institute for Systems Genomics, University of Connecticut

[3]Institute for Brain and Cognitive Science, University of Connecticut

Abstract

Oligodendrocyte precursor cells (OPCs), whose primary function is to generate myelinating oligodendrocytes, are distributed widely throughout the developing and mature central nervous system. They originate from several defined subdomains in the embryonic germinal zones at different developmental stages and in the adult. While many phenotypic differences have been observed among OPCs in different anatomical regions and among those arising from different germinal zones, we know relatively little about the molecular and cellular mechanisms by which the historical and current niches shape the behavior of oligodendrocyte lineage cells. This minireview will discuss how the behavior of oligodendrocyte lineage cells is influenced by the developmental niches from which subpopulations of OPCs emerge, by the current niches surrounding OPCs in different regions, and in pathological states that cause deviations from the normal density of oligodendrocyte lineage cells and myelin.

Keywords

Oligodendrocyte precursor; NG2; PDGF; niche; proliferation; myelin; astrocyte; development

1. Introduction

Oligodendrocyte progenitor cells (OPCs, also known as NG2 glia or polydendrocytes) are a major glial population in the central nervous system (CNS), comprising 2–9% of the total cell population [1–5]. They are distributed ubiquitously throughout the CNS and are identified by the expression of two cell surface molecules, the chondroitin sulfate proteoglycan NG2 and platelet-derived growth factor receptor alpha (PDGFRα). The primary known function of OPCs is to generate myelinating oligodendrocytes (OLs) not only during developmental myelination but also in the adult. While OPCs are regarded as

*Correspondence should be addressed to: Akiko Nishiyama, Department of Physiology and Neurobiology, University of Connecticut, 75 North Eagleville Road, Storrs, CT 06268-3156, Phone: 860-486-4561, Fax: 860-486-3303, akiko.nishiyama@uconn.edu.

tissue-committed precursor cells, their life-long ability to self-renew its population suggest that some rules that apply to the self-renewing capability of stem cells might apply to OPCs. In stem cell populations such as the hematopoietic stem cells and neural stem cells, the specific location in which they reside, known as the stem cell niche, provides signals that are critical for maintaining their stem-cell behavior [6–8]. OPCs are distinct from these stem cells in that they are distributed widely and are not clustered in specific regions. Despite their widespread distribution, recent studies have suggested that their behavior is influenced by various types of external signals. Here, we collectively refer to the microenvironment around OPCs as the “OL niche”.

OPCs arise from different germinal zones during embryonic development, and in many regions those from different origins become intermingled. Despite the rather surprising recent finding that OPCs from various sources are a transcriptionally homogeneous cell population [9], OPCs can exhibit different functional states (see for example [10]) that may be influenced by the niches of their origin and the niches in which they current reside in. For example, the rate of OPC proliferation and oligodendrocyte differentiation differ in gray and white matter (reviewed in [11, 12]) and appear to be correlated with the regional density of mature OLs [13]. Furthermore, perturbation of normal myelin or OL density elicits a robust proliferative response in OPCs, often leading to restoration of OL and myelin density [14] (reviewed in [2]). In this minireview, we will discuss recent findings and unanswered questions regarding how OPC proliferation and OL differentiation are modulated by 1) the niche of their birthplace, 2) the niche of their present anatomical location, and 3) niches created by deviations from the normal OL and myelin density. The discussion is drawn primarily from the findings in the rodent CNS. While many of the principles apply to the human CNS, there are some notable differences [15].

2. The properties of OL lineage cells in different anteroposterior (rostrocaudal) locations

OLs arise initially from discrete loci in the ventral germinal zones under the influence of the morphogen Sonic hedgehog (Shh), which induces the OL lineage transcription factors Olig1 and 2 (reviewed in [16]). OPCs first appear around embryonic day 12.5 (E12.5) in a subregion of the ventral ventricular zone (VZ) in the spinal cord and from the ventral germinal zones of the medial ganglionic eminence (MGE) and anterior entopeduncular area (AEP) in the forebrain [17, 18]. In both regions, after the initial ventrally derived wave of Shh-dependent OL lineage cells begins to populate the parenchyma, dorsal germinal zones begin to generate additional OPCs, and the later born cells replace or become intermingled with the earlier generated cells (see below).

The temporal sequence of OL development follows the general pattern of posterior to anterior sequence of development that is conserved through ontogeny and phylogeny. OL differentiation starts during late embryonic stages in the spinal cord, whereas OLs in the forebrain do not appear until a few days after birth. Anteroposterior patterning is mediated by region-specific expression of different transcription factors, primarily the Hox gene family in postnatal CNS and by a distinct set of transcription factors including the Otx and

FoxG families of factors in anterior regions [19] (Figure 1A). Historical developmental expression of distinct patterning genes could influence the behavior of OPCs along the anteroposterior axis. The following are some examples of anteroposterior differences in the phenotype of OL lineage cells that have been reported.

2.1. Properties of OL lineage cells in the brain and spinal cord

In vitro studies have noted differences in the behavior of OL lineage cells isolated from the spinal cord and forebrain of early postnatal rats. OPCs in mixed glial cultures from the spinal cord proliferate more robustly in response to PDGF compared to those from the optic nerve [20]. The differential proliferative response to PDGF was not observed when purified OPCs are used, suggesting that the spinal cord environment contains a factor that augments the proliferative response (Figure 1A1). Further analysis revealed that the chemokine GRO-α (CXCL1) is synthesized and released from spinal cord astrocytes and enhances the proliferative response of OPCs to PDGF [21]. Another study described an intrinsically lower proliferative and myelinogenic ability of cultured OPCs from early postnatal rat spinal cord compared with those from the forebrain [22]. The same study showed that immature OLs from the forebrain are more sensitive to kainate-induced death compared with those from the spinal cord, despite similar degrees of intracellular calcium elevation induced by kainate in both populations. While the latter study suggests cell intrinsic differences, the former study on CXCL1-dependent OL proliferation suggests a difference in the cellular niche around OPCs in the spinal cord and brain.

In adult rodents, the spinal cord and telencephalon show different sensitivity to experimental autoimmune encephalitis (EAE). EAE is used as a rodent model of multiple sclerosis (MS) and is induced by active immunization with a peptide from myelin proteins such as myelin oligodendrocyte glycoprotein [23, 24]. The injected animals exhibit a robust inflammatory response predominantly in the spinal cord and a much milder pathology in the brain. It is unclear whether this is caused by structural differences in the vascular or meningeal barriers leading to altered susceptibility to immune cell invasion or whether there are also intrinsic differences in OLs and myelin in the spinal cord that make them more susceptible to immune-mediated damage.

2.2. Are OLs in different anteroposterior regions functionally equivalent?

Studies have been conducted to examine whether OLs from different regions are functionally interchangeable. When OLs from the optic nerves that normally myelinate small-diameter axons are grafted into the ventral funiculus of the spinal cord, they myelinate different-sized axons, suggesting the adaptability of OLs and a lack of an intrinsic program that restricts OLs in a specific region to myelinate exclusively their original natural target axons [25]. A more recent study demonstrated that OLs from the spinal cord have an intrinsic propensity to make longer myelin internodes than those from the cortex [26]. Thus, while OLs from different regions may possess the basic ability to myelinate a target axon or an axon-like object, they may be pre-programmed or have adapted to generate the type of internodes that provide the ideal conduction properties for the specific axons in their local niche, and this property is not immediately lost when the OLs are transferred from their local environment into culture.

