HHS Public Access

Author manuscript

Curr Opin Neurobiol. Author manuscript; available in PMC 2015 May 14.

Published in final edited form as:

Curr Opin Neurobiol. 2013 December ; 23(6): 914–920. doi:10.1016/j.conb.2013.06.005.

Intrinsic and extrinsic control of oligodendrocyte development

J Bradley Zuchero and **Ben A Barres**

Department of Neurobiology, Stanford University, Fairchild Building D205, 299 Campus Drive West, Stanford, CA 94305, United States

Abstract

Oligodendrocytes (OLs) are the myelinating glia of the central nervous system. Myelin is essential for the rapid propagation of action potentials as well as for metabolic support of axons, and its loss in demyelinating diseases like multiple sclerosis has profound pathological consequences. The many steps in the development of OLs — from the specification of oligodendrocyte precursor cells (OPCs) during embryonic development to their differentiation into OLs that myelinate axons — are under tight regulation. Here we discuss recent advances in understanding how these steps of OL development are controlled intrinsically by transcription factors and chromatin remodeling and extrinsically by signaling molecules and neuronal activity. We also discuss how knowledge of these pathways is now allowing us to take steps toward generating patient-specific OPCs for disease modeling and myelin repair.

Origin and OPC specification

Oligodendrocyte precursor cells (OPCs) arise during development from neuroepithelial progenitor cells in the ventral neural tube (reviewed in Refs. [1–3]). They are specified in response to the secreted morphogen Sonic Hedgehog (Shh) derived from the floor-plate of the neural tube [4]. Before generating OPCs, these same neuroepithelial cells also give rise to motor neurons, and the mechanism of this important switch has recently been shown to involve the hedgehog family member Indian Hedgehog [5], as well as secreted sulfatase-1 [6]. Secreted signals of the Fibroblast Growth Factors family (FGFs) also regulate early OPC development, as loss of either FGF receptor 1 or 2 in ventral neuroepithelial progenitors blocks induction of OPCs [7•, 8•].

Are there functionally different types of OPCs? Recent studies have highlighted the dramatic degree of heterogeneity between astrocytes in different CNS regions [9], but it has been unclear if oligodendrocyte lineage cells might be similarly heterogeneous. In addition to the commonly appreciated ventral OPCs, work by Richardson and colleagues demonstrated that there are multiple waves of OPC specification in the CNS with OPCs being derived from both ventral and dorsal sources [10]. More recently, fate mapping studies showed that ventral and dorsal OPCs myelinate different regions of the brain, raising the possibility of functional differences between them [11]. The observation, however, that

Corresponding author: Zuchero, J Bradley (brad.zuchero@gmail.com).

This review comes from a themed issue on **Development of neurons and glia**

different populations of OPCs are functionally redundant and are able to replace each other if one source is ablated [10] would argue against differences. Further work, including a comparison of the gene expression profiles of the different OPC populations, may help elucidate whether they are functionally distinct. Additionally, it will be interesting to understand how dorsally derived OPCs are specified, since dorsally derived Bone Morphogenic Proteins (BMPs) are typically thought to compete with Shh to inhibit OPC specification.

Recently it has been found that OPCs are also generated in the adult brain from neural precursor cells in the subventricular zone [12]. Their specification may rely on the same signals as during development, including Shh and FGF-2 [13, 14]. Other work, however, suggests that additional signals may be required, including epidermal growth factor (EGF) and pigment epithelium-derived factor (PEDF) [15, 16]. A major challenge in demyelinating diseases like multiple sclerosis is the fact that, although OPCs are prevalent in demyelinated lesions, they often fail to differentiate into OLs and remyelinate. Are the signals that promote differentiation of adult OPCs different than the ones used during development, and if so, can we harness that knowledge to promote remyelination? One recent study by ffrench-Constant, Franklin and colleagues generated gene expression profiles for OL differentiation following focal demyelination [17]. Intriguingly, the authors found that signaling through the retinoid X receptor gamma is important for differentiation of adult OPCs and remyelination, despite not seeming to play a role in developmental myelination. In another elegant study, it was found that the systemic milieu of young mice promotes OL differentiation and remyelination when introduced into the aged mouse by heterochronic parabiosis (connecting the blood stream between the young and old mouse), by unknown mechanisms [18••]. These studies are of particular relevance for demyelinating disease, as understanding the signaling pathways that lead to the generation of new OPCs and their differentiation may prove useful for stimulating remyelination in patients [19].

How do intrinsic factors regulate the differentiation of OPCs into OLs?

