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Ben Emery
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REVIEW

Regulation of Oligodendrocyte Differentiation and Myelination

Ben Emery

Despite the importance of myelin for the rapid conduction of action potentials, the molecular bases of oligodendrocyte differentiation and central nervous system (CNS) myelination are still incompletely understood. Recent results have greatly advanced this understanding, identifying new transcriptional regulators of myelin gene expression, elucidating vital roles for microRNAs in controlling myelination, and clarifying the extracellular signaling mechanisms that orchestrate the development of myelin. Studies have also demonstrated an unexpected level of plasticity of myelin in the adult CNS. These recent advances provide new insight into how remyelination may be stimulated in demyelinating disorders such as multiple sclerosis.

Within the vertebrate nervous system, the efficiency and speed of action potentials relies on myelin. Myelin is a specialized structure generated by glial cells, which extend compacted spirals of membrane around the axons of many neurons. Within the central nervous system (CNS), myelin is formed by oligodendrocytes. Developmentally, these cells are generated by subventricular cells in the brain and spinal cord that give rise to committed oligodendrocyte progenitor cells (OPCs) that divide and migrate throughout the CNS. These OPCs appear in successive waves; at early developmental stages they predominantly arise from ventral regions of the neural tube, but at later developmental stages these are largely replaced by dorsally derived OPCs (*1*). These OPCs can then terminally differentiate into postmitotic, premyelinating oligodendrocytes which, given the appropriate environmental cues, will further mature and myelinate nearby receptive axons.

That oligodendrocytes have a role in myelination has been appreciated for nearly a century. Penfield noted in 1924, for instance, "That these cells have to do with the formation and maintenance of the myelin sheath is born out by the facts…they are very numerous, especially in the white matter, and the position and relation of their cytoplasmic expansions to the myelin sheaths is similar to the arrangement of the sheath of Schwann" (*2*); astute observations given that myelin and the oligodendrocyte cell bodies could not be stained in the same sections by the methods of the time (Fig. 1). The importance of myelin for CNS functioning has long been apparent from human diseases such as multiple sclerosis (MS) and inherited leukodystrophies in which the integrity of the myelin sheath is lost, and from the severe phenotype of mutant mouse and rat strains in which the myelination process is disrupted. To date, most myelination research has been directed toward identifying mechanisms that promote or inhibit it during development with the goal of developing strategies to promote repair in the demyelinated CNS. Myelin may exhibit substantial plasticity throughout adult life. This has sparked renewed interest in the myelination process given that this plasticity may have profound implications for neural functioning. Here, I present some of the major areas of research within the CNS myelination field and some recent discoveries about the biology of oligodendrocytes and their progenitors.

Centre for Neuroscience and Florey Neuroscience Institutes, Level 2, Alan Gilbert Building, The University of Melbourne, 161 Barry Street, Carlton South, Victoria 3053, Australia. E-mail: emeryb@unimelb.edu.au

Extrinsic Signaling Mechanisms Controlling Oligodendrocyte Differentiation and Myelination

Perhaps not surprisingly given the importance of myelination for the proper functioning of the CNS, the development of oligodendrocytes and myelination of individual axons is a highly regulated process controlled by a number of mechanisms. These include axonal surface ligands, secreted molecules, and axonal activity.

Extracellular ligands and secreted molecules. The simplest mechanism for determining whether an individual axon is myelinated would be the expression of inhibitory or permissive cues for myelination on the surface of the axon itself. This mechanism would also have the important benefit of allowing control of myelin at the subcellular level, explaining how individual axons proximal to an oligodendrocyte can be myelinated or unmyelinated rather than the oligodendrocyte indiscriminately myelinating the entire field of axons. Intriguingly, many of the axonally expressed ligands found to influence myelination to date have been inhibitory, preventing oligodendrocyte differentiation and/or myelination. These factors have included axonal expression of ligands such as Jagged, which signals via Notch in OPCs (*3*), PSA-NCAM (*4*), and LINGO-1 (*5*), all of which inhibit either OPC differentiation or myelination. In contrast to the peripheral nervous system in which axonal expression of neuregulins is the dominant permissive signal for myelination by Schwann cells, neuregulin signaling to oligodendrocytes is largely dispensable for myelination, though CNS overexpression of neuregulins does induce hypermyelination (*6*). This may be at least partially due to redundancies with other promyelination signals such as laminins (*7*), which can activate overlapping intracellular signaling pathways.