2.3. Transcriptomic differences in OPCs from the spinal cord and forebrain

A recent microarray study compared the transcriptome of OPCs cultured from the spinal cord and forebrain of perinatal rats [22] and demonstrated differential expression of transcription factors that are known to be important for anteroposterior patterning during embryogenesis. Genes encoding posterior transcription factors such as Hoxc8 and Hoxa5/6/9 are enriched in spinal cord OPCs, whereas genes encoding anterior transcription factors such as Foxg1 and Six3 are enriched in forebrain OPCs, although none of these genes except for Foxg1 are detected in a bulk RNA-seq dataset from P7 forebrain OPCs [27] (http://www.brainrnaseq.org/). This could reflect the rapid decline in the expression of these transcripts with postnatal age, as P7 mice are considerably "older" than perinatal rats. A more recent developmental single-cell RNA-sequencing study revealed a similar trend to the microarray findings, with higher levels of Hox genes in spinal cord OPCs compared to forebrain OPCs. The difference is significantly greater in OPCs from E13.5 compared with those from P7 spinal cord [28], suggesting that the early patterning genes are eventually downregulated in OL lineage cells during postnatal development (https://castelobranco.shinyapps.io/OPCsinglecell2017/). Conversely, OPCs from the forebrain but not those from the spinal cord have detectable transcripts for Foxg1 and Six3 in E13.5, and these transcripts are also downregulated by P7. The single-cell RNA-seq study also showed that OPCs from P7 spinal cord express higher levels of transcripts encoding mature OL and myelin genes compared with those from the forebrain, suggesting that OPCs are more differentiated in posterior CNS regions at P7.

3. Effects of dorsoventral developmental niches on OPC fate and function

3.1. Ventral and dorsal developmental origin of OPCs

Dorsoventral patterning follows anteroposterior patterning during embryogenesis. In the spinal cord, OPCs first appear from the ventral germinal zone around E12.5, while the dorsal germinal zone produces OPCs around E15.5 and contributes to ~20% of the OPC population [29–31]. Similarly, in the forebrain, the first wave of OPCs emerges around E12.5 from neural progenitor cells (NPCs) expressing the homeodomain transcription factor Nkx2.1 in the MGE and AEP, followed by a second population that emerges around E15.5 from NPCs in the lateral and caudal ganglionic eminences (LGE and CGE) that express Gsh2 [17]. The third and final wave of OPCs begins to appear perinatally from Emx1-expressing neural progenitors (NPCs) along the dorsal wall of the lateral ventricles [17] (Figure 1A). Ventrally derived OPCs initially migrate into the dorsal forebrain, but they become outnumbered by the later born dorsally derived population. In the Kessaris study, a similar proportion of OL lineage cells were shown to be derived from ventral Gsh2+ and dorsal Emx1+ NPCs. The contribution of Emx1+ NPCs is reported to be higher, reaching up to 80–90% of OL lineage cells in the neocortex in a more recent study using a similar reporter [32]. The exact timing of the production of OL lineage cells from the Emx1+ NPCs also differs between the two studies. The Kessaris study shows that at P0, Emx1-derived OL lineage cells constitute about 30% of the OL lineage cells in the motor cortex but none in the corpus callosum [17], while the Winkler study shows that in the E17 somatosensory cortex, 80–90% of the OL lineage cells are already generated from Emx1+ NPCs and remain at this level throughout the postnatal ages [32]. The latter study did not compare the Emx1-derived cells with the

ventral Gsh2-derived cells. It is possible that different cortical regions are populated differently by different sources of OPCs. Another possibility is that there is an overlap between the OL lineage cells marked by Emx1-cre fate mapping and Gsh2-cre fate mapping (see next section).

3.2. Oligodendrogliogenic potential of OPCs arising from ventral and dorsal germinal zones

3.2.1. Normal development—Genetic fate mapping studies have been conducted to determine whether OPCs that arise from different germinal zones differ in their ability to expand, migrate or generate OLs. In the forebrain, when the dual OL lineage cre reporter mice Sox10-loxP-EGFP-loxP-tdTomato (Sox10-GFP/tdTom) are crossed to Gsh2-cre or Emx1-cre mice, the progeny of OPCs arising from the ventral Gsh2+ germinal zone or the dorsal neocortical Emx1+ germinal zone can be identified, respectively, by tdTom expression [33]. Sox10 is expressed exclusively in the OL lineage in the CNS, and therefore, this reporter will not detect the progeny of Nkx2.1, Gsh2, or Emx1+ cells outside the OL lineage. Using this approach, it was shown that both ventrally and dorsally derived OPCs generate OLs. In the corpus callosum, OLs that are derived from dorsal or ventral sources myelinate a similar number of myelin internodes, although OLs with the smallest number of internodes are ventrally derived, and there is no significant difference in the passive membrane properties of ventrally and dorsally derived OPCs and OLs [33].

One caveat to this approach is that during mid-gestation, around E11.5, NPCs at the pallidal-subpallidal boundary (also known as the cortico-striatal border) express both transcription factors that specify dorsal LGE (high expression of Gsh2 in the VZ and Sp8 in the SVZ), as well as the transcription factor Pax6 that specifies the ventral pallium [34] (Figure 1A). While this overlap of pallial and LGE genes is resolved by E15.5, this can lead to recombination in cells in the ventral pallium and dorsal LGE in both Gsh2-cre and Emx1-cre mice. In fact, Gsh2-cre mice have been used to delete Pax6 [35], and Emx1-cre to delete Gsh2 [36] in this boundary region. Thus, considering a recent report that Emx1+ Gsh2− NPCs along the dorsal wall of the lateral ventricles rarely generate OL lineage cells [37], the origin of OPCs that are marked by Gsh2-cre or Emx1-cre fate mapping needs to be evaluated with caution. While tdTom+ OL lineage cells in Emx1-cre;Sox10-GFP/tdTom mice are likely to represent cells from the dorsal origin, tdTom+ OL lineage cells in the dorsal forebrain of Gsh2-cre;Sox10-GFP/tdTom mice could represent cells generated from the boundary area as well as those from the ventral LGE. This may have reduced the sensitivity to detect differences in the properties of OL lineage cells from dorsal and bona fide ventral dorsal MGE/LGE origin. One would need to use intersectional fate mapping with flp and cre recombinases in order to clearly segregate OL lineage cells from the dorsal, ventral, and boundary origin.

In the spinal cord, OL lineage cells from the dorsal dP1–5 germinal domains can be identified with Msx3-cre driver crossed to the dual Sox10-GFP/tdTom reporter mice. Fate mapping in the spinal cord revealed that while ventrally derived OPCs are dispersed throughout the spinal cord, Msx3+ NPC-derived OL lineage cells are found clustered in the dorsal column, suggesting lower migratory capacity of these cells [33]. Although the

mechanism underlying this difference is not known, the later born dorsal OPCs may be differentiating more quickly and thus losing their migratory ability more rapidly. Alternatively, the dorsal spinal cord environment may lack the signals to promote dispersion of OPCs, such as netrin and the chemokine CXCL1 [38, 39]. As in the forebrain, there is no difference in the number of myelin internodes formed by OLs from dorsal and ventral origins in the spinal cord. Nor is there any significant difference in their passive membrane properties, although the membrane resistance of dorsally derived OL lineage cells is slightly lower. In the dorsal column, >90% of the OL lineage cells in the corticospinal tract are initially ventrally derived at postnatal day 13 (P13), but by P67, the relative prevalence is reversed, so that 80% of the OL lineage cells in the tract are dorsally derived. Thus, as in the forebrain, dorsally derived OLs in the spinal cord displace some of the earlier generated OL lineage cells from ventral origin. It is not known what causes this developmental shift in the OL population or why dorsally derived OL lineage cells replace the early generated ventrally derived cells. One possibility is that the younger dorsally derived cells have a more robust proliferative capability (Figure 1A2). It is also possible, that the population shift reflects the reorganization of axons in the tract. For example, in the forebrain, a substantial number of callosal axons that are initially formed are lost and replaced during the first two postnatal weeks, coinciding with the period of rapid OL differentiation and synaptic remodeling [40, 41]. Thus, the replacement of the ventrally derived OLs with dorsally derived OLs may simply reflect the loss of the target of the first cohort of ventrally derived OLs, and the presence of a new axonal target for dorsally derived OLs promotes their survival. This is consistent with the recent observation that OL development in the neocortex is coupled with interneuron development (see minireview by Angulo and colleagues in this Special Issue).