OPCs undergo a defined series of steps to differentiate into a premyelinating OL, extend processes that wrap and compact around axons, and finally turn on genes required for myelin maintenance and the (still emerging) physiological functions of mature myelin [20] (Figure 1). There are many steps in this process that must be regulated in time and space, and thus there is a great need to uncover how the many transcriptional regulators in OPCs/OLs collaborate to precisely coordinate these cellular changes [21]. This involves both activation of genes to promote differentiation, and repression of genes that prevent differentiation [22]. How do OPCs/OLs control this very specific and coordinated timing of gene expression? Over the past decade it has become clear that chromatin remodeling is a key process that regulates OL development [22–24]. There are two major ways that chromatin is remodeled to change gene expression: Firstly, covalent modifications of histones such as deacetylation by HDACs to silence genes, or acetylation to activate them, and secondly, ATP-dependent remodeling by SWI/SNF enzymes such as Smarca4/Brg1, that control the position of nucleosomes and thus increase the accessibility of specific genes.

Work by Casaccia and colleagues first established that histone deacetylation by HDACs plays important roles in OL development [25]. Recently Lu and colleagues used genetic ablation to show that HDAC1 and HDAC2 are required for OL differentiation, and control the Wnt signaling pathway, a known inhibitor of OL differentiation [26]. Similarly, in the PNS, HDAC1 and HDAC2 are necessary to regulate transcription by Schwann cells [27, 28], suggesting that this is a conserved pathway in all myelinating glia. Intriguingly, extrinsic factors that regulate OL differentiation appear to do so, at least in part, by modifying histone acetylation. Shh, which promotes OL differentiation, induces histone deacetylation by HDACs; in contrast, inhibitory BMP4 appears to block deacetylation [29]. Bioinformatics approaches to identify sequential waves of co-regulated genes during OL differentiation found that genes with similar functions are co-regulated to turn on or off at the same time; importantly, putative inhibitory genes require HDAC activity to turn off at the onset of differentiation [21]. Taken together it seems that the major role of HDACs is to repress expression of genes that normally block OPC differentiation, thereby ‘releasing the brakes’ and allowing differentiation to proceed [21].

Once inhibition is relieved, what is the mechanism that drives transcription of genes required for differentiation? It has long been known that the OL-specific transcription factors Olig1 and Olig2 play an essential role in OL specification and differentiation [30, 31]. Until recently it was unknown how Olig1 and Olig2 actually function to promote differentiation. Lu and colleagues demonstrated that Olig2 binds to enhancers of OL-specific genes and recruits the SWI/SNF chromatin remodeling protein Smarca4/Brg1 [32••]. This suggests a model of Olig2 function in which it promotes ATP-dependent chromatin remodeling to make the promoters of OL genes accessible for transcription. Interestingly, their genome-wide analysis of Smarca4/Brg1 and Olig2 co-occupancy on chromatin suggests novel transcription factors and other genes that may be required for OL differentiation and myelination. Testing the roles of these genes, as well as determining whether chromatin remodeling by HDACs and Smarca4/Brg1 is important for remyelination, are important questions for future work [33].

It is likely that a number of transcription factors and other regulatory molecules collaborate to regulate OL differentiation. Both Myelin Gene Regulatory Factor (MYRF/gm98) and Zfp191 appear to be master regulators of myelin gene expression [34, 35], and MYRF is required in adult OLs to maintain OL identity [36•]. The precise mechanisms of how these genes regulate OL differentiation remain to be elucidated. An intriguing new study indicates that the OL transcription factor Sox10 directly interacts with the Mediator complex to recruit RNA polymerase II during OL differentiation [37]. Recent work suggests that master transcriptional regulators collaborate with the Mediator complex to recruit RNA polymerase II to ‘super enhancer’ domains, to regulate cell identity [38]. It will be interesting to know whether this is a general feature of OL differentiation.

Work in the past few years from multiple groups has also shown the importance of micro-RNAs (miRNAs) in OL development, myelination, and remyelination [39]. In addition to miRNAs, the list of functional types of noncoding RNA continues to grow, including long noncoding RNAs [40]. Increasingly it is appreciated that many of these play important roles in regulating gene expression directly or by acting as ‘sponges’ to compete with miRNAs or

endogenous RNA [41, 42]. With better technologies enabling the detection and quantification of these other RNA species (*e.g.* RNA-seq whole transcriptome sequencing technologies), it will be interesting to see whether they are expressed by OPCs/OLs and play unique roles in their development.

Extrinsic control of OL development: the role of neuronal activity

It has long been appreciated that neuronal activity is likely to be important for the development of OLs [43]. Within the past decade, work by Bergles and subsequent studies from multiple groups have demonstrated that OPCs receive functional synapses from neurons [44, 45], but the precise role of these synapses *in vivo* has yet to be determined. One attractive possibility is that OPCs sense neuronal activity to regulate their capacity to divide, differentiate, and myelinate [46]. Neuronal activity can influence OL differentiation and myelination *in vitro via* secreted signals, including glutamate and ATP [47•]. Confirmation of these results *in vivo*, perhaps using an optogenetic approach, would be an exciting step forward, and much of the groundwork has been laid.