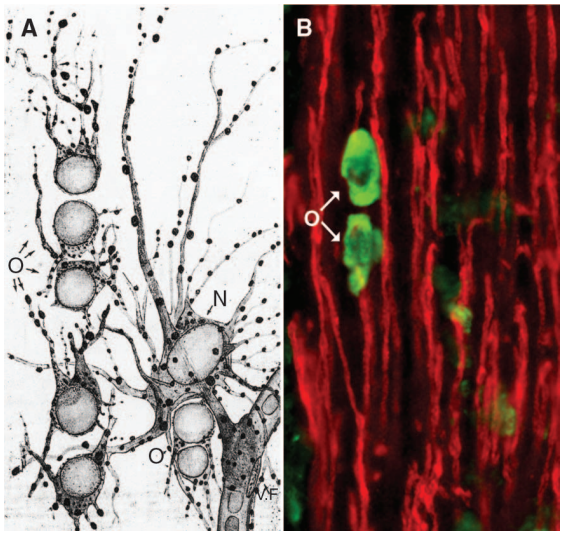

Fig. 1. (**A**) Drawing of silver-stained oligodendrocytes ("O") and a neuroglia/astrocyte ("N") by Penfield in 1924 (*2*). The myelin sheath was not stained in these preparations, thus the existence of a continual cytoplasmic link between oligodendrocytes and myelin was not demonstrated until the advent of electron microscopy. (**B**) Myelin sheathes in the developing mouse optic nerve stained with antibodies against myelin basic protein (red), with oligodendrocyte cell bodies stained with the β-catenin inhibitor adenomatous polyposis coli (green).

Signaling via the Wnt/β-catenin pathway has emerged as a key regulator of oligodendrocyte development, though one with somewhat paradoxical roles. Wnt signaling via the canonical pathway is transiently activated in OPCs concurrent with the initiation of terminal differentiation. Both β-catenin activity and the expression of Tcf4/Tcf7l2 (a transcription factor that mediates the transcriptional effects of the Wnt/β-Catenin pathway) are subsequently down-regulated in mature oligodendrocytes (*8*, *9*). This down-regulation of Wnt signaling may be necessary for oligodendrocyte differentiation, as mutant mice with elevated Wnt/β-catenin signaling in the oligodendrocyte lineage display blocked differentiation and hypomyelination (*8*). Paradoxically, however, deletion of the Wnt effector Tcf4 does not cause precocious oligodendrocyte differentiation as may be expected, but also blocks oligodendrocyte differentiation (*10*, *11*). Wnt signaling may thus exert complex roles in myelination, acting in conjunction with Tcf4 to promote the initial stages of oligo-

dendrocyte differentiation, but preventing subsequent differentiation steps and myelination unless down-regulated. These results have potential relevance for remyelination in human disease given that Wnt signaling components are present in MS lesions, suggesting that dysregulated Wnt/β-catenin signaling could contribute to the lack of remyelination often seen in this disease (*8*).

In addition to the above factors, it is almost certain that a number of extracellular ligands that modulate CNS myelination remain to be identified. For instance, the orphan G protein–coupled receptor (GPCR) Gpr17 is transiently expressed during oligodendrocyte differentiation. Overexpression of Gpr17 causes severe dysmyelination, with oligodendrocyte differentiation stalling at an early stage; conversely, deletion of the gene results in precocious differentiation of OPCs into oligodendrocytes (*12*). The relevant ligand(s) for Gpr17 in this context have yet to be identified, but based on the phenotype of Gpr17 mutants they are presumably potent inhibitors of oligodendrocyte differentiation. Similarly, inhibition of γ-secretase activity within oligodendrocytes during their differentiation in neuronal co-cultures promotes formation of myelin segments (*13*). This effect is not mediated through obvious candidate γ-secretase substrates such as Notch, indicating that myelination can be inhibited though additional extracellular signals that act through a γ-secretase–dependent pathway. An orphan GPCR has recently been identified in zebrafish as having a vital role in promoting myelination by Schwann cells, raising the possibility that functionally equivalent GPCRs that promote myelination will be identified in oligodendrocytes (*14*). Proteomics and gene array studies that identify neuronally expressed ligands and oligodendrocyte lineage expressed receptors will likely be instrumental in identifying some of these currently uncharacterized promyelination signals.