3.2.2. The extent of functional compensation by OPCs from different germinal zones—

The following study was conducted to examine whether OPCs arising from the ventral and dorsal germinal zones in the forebrain are functionally equivalent. When OPCs from one of the three germinal zones specified by the transcription factors Nkx2.1, Gsh2, or Emx1 are ablated, adjacent OPC populations spread and migrate into the vacant region resulting in a normal tiled distribution of OPCs with no myelination defects. This suggests that OPC populations arising from different germinal zones are functionally equivalent [17]. However, other studies suggest that there are differences in the behavior of OPCs from ventral and dorsal origins in pathological states. After acute demyelination in the corpus callosum or the ventral funiculus of the spinal cord, OPCs from the dorsal region respond more robustly and make a greater contribution to remyelination than those from the ventral origin (Figure 1A2) [42]. In the neocortex, loss of Olig2 function in dorsal NPCs or OPCs leads to severe deficits in myelin and OL lineage cells. Under these conditions, ventrally-derived OPCs do not fully repopulate the cortex and compensate for the myelination deficits [43, 44]. In the spinal cord, deletion of the transcription factor Nkx6.1 or Nkx6.2, which is critical for the induction of Olig2, in ventrally derived OPCs initially reduces OPC numbers, but new OPCs emerge after a delay and eventually populate the entire spinal cord [29], although the overall number of OPCs remains lower than that in wild type spinal cord. These studies indicate that the extent of functional compensation varies with the age, location, and method by which the original OL lineage cell population is eliminated. For example, if the earlier born ventral OPCs proliferate less robustly than the

dorsally derived younger OPCs, the replicative senescence of ventrally derived cells might explain their inability to compensate for OL lineage cells lost from the neocortex.

3.3. Astrocyte and neuronal fate of ventrally and dorsally derived OPCs

During normal embryonic development, a subpopulation of OPCs in the gray matter of the ventral forebrain spontaneously downregulate Olig2 and differentiate into protoplasmic astrocytes, producing one-third of the local astrocyte population. By contrast, in the dorsal forebrain OPCs remain in the OL lineage and contribute to less than 2% of protoplasmic astrocytes in the neocortex (Figure 1A3) [45–47]. Intriguingly, contrary to the prediction from earlier dissociated culture studies, OPCs in white matter tracts throughout the neuraxis do not generate astrocytes. When Olig2 is genetically deleted from all OPCs, those in the neocortex and corpus callosum change their fate to become protoplasmic astrocytes, while those in the ventral forebrain gray matter remain in the OL lineage and do not become astrocytes [43, 48]. It remains to be determined whether the differences in the astrogliogenic fate of OPCs during normal development and under Olig2-deleted conditions are intrinsically determined by the niche of their developmental origin, and whether there are intrinsic epigenetic differences among OPCs arising from ventral and dorsal germinal zones.

A few recent studies have attempted to reprogram OPCs in the forebrain into neurons by transducing them with neuronal reprogramming transcription factors. Transduction of OPCs in the normal neocortex with neurogenetic transcription factors failed to generate functional neurons. Successful reprogramming was achieved only in the injured brain, suggesting that the local environment of a lesion contributes to epigenetic modifications in OPCs that facilitate their fate switch [49, 50]. By contrast, transduction of OPCs in the striatum with a different set of transcription factors known to induce dopaminergic neuronal differentiation resulted in the production of functionally active interneurons [51]. It remains to be determined whether the different outcomes of these studies are due to the transduction method or to inherent differences in the sensitivity of OPCs from different germinal zones to neuronal reprogramming factors, possibly due to differences in the chromatin landscape around neuronal genes in OPCs [52].

3.4. Single-cell transcriptomic analyses

Single-cell RNA-sequencing studies have revealed transcriptional heterogeneity among OLs. By contrast, OPCs in the developing and mature brain appear to be transcriptionally homogeneous [9]. Single-cell RNA-sequencing of PDGFRα+ OPCs from P7 forebrains and spinal cords showed that OPCs with the characteristic OL lineage transcriptional profile are not detected at E13.5 but are abundant by P7. Three transcriptionally distinct states of OPCs were identified: 1) those with an enrichment of genes involved in metabolic function, 2) those with an enrichment of genes related to nervous system development and transcription regulation, and 3) those enriched for cell cycle genes [28]. This study failed to detect transcriptionally distinct subpopulations of OPCs. Comparison of the transcriptome of later born, dorsally derived OPCs with those from earlier ventral sources yielded similar profiles. Interestingly, another single-cell transcriptomic study of early postnatal progenitor cells from P5–6 hGFAP-GFP mice identified a small population (4.5%) of “intermediate glial cells” which exhibited transcriptional profile suggestive of a transitional state between

astrocytes and OPCs [53]. This could also explain an earlier observation that GFP (but not glial aspartate transporter GLAST) is detected in OPCs in hGFAP-GFP mice [54]. Furthermore, an RNA-binding zinc-finger protein Zfp36l1 was identified as a switch that suppresses astrocyte fate and promotes OL lineage, suggesting its role in astrocyte-OPC transition, for example in the postnatal SVZ. The study also revealed a sizable fraction of "primitive OPCs (pri-OPCs)" characterized by low expression of OPC signature genes Cspg4 and Pdgfra but the presence of Olig1/2 and progenitor genes such as Ascl1. The "priOPCs were also well represented in single-cell RNA-sequencing of P1–3 Pdgfra-GFP mouse cortical cells. How the niche affects the induction of Zfp36l1 or the progression of pri-OPCs to OPCs remains unknown.

While the lack of a clear segregation of OPCs could reflect their transcriptionally homogeneous nature regardless of the developmental dorsoventral origin, it could also reflect a low sensitivity of detecting the differences due to significant intermixing of the two OPC populations by P7. There may also be differences that are not reflected in the transcriptome but might significantly affect the cellular behavior, such as the chromatin landscape. Further resolution can be obtained by single-cell RNA-sequencing and chromatin analyses of OPCs from different origins with clearly defined tags.

4. Effects of current niches around OL lineage cells – effects of gray and white matter

In addition to the developmental niches discussed above, the current niches around OL lineage cells at any given age and location also play a critical role in regulating the dynamics of OL lineage cells so that they are finely tuned to the functional needs of the local neural network. The mature CNS contains anatomically distinct regions. Gray matter is an area where neuronal somata reside, while white matter consists of myelinated axon tracts that are largely devoid of neuronal soma. OL lineage cells in gray and white matter have been shown to exhibit distinct properties as summarized below (Figure 1B). The effects of specific niche components such as the influence of neurons and astrocytes are discussed extensively in other articles of this Special Issue.

4.1. Morphological and electrophysiological properties of OPCs in gray and matter

Morphologically, OPCs in gray matter are characterized by their symmetrically oriented processes that extend radially from the soma. By contrast, OPCs in white matter have a more elongated, bipolar morphology, with their longer axes parallel to the axons [1, 55, 56]. These differences may reflect differences in the physical constraints of the tissue in gray and white matter. OPCs in the neocortex have higher capacitance and lower input resistance and differ in their K^+ channel properties from those in the corpus callosum [56]. Within the white matter, OPCs with different Na^+ channel densities and currents have been noted [57]. However, and surprisingly, OPCs in both white matter and gray matter depolarize in response to vesicularly released glutamate and GABA from neurons [58, 59]. The presence of synaptic inputs onto OPCs appears to be ubiquitous and does not define subpopulations of OPCs, although the quantity of such synaptic inputs may vary among OPCs in different niches or in different states [10].

4.2. Differences in OPC proliferation and OL differentiation in gray and white matter

The most notable difference in the behavior of OPCs in gray and white matter is that those in white matter proliferate and differentiate into OLs more rapidly than those in gray matter [1, 60–65], and the slower kinetics of OL generation in gray matter has also been demonstrated in the human cortex [66]. Cross-transplantation studies in adult mice have suggested that the majority of OPCs from both gray and white matter differentiate into OL when they are placed in the host white matter, but when placed in the host gray matter, a significantly greater proportion of those from the white matter differentiate compared to those from the gray matter [65]. This suggests that while the white matter environment is conducive to OL differentiation, it could also exert long-lasting effects within OPCs that could be sustained over several weeks after they are extracted from the environment.