How do electrically active neurons signal to OPCs? In the case of excitatory neurons, the answer might be the neurotransmitter glutamate. Although ablating NMDA receptors from OPCs *in vivo* has no effect on OPC proliferation, myelination, or responses to white matter injury, this causes an upregulation of AMPA receptors that could also respond to neuronally derived glutamate [48, 49]. Indeed, it appears that AMPA receptors, as well as purinergic receptors that respond to ATP, help OPCs to respond to neuronal activity *in vitro* [50], but whether this also occurs *in vivo* remains to be established.

Several recent *in vivo* studies have provided intriguing evidence that neuronal activity regulates OL development and myelination. For instance, the formation of neuron-OPC synapses in the mouse barrel cortex is regulated by sensory input [51]. Strikingly, social experience also powerfully regulates myelination in the mouse prefrontal cortex, and in the adult this may be regulated by chromatin remodeling [52••, 53••]. As loss of the ErbB3 receptor leads to the same myelination defects as sensory deprivation, neuregulin-ErbB signaling likely plays a role in this form of myelin plasticity [52••]. This is especially interesting since neuregulin-ErbB is a master regulator of myelination in the PNS, but until now has appeared to be largely dispensable for CNS myelination. Another study showed that *in vivo* electrical stimulation of CNS neurons of the corticospinal tract with high-frequency stimulation induces proliferation of OPCs in the adult rat [54]. Moving forward, it will be important to determine whether these OPCs myelinate axons, and whether physiological (lower frequency) activity in neurons is sufficient to regulate OPC proliferation or differentiation. Clearly, a major goal for the field is to determine which stages of OPC/OL development and myelination are controlled by normal neuronal activity *in vivo*, and to elucidate the signaling pathways that regulate this developmentally and in disease. Whether OPCs respond to neural activity for functions other than regulating myelination remains an intriguing possibility [3, 45].

While much focus has been given to how neuronal activity may affect OPCs during development, it is also important to consider OPCs in the adult CNS. Given that the bulk of

myelination occurs early after birth, it is perhaps surprising that OPCs remain abundant in the adult brain. An elegant recent study by Young, Richardson and colleagues used lineage tracing and EdU labeling (of dividing cells) to measure the extent of OPC proliferation and differentiation into OLs in the adult mouse brain [55••]. This work establishes some general features of all OPCs in the adult CNS: they continue to divide throughout adulthood, and form new myelinating OLs with progressively more and shorter myelin internodes. The continual addition of new myelin suggests that, in contrast to long held views, there is normally much more myelin turnover in the adult brain than has been thought. The precise mechanism of this (turnover of OLs by apoptosis, turnover of individual internodes, or addition of new internodes between existing ones) and signals that regulate it remain to be determined. A provocative possibility is that myelin remodeling is involved in learning processes [46].

Generation of OPCs from stem cells and direct lineage conversion

How can we translate what we are learning about OL development into therapies for demyelinating diseases? A major goal in the field is to be able to generate patient-specific myelinating cells, both for disease modeling studies and eventually to be used therapeutically to regenerate myelin [56, 57]. Ideally these cells would be proliferative and maintain their ability to myelinate, so generating OPCs is preferred to generating mature OLs, which quickly lose their capacity to myelinate [58]. Our increasing understanding of the signals that regulate specification and development of OPCs has allowed major breakthroughs toward this goal in the past few years.

A useful assay has been developed utilizing the hypomyelinating *shiverer* mouse that lacks expression of Myelin Basic Protein (MBP). Injection of experimentally derived wild-type OPCs or progenitors into shiverer mice allows for unambiguous identification of transplanted cells, which uniquely express MBP after differentiating into OLs [59]. Importantly, these wild-type OLs can compete with endogenous (MBP-lacking) OLs and generate myelin, enabling researchers to determine whether generated OPCs are functional *in vivo*.

In one approach, human fetal OPCs are purified based on specific surface expressed epitopes; these can be expanded *in vitro*, and engraft and widely myelinate within the mouse CNS after transplantation [60]. A second approach relies on banked and proliferated human neural stem cells, which can also myelinate the mouse brain [61] and, strikingly, safely engraft in the human brain of patients [62•]. Toward the goal of generating patient-specific OPCs, several recent papers have built on work in the stem cell field to generate OPCs from pluripotent stem cells. Both rodent epiblast stem cells and human induced pluripotent stem cells (iPSCs) can myelinate *in vivo* and even appear to dramatically increase the survival of hypomyelinated *shiverer* animals [63, 64•]. A potentially more rapid method of generating patient-specific OPCs is to reprogram already differentiated cells, a technique known as direct lineage conversion [57]. In this approach, fibroblasts or other differentiated cells are directly converted into another cell type by forced expression of transcription factors or other regulatory molecules. Two recent papers demonstrated that rodent fibroblasts can be converted to the OL lineage by expression of three transcription factors: Olig2, Sox10, and

either Nkx6.2 or Zfp536 [65•, 66•]. Important next steps will be to translate these findings to human cells, and to test and optimize their ability to restore function to the de/dysmyelinated CNS.