Neuronal activity. In addition to genetically programmed extracellular ligands, there is evidence that myelination is at least in part driven by the level of electrical activity in the axons themselves (*15*, *16*). This is particularly noteworthy because neural activity may also modulate ongoing myelination in the adult CNS, representing a form of neural plasticity (see below). There are a number of potential mechanisms by which this neuronal activity may promote myelination. Neuronal activity may modulate the surface expression of the abovementioned axonal ligands or cytokines, though only limited evidence for such a mechanism exists at present (*17*). Alternatively, release of adenosine by active axons may activate purinergic receptors on OPCs and promote their differentiation and myelination (*18*). A less direct mechanism involves axonal release of ATP stimulating adjacent astrocytes to release the promyelination cytokine LIF, which in turn signals to oligodendrocytes (*19*).

Oligodendrocyte progenitor cells may be well equipped to receive synaptic input directly from neurons and respond accordingly. Direct stimulation of OPCs by glutamate released by synaptic-like structures was first described for the hippocampus (*20*) and has since also been observed in other gray and white matter regions and for the neurotransmitter γ-aminobutyric acid (GABA) (*21*, *22*). Because OPCs express ionotrophic glutamate receptors and voltage-gated ion channels (*23*), they can respond to this stimulation with a depolarization event not unlike the action potential of a neuron (Fig. 2). Although there is controversy over whether OPCs can generate bona fide action potentials and whether all OPCs can respond to synaptic input in this manner (*21*, *24*, *25*), the generation of miniature excitatory postsynaptic potentials by OPCs in response to glutamate stimulation has been a generally consistent finding. This synaptic input onto OPCs is also observed in the context of remyelination in the adult CNS (*26*) and is rapidly lost as the cells differentiate into mature oligodendrocytes (*24*, *26*), suggesting that it likely has a specific role in regulating OPC behavior. This suggests an elegant mechanism in which activity of unmyelinated axons is associated with direct synaptic release from axo-glial synaptic junctions onto adjacent OPCs, which differentiate and myelinate the axon at a certain signal threshold. However, hard experimental support for this concept is still lacking. Treatment of OPCs with glutamate in vitro can inhibit both their proliferation and subsequent differentiation via a block in rectifier K^+ channels (*27*); this suggests that the role of glutamatergic signaling to OPCs may be to limit, rather than promote, myelination, possibly maintaining a pool of nondividing NG2-positive cells in the adult CNS. Moreover, although it has been reported that there are distinct populations of excitable and nonexcitable OPCs, with only the first group receiving synaptic input (*25*), it is not yet clear whether these groups display different capacities to myelinate and how they relate to the dividing and nondividing populations of OPCs also described in the mature CNS (*28*).