Using slice cultures, we have shown that OPCs in the developing white matter proliferate more robustly than those in gray matter partly due to their greater response to PDGF AA acting through PDGFRα [63]. Cross transplantation of 300-μm^3 pieces from gray or white matter into gray or white matter in slice cultures showed that the proliferative response of OPCs of origin is retained in the host gray or white matter. This suggests that the factors that determine the proliferative response of OPCs to PDGF AA are present either cell intrinsically or exist in very close proximity to the OPCs, within a few cell diameters. Given the close spatial relation of OPC processes and somata to those of microglia [67] and astrocytes [68, 69], it is likely that neighboring glia in the micro-niches of OPCs differ in gray and white matter and differentially influence the proliferative behavior of OPCs.

There are examples that suggest that the micro-environmental niches affect the proliferative behavior of OPCs in vivo. When early stages of glioma formation was examined using the MADM (mosaic analysis of double markers) approach, the earliest foci of aberrant proliferation were detected adjacent to neuronal cell bodies [70], suggesting a role of neuronally derived signals in the initial proliferative stage of gliomagenesis. The secreted form of Neuroligin-3, a cell surface recognition molecule involved in synaptogenesis [71], was recently shown as a putative mitogen for glioma that is released from neurons in an activity-dependent manner [72]. The effects of neuronal activity on OL lineage cell dynamics are described in other reviews of this Special Issue by Thornton and Hughes, Chapman and Hill, Angulo and colleagues, and Voronova and colleagues. Microglia may also function as an important local regulator of OPC/OL density and myelin repair [73, 74] and (Sherafat et al., GLIA 2019 supplement).

4.3. Lack of evidence that OPCs in gray and white matter are transcriptionally distinct

The observed differences in OL lineage cell behavior between gray and white matter transcends the anterior/posterior and ventral/dorsal boundaries and are observed throughout the neuraxis, suggesting a universal mechanism for the effects of local axon-rich white matter environment or the neuron/synapse-rich gray matter environment. Microarray analysis of transcripts in human cortex and white matter has been performed [75], but the analysis focused on comparing normal OPCs to glioblastoma cells and did not directly compare OPCs in normal gray and white matter. Among the genes that are most highly differentially expressed between glioma and normal brain, there appears to be no significant

difference in their expression levels in gray and white matter. A more recent single-cell RNA-seq study also failed to reveal transcriptional heterogeneity among OPCs [9, 28]. In contrast to the transcriptionally uniform OPC population, single-cell RNA-seq studies have revealed several transcriptionally distinct subpopulations of mature OL [76, 77]. Further studies are needed to determine whether these subpopulations segregate spatially into distinct anatomical regions or into functionally distinct OL subpopulations with different target axon preferences. In zebrafish, transcriptomic differences have been noted among OPCs in neuron-rich central region and in axon-rich lateral region that appear to be correlated with the rate of their ability to generate OLs (Hoche et al., bioRxiv, July, 2019). Since these populations arise from the same origin, it is likely that the differences reflect different acquired states rather than intrinsic genetically determined differences in cell lineage.

5. Effects of OL / myelin pathology on OPC dynamics

5.1. Rapid proliferative response of OPCs to OL and myelin defects

OPCs undergo rapid proliferation in response to developmental hypomyelination or experimental demyelination [68] (Figure 1C1–2). In addition, when a subpopulation of OPCs are ablated, the remaining OPCs rapidly proliferate to restore the original density within two weeks (Figure 1C3) [14, 78–83]. The proliferative response seems to be more robustly induced by a demyelinating insult than by other types of insults such as inflammatory pathologies [78]. New single-cell RNA sequencing studies have provided new insight into the changes in the transcriptome of OL lineage cells in various types of myelin pathologies. In the mouse experimental autoimmune encephalitis (EAE), the presence immune cells induces major histocompatibility class II (MHCII) antigens on OPCs, endowing them with antigen-presentation capability, so that OPCs from EAE can stimulate proliferation of memory CD4+ T cells in the presence of peptides from myelin oligodendrocyte glycoprotein [84]. MHCII induction in OPCs is also detected in human MS brain. Furthermore, single-cell RNA sequencing of cells from white matter with MS lesions as well as from normal-appearing white matter adjacent to MS lesions revealed that OPCs, intermediate OL lineage cells, and very mature OLs are reduced, while subclusters corresponding to immune OLs and actively myelinating OL are over-represented [85]. These findings suggest that the inflammatory or demyelinating microenvironment around OL lineage cells can dramatically alter their behavior. The specific signals that maintain homeostasis of OPC, OL, and myelin density under physiological and pathological conditions are not known. Death or degeneration of OL lineage cells and myelin could trigger local microglia to become activated and transmit signals to OPCs to proliferate. Moreover, when excess OLs are generated, they fail to survive long term, unless there is a need to produce more myelin (Figure 1C4) [81, 86]. Future studies could be directed toward identifying the precise feedback signaling mechanism that is involved in maintaining the exquisitely tight regulation of the correct number of OLs needed to myelinate the correct number of internodes to match the circuit function. Such signals may be mediated by direct communication between differentiated OLs and OPCs or by paracrine communication that requires other cell types in the micro-niche.

5.2. Differential contribution of local parenchymal OPCs and those arising from the subventricular zone (SVZ) to remyelination

In the rodent CNS, the subventricular zone (SVZ) provides one of the two loci of persistent neurogenesis and gliogenesis that continues in the adult. The NPCs in the SVZ generates OL lineage cells as well as astrocytes and a subset of neurons [87]. Several reports have examined the relative contribution of local OPCs and SVZ-derived new OPCs to the repair of demyelinated lesions. Following demyelination induced by feeding mice with cuprizone for 3–4 weeks, there is a strong reparative OPC response that leads to remyelination when cuprizone is withdrawn. Under these conditions, SVZ-derived OPCs robustly regenerate OLs that fully remyelinate demyelinated axons, occasionally with more wraps of myelin lamellae than axons remyelinated by local OPC-derived OLs [88, 89]. By contrast, after acute lysolecithin-induced demyelination, SVZ-derived OPCs do not initially contribute significantly to remyelinating OLs that are regenerated two weeks after lesioning [90, 91]. However, by four weeks after acute demyelination, a significant number of SVZ-derived OPCs appear around the repaired lesion [91], suggesting that SVZ-derived OPCs are necessary to replenish the OPC population that is diminished due to their differentiation into regenerating OLs. Collectively, these observations suggest that although local parenchymal OPCs are more rapidly mobilized to initiate a reparative response within days of injury, SVZ-derived OPCs that appear after a delay have superior ability to regenerate OLs and myelin.

The mechanism underlying why SVZ-derived OPCs exhibit a more robust remyelinating capability than local OPCs that exist in the corpus callosum remains unknown. Replicative senescence could again be invoked to explain the relatively superior ability of SVZ-derived new OPCs to regenerate OLs and myelin. Local white matter OPCs have presumably undergone multiple rounds of cell divisions and may have reached replicative senescence. One could speculate that the greater extent of remyelination that is known to occur in cortical MS lesions compared to more typical white matter lesions [92–94] may in part be partly attributed to the “mitotically young” OPCs that reside in the cortex and have not undergone as many divisions as those in white matter. The SVZ niche may provide a local environment that suppresses cycling of newly generated OPCs so that they are maintained in a relatively quiescent state, protecting them from replicative senescence, to ensure an adequate supply of young, robustly proliferative OPCs that can be mobilized to repair a lesion. The availability of “young” replication competent OPCs may be an important determinant of whether demyelinated MS lesions are adequately remyelinated.