Summary and outlook

It is an exciting time in the OL field, and recent advances have provided a great deal of mechanistic insight into how OLs develop in response to intrinsic and extrinsic signals. However, there are still many fundamental questions remaining about the functions of OPCs and OLs in the CNS, and exactly how OPCs differentiate into OLs. A clear goal of future work is to test, *in vivo*, the many predictions made from *in vitro* studies. This includes further work to elucidate how sequential stages of OL differentiation and myelination are regulated transcriptionally, understanding the roles of OPC-neuron synapses and other OPC functions in the adult brain, and determining how neuronal activity affects OL development and myelination. In addition, a major translational goal is to refine current methods to generate and transplant OPCs into patients, with an ultimate goal of regenerating lost myelin in the human CNS.

Acknowledgments

We would like to thank Erin Gibson Valdez for reading and discussing the manuscript in preparation. J.B.Z is a Howard Hughes Medical Institute Fellow of the Life Sciences Research Foundation.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

• of special interest

•• of outstanding interest

1. Rowitch DH. Glial specification in the vertebrate neural tube. Nat Rev Neurosci. 2004; 5:409–419. [PubMed: 15100723]
2. Richardson WD, Kessaris N, Pringle N. Oligodendrocyte wars. Nat Rev Neurosci. 2006; 7:11–18. [PubMed: 16371946]
3. Richardson WD, Young KM, Tripathi RB, McKenzie I. NG2-glia as multipotent neural stem cells: fact or fantasy? Neuron. 2011; 70:661–673. [PubMed: 21609823]
4. Yu K, McGlynn S, Matise MP. Floor plate-derived sonic hedgehog regulates glial and ependymal cell fates in the developing spinal cord. Development. 2013; 140:1594–1604. [PubMed: 23482494]
5. Chung AY, Kim S, Kim E, Kim D, Jeong I, Cha YR, Bae YK, Park SW, Lee J, Park HC. Indian hedgehog b function is required for the specification of oligodendrocyte progenitor cells in the zebrafish CNS. J Neurosci. 2013; 33:1728–1733. [PubMed: 23345245]
6. Touahri Y, Escalas N, Benazeraf B, Cochard P, Danesin C, Soula C. Sulfatase 1 promotes the motor neuron-to-oligodendrocyte fate switch by activating Shh signaling in Olig2 progenitors of the embryonic ventral spinal cord. J Neurosci. 2012; 32:18018–18034. [PubMed: 23238718]
7•. Furusho M, Kaga Y, Ishii A, Hébert JM, Bansal R. Fibroblast growth factor signaling is required for the generation of oligodendrocyte progenitors from the embryonic forebrain. J Neurosci. 2011; 31:5055–5066. In this paper, the authors test the role of FGF signaling in the OL lineage *in vivo*, by generating conditional knockouts of FGF receptors at different stages. FGFR1 and 2 were found to be essential for the specification of OPCs, and also critical for regulating myelin

sheath thickness, despite not being required for OPC proliferation or differentiation. [PubMed: 21451043]

8•. Furusho M, Dupree JL, Nave K-A, Bansal R. Fibroblast growth factor receptor signaling in oligodendrocytes regulates myelin sheath thickness. J Neurosci. 2012; 32:6631–6641. See annotation to Ref. [7•]. [PubMed: 22573685]

9. Tsai H-H, Li H, Fuentealba LC, Molofsky AV, Taveira-Marques R, Zhuang H, Tenney A, Murnen AT, Fancy SPJ, Merkle F, et al. Regional astrocyte allocation regulates CNS synaptogenesis and repair. Science. 2012; 337:358–362. [PubMed: 22745251]

10. 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. [PubMed: 16388308]

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

12. Gonzalez-Perez O, Alvarez-Buylla A. Oligodendrogenesis in the subventricular zone and the role of epidermal growth factor. Brain Res Rev. 2011; 67:147–156. [PubMed: 21236296]

13. Azim K, Raineteau O, Butt AM. Intraventricular injection of FGF2 promotes generation of oligodendrocyte-lineage cells in the postnatal and adult forebrain. Glia. 2012; 60:1977–1990. [PubMed: 22951928]

14. Ferent J, Zimmer C, Durbec P, Ruat M, Traiffort E. Sonic hedgehog signaling is a positive oligodendrocyte regulator during demyelination. J Neurosci. 2013; 33:1759–1772. [PubMed: 23365216]

15. Gonzalez-Perez O, Romero-Rodriguez R, Soriano-Navarro M, Garcia-Verdugo JM, Alvarez-Buylla A. Epidermal growth factor induces the progeny of subventricular zone type B cells to migrate and differentiate into oligodendrocytes. Stem Cells. 2009; 27:2032–2043. [PubMed: 19544429]