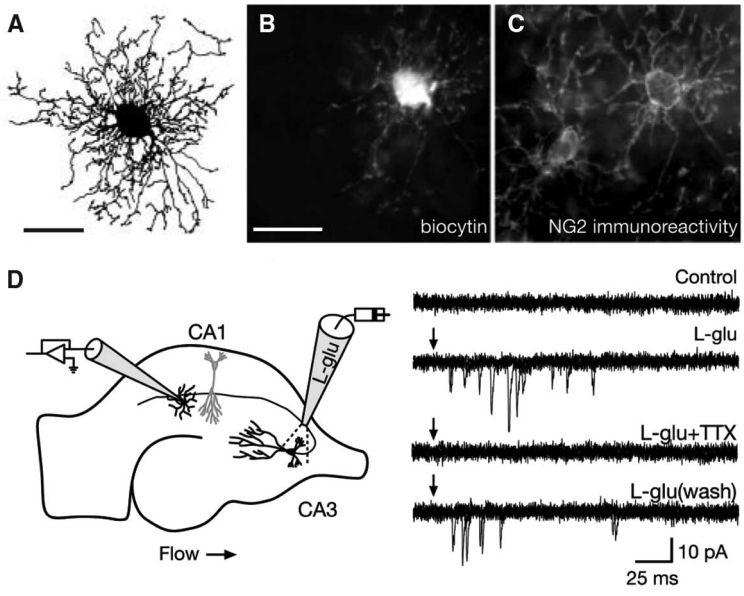

Fig. 2. Demonstration of OPC depolarization in response to synaptic input. [Reprinted by permission from Macmillan Publishers Ltd. (*20*)] (**A** to **C**) Example of one of the hippocampal OPCs recorded by Bergles *et al.* filled with biocytin (A and B) and stained with antibodies against the OPC marker NG2 (C). Scale bar, 20 μm. (**D**) OPCs in the CA1 region were patch clamped and their membrane potentials measured in response to L-glutamate stimulation of CA3 neurons. Neuronal activity elicited bursts of inward currents in the OPCs (blocked by tetrodotoxin). The physiological role of these synaptic inputs to OPCs and the OPCs' ability to depolarize in response to them remains unknown.

Intrinsic Control of Oligodendrocyte Differentiation and Myelination

It has long been appreciated that much of the regulation of oligodendrocyte behavior is intrinsic in nature, with mechanisms such as an internal "clock" limiting the number of cell divisions in OPC cultures grown in the absence of neurons (*29*). The past decade has seen great advances in our understanding of the nature of these intrinsic factors, which operate through transcriptional, posttranscriptional, and epigenetic mechanisms.

Transcriptional regulation. Chick electroporation and knockout mouse studies have proven instrumental in identifying a number of transcription factors required for the specification or differentiation of oligodendrocytes (Fig. 3). The initial specification of the oligodendrocyte lineage is reliant on the transcription factor Olig2; ventrally derived oligodendrocytes (and lower motor neurons) are derived from Olig2-expressing subventricular zone progenitors, and the oligodendrocyte lineage is absent in Olig2-null mice (*30*, *31*). Subsequently, the downstream induction of a number of transcription factors, most notably Olig1, Ascl1, Nkx2.2, Sox10, YY1, and Tcf4, is required for the generation of mature, postmitotic oligodendrocytes (*32*). All these factors are present in OPCs as well as in postmitotic oligodendrocytes, with the exception of Tcf4, which is transiently expressed during differentiation (*8*, *11*). This suggests that their roles

in promoting differentiation and activity at myelin gene promoters must be subject to regulation by additional factors differentially expressed between OPCs and myelinating cells. In this regard, a number of transcription factors, most notably Id2, Id4, Hes5, and Sox6, have been identified that are active in maintaining OPCs in their undifferentiated state and repressing myelin gene expression. This has led to a general "derepression" model of oligodendrocyte differentiation and myelination, whereby relief of extracellular inhibitory signals causes the down-regulation of these inhibitory factors or changes in their cellular localization, allowing pro-differentiation factors to induce differentiation and the expression of myelin genes.

The advent of wide-based gene expression analysis such as DNA microarrays has allowed for identification of many oligodendrocyte-specific or regulated genes with likely roles in regulating the myelination process (*12*, *33*, *34*). This enabled the identification of myelin gene regulatory factor (MRF), which is expressed within the CNS only by postmitotic oligodendrocytes, its expression being induced concurrent with terminal differentiation (*33*). Conditional inactivation of MRF within the oligodendrocyte lineage causes differentiation to stall at an early premyelinating stage, with the cells unable to express myelin genes or to myelinate. Conversely, forced expression of MRF within OPCs causes their precocious expression of myelin proteins (*35*). Given that the differentiation deficit seen in the absence of MRF appears broadly similar to that seen in the absence of factors such as Sox10 or Olig1, it is possible that cooperation with MRF upon its induction may allow these factors to have relatively specific roles in oligodendrocyte differentiation and myelin gene expression despite their earlier expression in OPCs. These findings add to the derepression model of oligodendrocyte differentiation by demonstrating that the transition from an OPC into a myelinating oligodendrocyte requires the induction of promyelination factors, such as MRF, in addition to the down-regulation of inhibitory factors.