6. Concluding remarks

Recent studies indicate that the ability of OPCs to proliferate and undergo OL differentiation is greatly influenced by their current local cellular micro-environment and to a lesser extent by their developmental history. These differences are likely to reflect different states of OPCs rather than the development of transcriptionally distinct subpopulations of OPCs. Many of the reported differences could be explained by the hypothesis that they reflect different “mitotic age”. Replicative senescence of OPCs [95] may be a significant contributing factor to the efficacy of a given OPC to robustly generate robustly myelinating

OLs. It will be interesting to determine whether this is a simple function of the number of prior divisions, as suggested by Raff and colleagues [96] or whether other niche-dependent factors influence this state. Further studies using higher resolution approaches to obtaining mitotic indices of OPCs [97] would be necessary to explore this.

Acknowledgments

FUNDING SOURCES

This work was supported by the National Institutes of Health (R01 NS073425, R01 NS074870); and the National Multiple Sclerosis Society (RG-1612-26501).

REFERENCES

1. Dawson MR, Polito A, Levine JM, and Reynolds R (2003). NG2-expressing glial progenitor cells: an abundant and widespread population of cycling cells in the adult rat CNS. Mol Cell Neurosci 24, 476–488. [PubMed: 14572468]
2. Nishiyama A (2007). Polydendrocytes: NG2 cells with many roles in development and repair of the CNS. Neuroscientist 13, 62–76. [PubMed: 17229976]
3. Nishiyama A, Komitova M, Suzuki R, and Zhu X (2009). Polydendrocytes (NG2 cells): multifunctional cells with lineage plasticity. Nat Rev Neurosci 10, 9–22. [PubMed: 19096367]
4. Richardson WD, Young KM, Tripathi RB, and McKenzie I (2011). NG2-glia as multipotent neural stem cells: fact or fantasy? Neuron 70, 661–673. [PubMed: 21609823]
5. Nishiyama A, Boshans L, Goncalves CM, Wegrzyn J, and Patel KD (2016). Lineage, fate, and fate potential of NG2-glia. Brain Res 1638, 116–128. [PubMed: 26301825]
6. Schofield R (1978). The relationship between the spleen colony-forming cell and the haemopoietic stem cell. Blood Cells 4, 7–25. [PubMed: 747780]
7. Ma DK, Ming GL, and Song H (2005). Glial influences on neural stem cell development: cellular niches for adult neurogenesis. Curr Opin Neurobiol 15, 514–520. [PubMed: 16144763]
8. Riquelme PA, Drapeau E, and Doetsch F (2008). Brain micro-ecologies: neural stem cell niches in the adult mammalian brain. Philos Trans R Soc Lond B Biol Sci 363, 123–137. [PubMed: 17322003]
9. Marques S, Zeisel A, Codeluppi S, van Bruggen D, Mendanha Falcao A, Xiao L, Li H, Haring M, Hochgerner H, Romanov RA, et al. (2016). Oligodendrocyte heterogeneity in the mouse juvenile and adult central nervous system. Science 352, 1326–1329. [PubMed: 27284195]
10. Spitzer SO, Sitnikov S, Kamen Y, Evans KA, Kronenberg-Versteeg D, Dietmann S, de Faria O Jr., Agathou S, and Karadottir RT (2019). Oligodendrocyte Progenitor Cells Become Regionally Diverse and Heterogeneous with Age. Neuron 101, 459–471 e455. [PubMed: 30654924]
11. Hill RA, and Nishiyama A (2014). NG2 cells (polydendrocytes): listeners to the neural network with diverse properties. Glia 62, 1195–1210. [PubMed: 24753030]
12. Dimou L, and Simons M (2017). Diversity of oligodendrocytes and their progenitors. Curr Opin Neurobiol 47, 73–79. [PubMed: 29078110]
13. Tomassy GS, Berger DR, Chen HH, Kasthuri N, Hayworth KJ, Vercelli A, Seung HS, Lichtman JW, and Arlotta P (2014). Distinct profiles of myelin distribution along single axons of pyramidal neurons in the neocortex. Science 344, 319–324. [PubMed: 24744380]
14. Hughes EG, Kang SH, Fukaya M, and Bergles DE (2013). Oligodendrocyte progenitors balance growth with self-repulsion to achieve homeostasis in the adult brain. Nat Neurosci 16, 668–676. [PubMed: 23624515]
15. van Tilborg E, de Theije CGM, van Hal M, Wagenaar N, de Vries LS, Benders MJ, Rowitch DH, and Nijboer CH (2018). Origin and dynamics of oligodendrocytes in the developing brain: Implications for perinatal white matter injury. Glia 66, 221–238. [PubMed: 29134703]
16. Richardson WD, Smith HK, Sun T, Pringle NP, Hall A, and Woodruff R (2000). Oligodendrocyte lineage and the motor neuron connection. Glia 29, 136–142. [PubMed: 10625331]

17. Kessaris N, Fogarty M, Iannarelli P, Grist M, Wegner M, and Richardson WD (2006). Competing waves of oligodendrocytes in the forebrain and postnatal elimination of an embryonic lineage. Nat Neurosci 9, 173–179. [PubMed: 16388308]

18. Spassky N, Goujet-Zalc C, Parmantier E, Olivier C, Martinez S, Ivanova A, Ikenaka K, Macklin W, Cerruti I, Zalc B, et al. (1998). Multiple restricted origin of oligodendrocytes. Journal of Neuroscience 18, 8331–8343. [PubMed: 9763477]

19. Reichert H (2002). Conserved genetic mechanisms for embryonic brain patterning. Int J Dev Biol 46, 81–87. [PubMed: 11902691]

20. Robinson S, and Miller R (1996). Environmental enhancement of growth factor-mediated oligodendrocyte precursor proliferation. Molecular and Cellular Neuroscience 8, 38–52. [PubMed: 8923454]

21. Robinson S, Tani M, Strieter RM, Ransohoff RM, and Miller RH (1998). The chemokine growth-regulated oncogene-alpha promotes spinal cord oligodendrocyte precursor proliferation. Journal of Neuroscience 18, 10457–10463. [PubMed: 9852583]

22. Horiuchi M, Suzuki-Horiuchi Y, Akiyama T, Itoh A, Pleasure D, Carstens E, and Itoh T (2017). Differing intrinsic biological properties between forebrain and spinal oligodendroglial lineage cells. J Neurochem 142, 378–391. [PubMed: 28512742]

23. Ransohoff RM (2012). Animal models of multiple sclerosis: the good, the bad and the bottom line. Nat Neurosci 15, 1074–1077. [PubMed: 22837037]

24. Ben-Nun A, Kaushansky N, Kawakami N, Krishnamoorthy G, Berer K, Liblau R, Hohlfeld R, and Wekerle H (2014). From classic to spontaneous and humanized models of multiple sclerosis: impact on understanding pathogenesis and drug development. J Autoimmun 54, 33–50. [PubMed: 25175979]

25. Fanarraga ML, Griffiths IR, Zhao M, and Duncan ID (1998). Oligodendrocytes are not inherently programmed to myelinate a specific size of axon. J Comp Neurol 399, 94–100. [PubMed: 9725703]

26. Bechler ME, Byrne L, and Ffrench-Constant C (2015). CNS Myelin Sheath Lengths Are an Intrinsic Property of Oligodendrocytes. Curr Biol 25, 2411–2416. [PubMed: 26320951]

27. Zhang Y, Chen K, Sloan SA, Bennett ML, Scholze AR, O'Keeffe S, Phatnani HP, Guarnieri P, Caneda C, Ruderisch N, et al. (2014). An RNA-sequencing transcriptome and splicing database of glia, neurons, and vascular cells of the cerebral cortex. J Neurosci 34, 11929–11947. [PubMed: 25186741]

28. Marques S, van Bruggen D, Vanichkina DP, Floriddia EM, Munguba H, Varemo L, Giacomello S, Falcao AM, Meijer M, Bjorklund AK, et al. (2018). Transcriptional Convergence of Oligodendrocyte Lineage Progenitors during Development. Dev Cell 46, 504–517 e507. [PubMed: 30078729]

29. Cai J, Qi Y, Hu X, Tan M, Liu Z, Zhang J, Li Q, Sander M, and Qiu M (2005). Generation of oligodendrocyte precursor cells from mouse dorsal spinal cord independent of Nkx6 regulation and Shh signaling. Neuron 45, 41–53. [PubMed: 15629701]