16. Sohn J, Selvaraj V, Wakayama K, Orosco L, Lee E, Crawford SE, Guo F, Lang J, Horiuchi M, Zarbalis K. PEDF is a novel oligodendrogenic morphogen acting on the adult SVZ and corpus callosum. J Neurosci. 2012; 32:12152–12164. [PubMed: 22933798]

17. Huang JK, Jarjour AA, Oumesmar BN, Kerninon C, Williams A, Krezel W, Kagechika H, Bauer J, Zhao C, Evercooren AB-V, et al. Retinoid X receptor gamma signaling accelerates CNS remyelination. Nat Neurosci. 2011; 14:45–53. [PubMed: 21131950]

18••. Ruckh JM, Zhao J-W, Shadrach JL, van Wijngaarden P, Rao TN, Wagers AJ, Franklin RJM. Rejuvenation of regeneration in the aging central nervous system. Stem Cell. 2012; 10:96–103. This study used a combination of focal demyelination and parabiosis (joining two animals' circulatory systems) to test the ability of the aged brain to regenerate myelin in the presence of blood-bourn monocytes and secreted factors from young mice. Strikingly, OPC proliferation, differentiation, and remyelination were all enhanced in the aged mice, but only when receiving blood from young (donor) mice. This is in part driven not only by donor macrophages, but also potentially by soluble factors in the blood. Future identification of the pro-myelinating signals from young mice could yield putative therapies.

19. Fancy SPJ, Chan JR, Baranzini SE, Franklin RJM, Rowitch DH. Myelin regeneration: a recapitulation of development? Annu Rev Neurosci. 2011; 34:21–43. [PubMed: 21692657]

20. Nave K-A. Myelination and the trophic support of long axons. Nat Rev Neurosci. 2010; 11:275–283. [PubMed: 20216548]

21. Swiss VA, Nguyen T, Dugas J, Ibrahim A, Barres B, Androulakis IP, Casaccia P. Identification of a gene regulatory network necessary for the initiation of oligodendrocyte differentiation. PLoS ONE. 2011; 6:e18088. [PubMed: 21490970]

22. He L, Lu QR. Coordinated control of oligodendrocyte development by extrinsic and intrinsic signaling cues. Neurosci Bull. 2013; 29:129–143. [PubMed: 23494530]

23. Emery B. Transcriptional and post-transcriptional control of CNS myelination. Curr Opin Neurobiol. 2010; 20:601–607. [PubMed: 20558055]

24. Jacob C, Lebrun-Julien F, Suter U. How histone deacetylases control myelination. Mol Neurobiol. 2011; 44:303–312. [PubMed: 21861092]

25. 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. [PubMed: 12451133]

26. Ye F, Chen Y, Hoang T, Montgomery RL, Zhao X-H, Bu H, Hu T, Taketo MM, van Es JH, Clevers H, et al. HDAC1 and HDAC2 regulate oligodendrocyte differentiation by disrupting the β-catenin-TCF interaction. Nat Neurosci. 2009; 12:829–838. [PubMed: 19503085]

27. Chen Y, Wang H, Yoon SO, Xu X, Hottiger MO, Svaren J, Nave KA, Kim HA, Olson EN, Lu QR. HDAC-mediated deacetylation of NF-kB is critical for Schwann cell myelination. Nat Neurosci. 2011; 14:437–441. [PubMed: 21423191]

28. Jacob C, Christen CN, Pereira JA, Somandin C, Baggiolini A, Lötscher P, Ozçelik M, Tricaud N, Meijer D, Yamaguchi T, et al. HDAC1 and HDAC2 control the transcriptional program of myelination and the survival of Schwann cells. Nat Neurosci. 2011; 14:429–436. [PubMed: 21423190]

29. Wu M, Hernandez M, Shen S, Sabo JK, Kelkar D, Wang J, O'Leary R, Phillips GR, Cate HS, Casaccia P. Differential modulation of the oligodendrocyte transcriptome by sonic hedgehog and bone morphogenetic protein 4 via opposing effects on histone acetylation. J Neurosci. 2012; 32:6651–6664. [PubMed: 22573687]

30. Meijer DH, Kane MF, Mehta S, Liu H, Harrington E, Taylor CM, Stiles CD, Rowitch DH. Separated at birth? The functional and molecular divergence of OLIG1 and OLIG2. Nat Rev Neurosci. 2012; 13:819–831. [PubMed: 23165259]

31. Zhu X, Zuo H, Maher BJ, Serwanski DR, LoTurco JJ, Lu QR, Nishiyama A. Olig2-dependent developmental fate switch of NG2 cells. Development. 2012; 139:2299–2307. [PubMed: 22627280]