Chromatin remodeling. Oligodendrocyte differentiation is also regulated at the level of chromatin remodeling by histone deacetylases (HDACs), as pharmacological inhibition of HDAC activity in postnatal rats causes a delay in oligodendrocyte differentiation and myelination (*36*). Conditional deletion of HDAC1 and HDAC2 in the oligodendrocyte lineage causes a loss of both OPCs and oligodendrocytes (*11*), suggesting that this HDAC activity is required at multiple stages of the lineage. Generation of OPCs is retained in cortical progenitor-derived cultures from these conditional knockout mice; nevertheless, the differentiation of the OPCs into oligodendrocytes is still blocked, consistent with the in vivo pharmacological studies (*36*). Histone deacetylases likely promote oligodendrocyte differentiation by inhibiting the expression of pathways and genes that otherwise act to block differentiation. These include HDAC-mediated inhibition of the Wnt/β-Catenin pathway (*11*) and HDACs acting in conjunction with the transcription factor YY1 to inhibit expression of factors such as Id4 and Tcf4 (*37*).

MicroRNAs. Posttranscriptional control of gene expression by microRNAs also plays a pivotal role in controlling CNS myelination. Conditional ablation of the Dicer enzyme (necessary for processing microRNAs into their active form) within the oligodendrocyte lineage in mice results in profound dysmyelination (*38*–*40*). Dicer (and by extension, microRNAs) is largely dispensable for the generation of OPCs in these mice; only the postmitotic stage of the linage is severely disrupted. Consistent with this, the expression of Dicer itself increases during oligodendrocyte differentiation (*33*, *38*, *39*). Use of microRNA profiling identified several microRNAs, most notably miR-219 and miR-338, that are induced concurrent with oligodendrocyte differentiation. These microRNAs target genes that usually act to maintain OPCs in the undifferentiated state, including PDGFRα, Sox6, and Hes5 (*38*, *39*). This suggests a mechanism in which microRNAs form a positive-feedback loop during oligodendrocyte differentiation, such that key microRNAs induced early in differentiation act to inhibit the expression of genes that promote OPC maintenance, thus further inhibiting proliferation and promoting differentiation. More subtle but important roles have also been identified for microRNAs at other stages of the lineage. The miR-17-92 cluster regulates OPC proliferation via regulation of PTEN and thus Akt phosphorylation (*41*). Similarly, expression of microRNAs is required on a continual basis in mature oligodendrocytes for the proper maintenance of myelin, because conditional ablation of Dicer in mature oligodendrocytes causes a dysregulation of the expression of Elovl7 and lipid homeostasis (*40*). These findings clearly demonstrate important roles for microRNAs in controlling CNS myelination at multiple stages.

Plasticity of Myelination in the Adult CNS

Although most myelination occurs early in life, myelination continues at least into late adolescence and, in some regions of the CNS, may increase throughout much of adult life (*42*, *43*). In addition, there is evidence of plasticity of myelin in the adult CNS in response to changes in neural activity. Successful learning of juggling is associated with an increase in fractional anisotropy in the white matter underlying the intraparietal sulcus (a region of the brain involved in perceptual-motor coordination), suggesting an increase in myelination (*44*). Similar structural changes in white matter are associated with piano practice during childhood, and to a lesser extent, adulthood (*45*). The neuroimaging measures used in these studies are not especially