30. Fogarty M, Richardson WD, and Kessaris N (2005). A subset of oligodendrocytes generated from radial glia in the dorsal spinal cord. Development 132, 1951–1959. [PubMed: 15790969]

31. Vallstedt A, Klos JM, and Ericson J (2005). Multiple dorsoventral origins of oligodendrocyte generation in the spinal cord and hindbrain. Neuron 45, 55–67. [PubMed: 15629702]

32. Winkler CC, Yabut OR, Fregoso SP, Gomez HG, Dwyer BE, Pleasure SJ, and Franco SJ (2018). The Dorsal Wave of Neocortical Oligodendrogenesis Begins Embryonically and Requires Multiple Sources of Sonic Hedgehog. J Neurosci 38, 5237–5250. [PubMed: 29739868]

33. Tripathi RB, Clarke LE, Burzomato V, Kessaris N, Anderson PN, Attwell D, and Richardson WD (2011). Dorsally and ventrally derived oligodendrocytes have similar electrical properties but myelinate preferred tracts. J Neurosci 31, 6809–6819. [PubMed: 21543611]

34. Yun K, Potter S, and Rubenstein JL (2001). Gsh2 and Pax6 play complementary roles in dorsoventral patterning of the mammalian telencephalon. Development 128, 193–205. [PubMed: 11124115]

35. Cocas LA, Georgala PA, Mangin JM, Clegg JM, Kessaris N, Haydar TF, Gallo V, Price DJ, and Corbin JG (2011). Pax6 is required at the telencephalic pallial-subpallial boundary for the

generation of neuronal diversity in the postnatal limbic system. J Neurosci 31, 5313–5324. [PubMed: 21471366]

36. Waclaw RR, Wang B, Pei Z, Ehrman LA, and Campbell K (2009). Distinct temporal requirements for the homeobox gene Gsx2 in specifying striatal and olfactory bulb neuronal fates. Neuron 63, 451–465. [PubMed: 19709628]
37. Naruse M, Ishizaki Y, Ikenaka K, Tanaka A, and Hitoshi S (2017). Origin of oligodendrocytes in mammalian forebrains: a revised perspective. J Physiol Sci 67, 63–70. [PubMed: 27573166]
38. Tsai HH, Frost E, To V, Robinson S, Ffrench-Constant C, Geertman R, Ransohoff RM, and Miller RH (2002). The chemokine receptor CXCR2 controls positioning of oligodendrocyte precursors in developing spinal cord by arresting their migration. Cell 110, 373–383. [PubMed: 12176324]
39. Tsai HH, Tessier-Lavigne M, and Miller RH (2003). Netrin 1 mediates spinal cord oligodendrocyte precursor dispersal. Development 130, 2095–2105. [PubMed: 12668624]
40. Innocenti GM (1986). General Organization of Callosal Connections in the Cerebral Cortex, Volume 5, (New York: Plenum Press).
41. Innocenti GM, and Caminiti R (1980). Postnatal shaping of callosal connections from sensory areas. Exp Brain Res 38, 381–394. [PubMed: 7363973]
42. Crawford AH, Tripathi RB, Richardson WD, and Franklin RJM (2016). Developmental Origin of Oligodendrocyte Lineage Cells Determines Response to Demyelination and Susceptibility to Age-Associated Functional Decline. Cell Rep 15, 761–773. [PubMed: 27149850]
43. Zhu X, Zuo H, Maher BJ, Serwanski DR, LoTurco JJ, Lu QR, and Nishiyama A (2012). Olig2-dependent developmental fate switch of NG2 cells. Development 139, 2299–2307. [PubMed: 22627280]
44. Zuo H, Wood WM, Sherafat A, Hill RA, Lu QR, and Nishiyama A (2018). Age-Dependent Decline in Fate Switch from NG2 Cells to Astrocytes After Olig2 Deletion. J Neurosci 38, 2359–2371. [PubMed: 29382710]
45. Zhu X, Bergles DE, and Nishiyama A (2008). NG2 cells generate both oligodendrocytes and gray matter astrocytes. Development 135, 145–157. [PubMed: 18045844]
46. Zhu X, Hill RA, and Nishiyama A (2008). NG2 cells generate oligodendrocytes and gray matter astrocytes in the spinal cord. Neuron Glia Biol 4, 19–26. [PubMed: 19006598]
47. Huang W, Zhao N, Bai X, Karram K, Trotter J, Goebbels S, Scheller A, and Kirchhoff F (2014). Novel NG2-CreERT2 knock-in mice demonstrate heterogeneous differentiation potential of NG2 glia during development. Glia 62, 896–913. [PubMed: 24578301]
48. Zhang L, He X, Liu L, Jiang M, Zhao C, Wang H, He D, Zheng T, Zhou X, Hassan A, et al. (2016). Hdac3 Interaction with p300 Histone Acetyltransferase Regulates the Oligodendrocyte and Astrocyte Lineage Fate Switch. Dev Cell 36, 316–330. [PubMed: 26859354]
49. Heinrich C, Bergami M, Gascon S, Lepier A, Vigano F, Dimou L, Sutor B, Berninger B, and Gotz M (2014). Sox2-mediated conversion of NG2 glia into induced neurons in the injured adult cerebral cortex. Stem Cell Reports 3, 1000–1014. [PubMed: 25458895]
50. Guo Z, Zhang L, Wu Z, Chen Y, Wang F, and Chen G (2014). In vivo direct reprogramming of reactive glial cells into functional neurons after brain injury and in an Alzheimer's disease model. Cell Stem Cell 14, 188–202. [PubMed: 24360883]
51. Pereira M, Birtele M, Shrigley S, Benitez JA, Hedlund E, Parmar M, and Ottosson DR (2017). Direct Reprogramming of Resident NG2 Glia into Neurons with Properties of Fast-Spiking Parvalbumin-Containing Interneurons. Stem Cell Reports 9, 742–751. [PubMed: 28844658]
52. Boshans LL, Factor DC, Singh V, Liu J, Zhao C, Mandoiu I, Lu QR, Casaccia P, Tesar PJ, and Nishiyama A (2019). The chromatin environment around interneuron genes in oligodendrocyte precursor cells and their potential for interneuron reprogramming. Frontiers in Neuroscience.
53. Weng Q, Wang J, Wang J, He D, Cheng Z, Zhang F, Verma R, Xu L, Dong X, Liao Y, et al. (2019). Single-Cell Transcriptomics Uncovers Glial Progenitor Diversity and Cell Fate Determinants during Development and Gliomagenesis. Cell Stem Cell 24, 707–723 e708. [PubMed: 30982771]
54. Matthias K, Kirchhoff F, Seifert G, Huttmann K, Matyash M, Kettenmann H, and Steinhauser C (2003). Segregated expression of AMPA-type glutamate receptors and glutamate transporters defines distinct astrocyte populations in the mouse hippocampus. J Neurosci 23, 1750–1758. [PubMed: 12629179]