32••. Yu Y, Chen Y, Kim B, Wang H, Zhao C, He X, Liu L, Liu W, Wu LMN, Mao M, et al. Olig2 targets chromatin remodelers to enhancers to initiate oligodendrocyte differentiation. Cell. 2013; 152:248–261. To understand how OL differentiation is regulated mechanistically, the authors leveraged the power of ChIP-seq (chromatin immunoprecipitation sequencing) to globally characterize transcription at specific stages of differentiation. By looking at which genes are actively transcribed at the start of myelination, they identify chromatin remodeling factor Smarca4/Brg1 as an essential regulator of myelination. Combining conditional knockout studies and further ChIP-seq to identify Olig2 and Smarca4/Brg1 binding sites across the genome, they build an elegant model of how stepwise transcriptional control of OL differentiation is orchestrated. [PubMed: 23332759]

33. Shen S, Sandoval J, Swiss VA, Li J, Dupree J, Franklin RJM, Casaccia-Bonnefil P. Age-dependent epigenetic control of differentiation inhibitors is critical for remyelination efficiency. Nat Neurosci. 2008; 11:1024–1034. [PubMed: 19160500]

34. Emery B, Agalliu D, Cahoy JD, Watkins TA, Dugas JC, Mulinyawe SB, Ibrahim A, Ligon KL, Rowitch DH, Barres BA. Myelin gene regulatory factor is a critical transcriptional regulator required for CNS myelination. Cell. 2009; 138:172–185. [PubMed: 19596243]

35. Howng SYB, Avila RL, Emery B, Traka M, Lin W, Watkins T, Cook S, Bronson R, Davisson M, Barres BA, et al. ZFP191 is required by oligodendrocytes for CNS myelination. Genes Dev. 2010; 24:301–311. [PubMed: 20080941]

36•. Koenning M, Jackson S, Hay CM, Faux C, Kilpatrick TJ, Willingham M, Emery B. Myelin gene regulatory factor is required for maintenance of myelin and mature oligodendrocyte identity in the adult CNS. J Neurosci. 2012; 32:12528–12542. Inducibly knocking out the master myelin gene regulator MYRF (formerly MRF/gm98) from mature OLs in the adult leads to downregulation of myelin genes and loss of myelin, suggesting that myelin remains a dynamic structure through adulthood. [PubMed: 22956843]

37. Vogl MR, Reiprich S, Küspert M, Kosian T, Schrewe H, Nave K-A, Wegner M. Sox10 cooperates with the mediator subunit 12 during terminal differentiation of myelinating glia. J Neurosci. 2013; 33:6679–6690. [PubMed: 23575864]

38. Whyte WA, Orlando DA, Hnisz D, Abraham BJ, Lin CY, Kagey MH, Rahl PB, Lee TI, Young RA. Master transcription factors and mediator establish super-enhancers at key cell identity genes. Cell. 2013; 153:307–319. [PubMed: 23582322]

39. Li J-S, Yao Z-X. MicroRNAs: novel regulators of oligodendrocyte differentiation and potential therapeutic targets in demyelination-related diseases. Mol Neurobiol. 2012; 45:200–212. [PubMed: 22218763]

40. Lee JT. Epigenetic regulation by long noncoding RNAs. Science. 2012; 338:1435–1439. [PubMed: 23239728]

41. Hansen TB, Jensen TI, Clausen BH, Bramsen JB, Finsen B, Damgaard CK, Kjems J. Natural RNA circles function as efficient microRNA sponges. Nature. 2013; 495:384–388. [PubMed: 23446346]

42. Wang, Y.; Xu, Z.; Jiang, J.; Xu, C.; Kang, J.; Xiao, L.; Wu, M.; Xiong, J.; Guo, X.; Liu, H. Endogenous miRNA sponge lincRNA-RoR regulates Oct4, nanog, and Sox2 in human embryonic stem cell self-renewal. Dev Cell. 2013. http://dx.doi.org/10.1016/j.devcel.2013.03.002

43. Barres BA, Raff MC. Proliferation of oligodendrocyte precursor cells depends on electrical activity in axons. Nature. 1993; 361:258–260. [PubMed: 8093806]

44. Bergles DED, Roberts JDJ, Somogyi PP, Jahr CEC. Glutamatergic synapses on oligodendrocyte precursor cells in the hippocampus. Nature. 2000; 405:187–191. [PubMed: 10821275]

45. Mangin J-M, Gallo V. The curious case of NG2 cells: transient trend or game changer? ASN Neuro. 2011; 3:e00052. [PubMed: 21288204]

46. Emery B. Regulation of oligodendrocyte differentiation and myelination. Science. 2010; 330:779–782. [PubMed: 21051629]

47•. Wake H, Lee PR, Fields RD. Control of local protein synthesis and initial events in myelination by action potentials. Science. 2011; 333:1647–1651. This paper uses cocultures of OLs and dorsal root ganglion neurons to show that OPCs respond to vesicular release of glutamate and ATP from neurons, which drives translation of myelin basic protein mediated by Fyn kinase signaling. [PubMed: 21817014]

48. DeBiase LM, Kang SH, Baxi EG, Fukaya M, Pucak ML, Mishina M, Calabresi PA, Bergles DE. NMDA receptor signaling in oligodendrocyte progenitors is not required for oligodendrogenesis and myelination. J Neurosci. 2011; 31:12650–12662. [PubMed: 21880926]

49. Guo F, Maeda Y, Ko EM, Delgado M, Horiuchi M, Soulika A, Miers L, Burns T, Itoh T, Shen H, et al. Disruption of NMDA receptors in oligodendroglial lineage cells does not alter their susceptibility to experimental autoimmune encephalomyelitis or their normal development. J Neurosci. 2012; 32:639–645. [PubMed: 22238099]

50. Zonouzi M, Renzi M, Farrant M, Cull-Candy SG. Bidirectional plasticity of calcium-permeable AMPA receptors in oligodendrocyte lineage cells. Nat Neurosci. 2011; 14:1430–1438. [PubMed: 21983683]

51. Mangin J-M, Li P, Scafidi J, Gallo V. Experience-dependent regulation of NG2 progenitors in the developing barrel cortex. Nat Neurosci. 2012; 15:1192–1194. [PubMed: 22885848]

52••. Makinodan M, Rosen KM, Ito S, Corfas G. A critical period for social experience-dependent oligodendrocyte maturation and myelination. Science. 2012; 337:1357–1360. This study demonstrates that early social isolation irreversibly impairs myelin development in the prefrontal cortex, causing defects in OL morphology and myelin protein content, myelin thickness, and behavior. Strikingly, loss of the neuregulin receptor ErbB3 phenocopies this, including behavioral defects like sociability and working memory. This may help resolve the long-debated role of neuregulin signaling in CNS myelination. [PubMed: 22984073]

53••. Liu J, Dietz K, DeLoyht JM, Pedre X, Kelkar D, Kaur J, Vialou V, Lobo MK, Dietz DM, Nestler EJ, et al. Impaired adult myelination in the prefrontal cortex of socially isolated mice. Nat Neurosci. 2012; 15:1621–1623. In work complementary to Ref. [50] the authors show that long-term social isolation of adult mice also leads to defects in myelination and behavior, and also differences in chromatin organization. Shorter periods of isolation that do not affect behavior still affect OL chromatin, suggesting that chromatin changes in response to social experience drive myelin plasticity in the adult. [PubMed: 23143512]

54. Li Q, Brus-Ramer M, Martin JH, McDonald JW. Electrical stimulation of the medullary pyramid promotes proliferation and differentiation of oligodendrocyte progenitor cells in the corticospinal tract of the adult rat. Neurosci Lett. 2010; 479:128–133. [PubMed: 20493923]

55••. Young KM, Psachoulia K, Tripathi RB, Dunn S-J, Cossell L, Attwell D, Tohyama K, Richardson WD. Oligodendrocyte dynamics in the healthy adult CNS: evidence for myelin remodeling.

Neuron. 2013; 77:873–885. The authors measured OPC proliferation and differentiation in multiple regions of the adult mouse CNS, and found that even in regions where all axons are fully myelinated, there is continual addition of myelin internodes from newly generated OLs. Whether this new myelin replaces old myelin or rather intercalates between existing internodes, and whether this represents a form of plasticity in the adult, remain open questions. [PubMed: 23473318]