55. Nishiyama A, Chang A, and Trapp BD (1999). NG2+ glial cells: a novel glial cell population in the adult brain. Journal of Neuropathology and Experimental Neurology 58, 1113–1124. [PubMed: 10560654]
56. Chittajallu R, Aguirre A, and Gallo V (2004). NG2-positive cells in the mouse white and grey matter display distinct physiological properties. J Physiol 561, 109–122. [PubMed: 15358811]
57. Clarke LE, Young KM, Hamilton NB, Li H, Richardson WD, and Attwell D (2012). Properties and fate of oligodendrocyte progenitor cells in the corpus callosum, motor cortex, and piriform cortex of the mouse. J Neurosci 32, 8173–8185. [PubMed: 22699898]
58. Bergles DE, Jabs R, and Steinhauser C (2010). Neuron-glia synapses in the brain. Brain Res Rev 63, 130–137. [PubMed: 20018210]
59. Zonouzi M, Scafidi J, Li P, McEllin B, Edwards J, Dupree JL, Harvey L, Sun D, Hubner CA, Cull-Candy SG, et al. (2015). GABAergic regulation of cerebellar NG2 cell development is altered in perinatal white matter injury. Nat Neurosci 18, 674–682. [PubMed: 25821912]
60. Dimou L, Simon C, Kirchhoff F, Takebayashi H, and Gotz M (2008). Progeny of Olig2-expressing progenitors in the gray and white matter of the adult mouse cerebral cortex. J Neurosci 28, 10434–10442. [PubMed: 18842903]
61. Kang SH, Fukaya M, Yang JK, Rothstein JD, and Bergles DE (2010). NG2+ CNS glial progenitors remain committed to the oligodendrocyte lineage in postnatal life and following neurodegeneration. Neuron 68, 668–681. [PubMed: 21092857]
62. Zhu X, Hill RA, Dietrich D, Komitova M, Suzuki R, and Nishiyama A (2011). Age-dependent fate and lineage restriction of single NG2 cells. Development 138, 745–753. [PubMed: 21266410]
63. Hill RA, Patel KD, Medved J, Reiss AM, and Nishiyama A (2013). NG2 cells in white matter but not gray matter proliferate in response to PDGF. J Neurosci 33, 14558–14566. [PubMed: 24005306]
64. Young KM, Psachoulia K, Tripathi RB, Dunn SJ, Cossell L, Attwell D, Tohyama K, and Richardson WD (2013). Oligodendrocyte dynamics in the healthy adult CNS: evidence for myelin remodeling. Neuron 77, 873–885. [PubMed: 23473318]
65. Vigano F, Mobius W, Gotz M, and Dimou L (2013). Transplantation reveals regional differences in oligodendrocyte differentiation in the adult brain. Nat Neurosci 16, 1370–1372. [PubMed: 23995069]
66. Yeung MS, Zdunek S, Bergmann O, Bernard S, Salehpour M, Alkass K, Perl S, Tisdale J, Possnert G, Brundin L, et al. (2014). Dynamics of oligodendrocyte generation and myelination in the human brain. Cell 159, 766–774. [PubMed: 25417154]
67. Nishiyama A, Yu M, Drazba JA, and Tuohy VK (1997). Normal and reactive NG2+ glial cells are distinct from resting and activated microglia. Journal of Neuroscience Research 48, 299–312. [PubMed: 9169856]
68. Nishiyama A, Watanabe M, Yang Z, and Bu J (2002). Identity, distribution, and development of polydendrocytes: NG2-expressing glial cells. J Neurocytol 31, 437–455. [PubMed: 14501215]
69. Hamilton N, Vayro S, Wigley R, and Butt AM (2010). Axons and astrocytes release ATP and glutamate to evoke calcium signals in NG2-glia. Glia 58, 66–79. [PubMed: 19533604]
70. Liu C, Sage JC, Miller MR, Verhaak RG, Hippenmeyer S, Vogel H, Foreman O, Bronson RT, Nishiyama A, Luo L, et al. (2011). Mosaic analysis with double markers reveals tumor cell of origin in glioma. Cell 146, 209–221. [PubMed: 21737130]
71. Scheiffele P, Fan J, Choih J, Fetter R, and Serafini T (2000). Neuroligin expressed in nonneuronal cells triggers presynaptic development in contacting axons. Cell 101, 657–669. [PubMed: 10892652]
72. Venkatesh HS, Johung TB, Caretti V, Noll A, Tang Y, Nagaraja S, Gibson EM, Mount CW, Polepalli J, Mitra SS, et al. (2015). Neuronal Activity Promotes Glioma Growth through Neuroligin-3 Secretion. Cell 161, 803–816. [PubMed: 25913192]
73. Wlodarczyk A, Holtman IR, Krueger M, Yogev N, Bruttger J, Khorooshi R, Benmamar-Badel A, de Boer-Bergsma JJ, Martin NA, Karram K, et al. (2017). A novel microglial subset plays a key role in myelinogenesis in developing brain. EMBO J 36, 3292–3308. [PubMed: 28963396]

74. Hagemeyer N, Hanft KM, Akriditou MA, Unger N, Park ES, Stanley ER, Staszewski O, Dimou L, and Prinz M (2017). Microglia contribute to normal myelinogenesis and to oligodendrocyte progenitor maintenance during adulthood. Acta Neuropathol 134, 441–458. [PubMed: 28685323]

75. Auvergne RM, Sim FJ, Wang S, Chandler-Militello D, Burch J, Al Fanek Y, Davis D, Benraiss A, Walter K, Achanta P, et al. (2013). Transcriptional differences between normal and glioma-derived glial progenitor cells identify a core set of dysregulated genes. Cell Rep 3, 2127–2141. [PubMed: 23727239]

76. Tasic B, Menon V, Nguyen TN, Kim TK, Jarsky T, Yao Z, Levi B, Gray LT, Sorensen SA, Dolbeare T, et al. (2016). Adult mouse cortical cell taxonomy revealed by single cell transcriptomics. Nat Neurosci 19, 335–346. [PubMed: 26727548]

77. Zeisel A, Munoz-Manchado AB, Codeluppi S, Lonnerberg P, La Manno G, Jureus A, Marques S, Munguba H, He L, Betsholtz C, et al. (2015). Brain structure. Cell types in the mouse cortex and hippocampus revealed by single-cell RNA-seq. Science 347, 1138–1142. [PubMed: 25700174]

78. Di Bello CI, Dawson MR, Levine JM, and Reynolds R (1999). Generation of oligodendroglial progenitors in acute inflammatory demyelinating lesions of the rat brain stem is associated with demyelination rather than inflammation. J Neurocytol 28, 365–381. [PubMed: 10739577]

79. Wu Q, Miller RH, Ransohoff RM, Robinson S, Bu J, and Nishiyama A (2000). Elevated levels of the chemokine GRO-1 correlate with elevated oligodendrocyte progenitor proliferation in the jimpy mutant. Journal of Neuroscience 20, 2609–2617. [PubMed: 10729341]

80. Watanabe M, Toyama Y, and Nishiyama A (2002). Differentiation of proliferated NG2-positive glial progenitor cells in a remyelinating lesion. J Neurosci Res 69, 826–836. [PubMed: 12205676]

81. Bu J, Banki A, Wu Q, and Nishiyama A (2004). Increased NG2(+) glial cell proliferation and oligodendrocyte generation in the hypomyelinating mutant shiverer. Glia 48, 51–63. [PubMed: 15326615]

82. Robins SC, Villemain A, Liu X, Djogo T, Kryzskaya D, Storch KF, and Kokoeva MV (2013). Extensive regenerative plasticity among adult NG2-glia populations is exclusively based on self-renewal. Glia 61, 1735–1747. [PubMed: 23918524]

83. Birey F, Kloc M, Chavali M, Hussein I, Wilson M, Christoffel DJ, Chen T, Frohman MA, Robinson JK, Russo SJ, et al. (2015). Genetic and Stress-Induced Loss of NG2 Glia Triggers Emergence of Depressive-like Behaviors through Reduced Secretion of FGF2. Neuron 88, 941–956. [PubMed: 26606998]

84. Falcao AM, van Bruggen D, Marques S, Meijer M, Jakel S, Agirre E, Samudyata Floriddia, E.M., Vanichkina DP, Ffrench-Constant C, et al. (2018). Disease-specific oligodendrocyte lineage cells arise in multiple sclerosis. Nat Med 24, 1837–1844. [PubMed: 30420755]

85. Jakel S, Agirre E, Mendanha Falcao A, van Bruggen D, Lee KW, Knuesel I, Malhotra D, Ffrench-Constant C, Williams A, and Castelo-Branco G (2019). Altered human oligodendrocyte heterogeneity in multiple sclerosis. Nature 566, 543–547. [PubMed: 30747918]

86. McKenzie IA, Ohayon D, Li H, de Faria JP, Emery B, Tohyama K, and Richardson WD (2014). Motor skill learning requires active central myelination. Science 346, 318–322. [PubMed: 25324381]