56. Goldman SA, Nedergaard M, Windrem MS. Glial progenitor cell-based treatment and modeling of neurological disease. Science. 2012; 338:491–495. [PubMed: 23112326]
57. Vierbuchen T, Wernig M. Molecular roadblocks for cellular reprogramming. Mol Cell. 2012; 47:827–838. [PubMed: 23020854]
58. 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. [PubMed: 19038214]
59. Windrem MS, Nunes MC, Rashbaum WK, Schwartz TH, Goodman RA, McKhann G, Roy NS, Goldman SA. Fetal and adult human oligodendrocyte progenitor cell isolates myelinate the congenially dysmyelinated brain. Nat Med. 2004; 10:93–97. [PubMed: 14702638]
60. McClain CR, Schanz SJ, Protack TL, Windrem MS, Sim FJ, Goldman SA. CD140a identifies a population of highly myelinogenic, migration-competent and efficiently engrafting human oligodendrocyte progenitor cells. Nat Biotechnol. 2011; 29:934–941. [PubMed: 21947029]
61. Uchida N, Chen K, Dohse M, Hansen KD, Dean J, Buser JR, Riddle A, Beardsley DJ, Wan Y, Gong X, et al. Human neural stem cells induce functional myelination in mice with severe dysmyelination. Sci Transl Med. 2012; 4:155ra136.
62•. Gupta N, Henry RG, Strober J, Kang S-M, Lim DA, Bucci M, Caverzasi E, Gaetano L, Mandelli ML, Ryan T, et al. Neural stem cell engraftment and myelination in the human brain. Sci Transl Med. 2012; 4:155ra137. The authors report a phase I study using human CNS stem cells to treat the severe leukodystrophy Pelizaeus-Merzbacher disease (PMD). They provide evidence for the safety of this approach, and their data suggest that the stem cells can engraft and myelinate the brains of patients.
63. Najm FJ, Zaremba A, Caprariello AV, Nayak S, Freundt EC, Scacheri PC, Miller RH, Tesar PJ. Rapid and robust generation of functional oligodendrocyte progenitor cells from epiblast stem cells. Nat Meth. 2011; 8:957–962.
64•. Wang S, Bates J, Li X, Schanz S, Chandler-Militello D, Levine C, Maherali N, Studer L, Hochedlinger K, Windrem M, et al. Human iPSC-derived oligodendrocyte progenitor cells can myelinate and rescue a mouse model of congenital hypomyelination. Cell Stem Cell. 2013; 12:252–264. OPCs derived from human induced pluripotent stem cells (hiPSCs) show robust engraftment, migration, and myelination of the hypomyelinated *shiverer* brain, and increase the survival of these animals. [PubMed: 23395447]
65•. Najm, FJ.; Lager, AM.; Zaremba, A.; Wyatt, K.; Caprariello, AV.; Factor, DC.; Karl, RT.; Maeda, T.; Miller, RH.; Tesar, PJ. Transcription factor-mediated reprogramming of fibroblasts to expandable, myelinogenic oligodendrocyte progenitor cells. Nat Biotechnol. 2013. http://dx.doi.org/10.1038/nbt.2561. In this paper, the authors utilize direct lineage conversion to induce rodent fibroblasts to become OPC-like cells, which can differentiate into OLs and myelinate when transplanted into *shiverer* mouse brains lacking myelin.
66•. Yang, N.; Zuchero, JB.; Ahlenius, H.; Marro, S.; Ng, YH.; Vierbuchen, T.; Hawkins, JS.; Geissler, R.; Barres, BA.; Wernig, M. Generation of oligodendroglial cells by direct lineage conversion. Nat Biotechnol. 2013. http://dx.doi.org/10.1038/nbt.2564 See annotation to Ref. [65•].

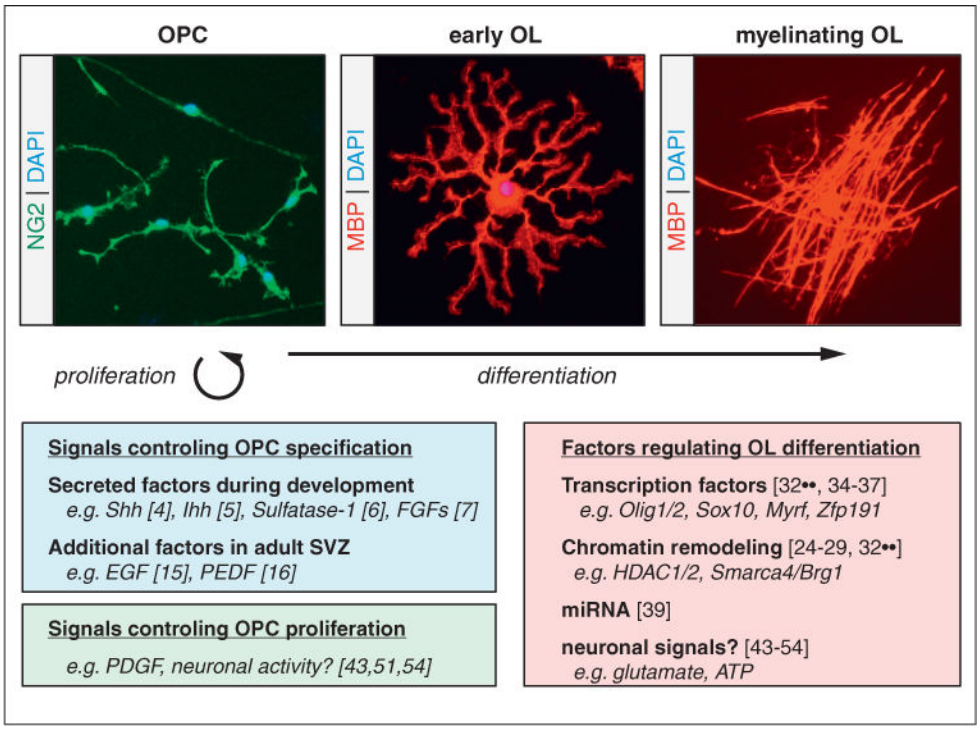

Figure 1.

Regulation of oligodendrocyte development. *Top*: Fluorescence micrographs of primary cultured oligodendrocyte precursor cells (OPCs), premyelinating oligodendrocytes (early OLs), and OLs myelinating unlabeled CNS axons. NG2 chondroitin sulfate proteoglycan (green) labels OPCs, while myelin basic protein (MBP, red) labels differentiated OLs and is found in compact myelin. *Bottom*: Summary of extrinsic signals that regulate OPC specification and proliferation, and intrinsic factors affecting OL differentiation, as described in the text.