87. Ortega F, Gascon S, Masserdotti G, Deshpande A, Simon C, Fischer J, Dimou L, Chichung Lie D, Schroeder T, and Berninger B (2013). Oligodendrogliogenic and neurogenic adult subependymal zone neural stem cells constitute distinct lineages and exhibit differential responsiveness to Wnt signalling. Nat Cell Biol 15, 602–613. [PubMed: 23644466]

88. Xing YL, Roth PT, Stratton JA, Chuang BH, Danne J, Ellis SL, Ng SW, Kilpatrick TJ, and Merson TD (2014). Adult neural precursor cells from the subventricular zone contribute significantly to oligodendrocyte regeneration and remyelination. J Neurosci 34, 14128–14146. [PubMed: 25319708]

89. Brousse B, Magalon K, Durbec P, and Cayre M (2015). Region and dynamic specificities of adult neural stem cells and oligodendrocyte precursors in myelin regeneration in the mouse brain. Biol Open 4, 980–992. [PubMed: 26142314]

90. Kazanis I, Evans KA, Andreopoulou E, Dimitriou C, Koutsakis C, Karadottir RT, and Franklin RJM (2017). Subependymal Zone-Derived Oligodendroblasts Respond to Focal Demyelination but

Fail to Generate Myelin in Young and Aged Mice. Stem Cell Reports 8, 685–700. [PubMed: 28196689]

91. Serwanski DR, Rasmussen AL, Brunquell CB, Perkins SS, and Nishiyama A (2018). Sequential Contribution of Parenchymal and Neural Stem Cell-Derived Oligodendrocyte Precursor Cells toward Remyelination. Neuroglia 1, 91–105. [PubMed: 30662979]
92. Strijbis EMM, Kooi EJ, van der Valk P, and Geurts JJG (2017). Cortical Remyelination Is Heterogeneous in Multiple Sclerosis. J Neuropathol Exp Neurol 76, 390–401. [PubMed: 28521040]
93. Albert M, Antel J, Bruck W, and Stadelmann C (2007). Extensive cortical remyelination in patients with chronic multiple sclerosis. Brain Pathol 17, 129–138. [PubMed: 17388943]
94. Gardner C, Magliozzi R, Durrenberger PF, Howell OW, Rundle J, and Reynolds R (2013). Cortical grey matter demyelination can be induced by elevated pro-inflammatory cytokines in the subarachnoid space of MOG-immunized rats. Brain 136, 3596–3608. [PubMed: 24176976]
95. Kujuro Y, Suzuki N, and Kondo T (2010). Esophageal cancer-related gene 4 is a secreted inducer of cell senescence expressed by aged CNS precursor cells. Proc Natl Acad Sci U S A 107, 8259–8264. [PubMed: 20404145]
96. Durand B, and Raff M (2000). A cell-intrinsic timer that operates during oligodendrocyte development. BioEssays 22, 64–71. [PubMed: 10649292]
97. Gonsalvez DG, Cane KN, Landman KA, Enomoto H, Young HM, and Anderson CR (2013). Proliferation and cell cycle dynamics in the developing stellate ganglion. J Neurosci 33, 5969–5979. [PubMed: 23554478]

HIGHLIGHTS

- OPCs from different developmental origins exhibit different proliferative behaviors
- OPCs from ventral but not dorsal germinal zones generate astrocytes prenatally
- OPCs in white matter proliferate and differentiate faster than those in gray matter
- OPCs from the SVZ can generate robustly remyelinating OLs after a latency
- Transcriptionally homogeneous OPCs exhibit different niche-specific behaviors

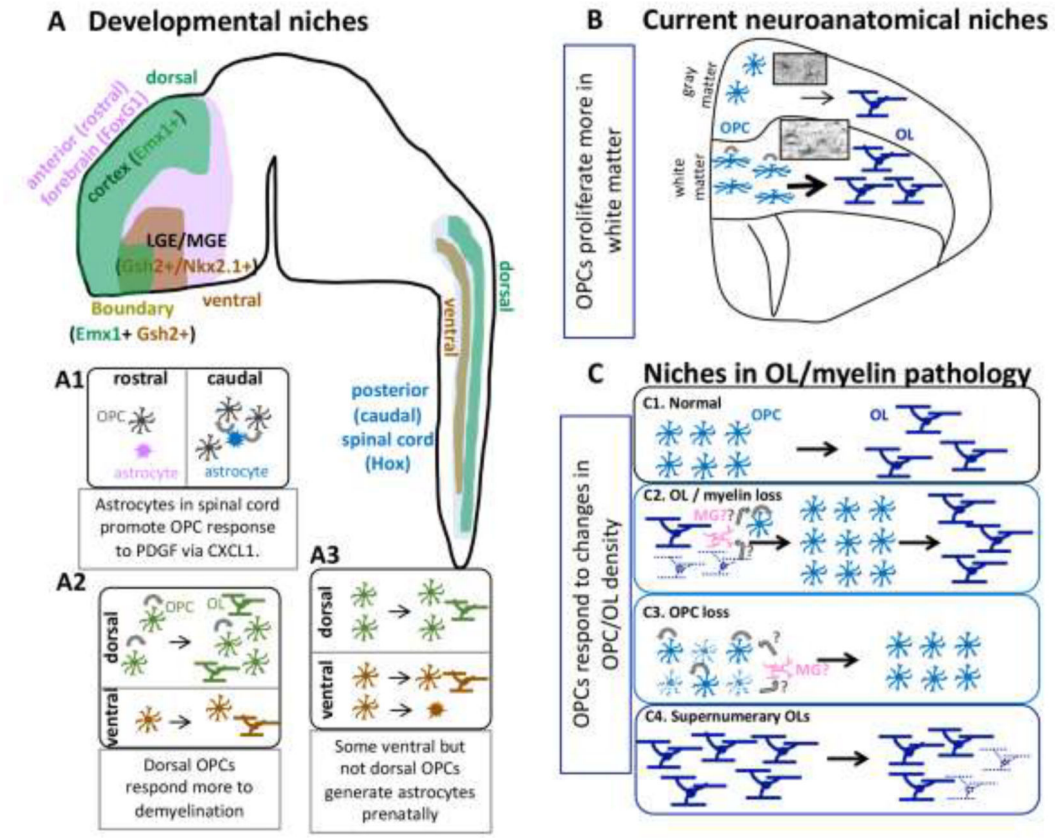

Figure 1.

Schematics showing the effects of various niches on OPC and OL dynamics

A. Influence of developmental niches

A1. OPCs in the posterior (caudal) regions (blue) exhibit greater proliferative response to PDGF compared to those in the anterior (rostral) regions of the brain (pink), partly due to the chemokine GRO-α (CXCL1) secreted by astrocytes. Gray curved arrows denote greater proliferation. A2. OPCs arising from the dorsal germinal zones (green) appear to be endowed with greater proliferative abilities, both in the brain and spinal cord, than those from ventral origin (brown). A3. OPCs from the dorsal germinal zones remain primarily in the OL lineage, whereas, some OPCs in the prenatal ventral forebrain, presumably of ventral origin, differentiate into protoplasmic astrocytes.

B. Influence of the current neuroanatomical niches – the gray and white matter

OPCs in the white matter (corpus callosum) appear more elongated, proliferate more extensively (gray curved arrows), and differentiate into OLs more rapidly than those in the gray matter (neocortex).

Insets indicate NG2 immunolabeling showing differences in density and morphology of OPCs in the gray and white matter.

C. Influence of the niches created in pathological states of OLs and myelin

C1. Under normal state, the density of OPCs and OLs is tightly regulated.

C2. When there is loss of mature OLs or myelin, OPCs proliferate (gray curved arrows) and restore the original OL/myelin density. Hollow arrows indicate possible signaling from dead

cells to microglia (pink, MG), and possible subsequent signaling from activated microglia to OPCs. Cells with dotted lines indicate dying cells.

C3. When there is loss of OPCs, remaining OPCs proliferate to maintain original density.

C4. Conversely, when excess OLs are generated, they do not survive, and normal OL/myelin density is restored.