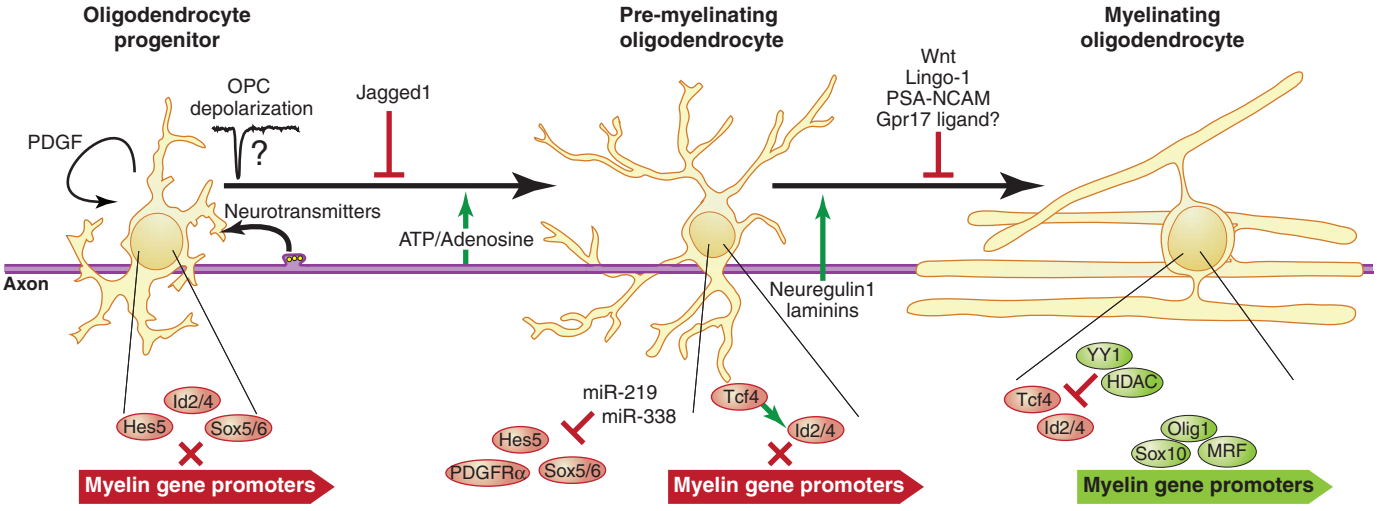

Fig. 3. Schematic of the oligodendrocyte lineage showing some of the intrinsic and extrinsic factors that influence oligodendrocyte differentiation and the myelination of individual axons. Oligodendrocyte differentiation requires the integration of multiple extracellular signals through coordination of multiple intrinsic pathways. Myelination is regulated both at the level of oligodendrocyte differentiation and more subtly at the level of individual axons.

specific to myelination; other potential changes such as axonal diameter could contribute to the change in signal. Nevertheless, they do correlate well with previous findings in animal models that have documented increases in myelination after manipulations such as environmental enrichment (*46*). These findings have led to proposals that activity-related changes in CNS myelin could be considered a form of neural plasticity, whereby (presumably active) axons undergo myelination to improve the speed and efficiency of nerve conduction, thus strengthening or synchronizing specific connections (*47*).

This is still a largely uncharted area, and the real extent to which myelin plasticity may underlie forms of learning in the adult CNS is essentially untested. The question has profound implications both for normal learning and plasticity, and in light of findings of reduced myelination in psychiatric disorders such as bipolar disorder and schizophrenia (*48*). If aspects of learning in the adult CNS are mediated by ongoing myelination, an obvious question will be whether this adult myelination is regulated by the same mechanisms that drive myelination during development. Another open question is the source of new myelin in the adult CNS; is it generated by newly differentiated oligodendrocytes, or do mature oligodendrocytes display sufficient plasticity to respond to axonal signals and generate additional myelin segments? In support of the first hypothesis, there is a continuous differentiation of OPCs into myelinating oligodendrocytes in the adult CNS (*28*). The degree to which this ongoing differentiation is activity dependent is unknown; however, electrical stimulation of the corticospinal tract at the level of the hindbrain in the adult rat promotes the proliferation of OPCs within the spinal cord (*49*). At least some of these OPCs differentiate into postmitotic oligodendrocytes that closely appose the corticospinal axons, though whether they go on to myelinate the stimulated corticospinal tract axons preferentially over neighboring unstimulated axons is not clear.

Conclusions and Future Directions

The past decade has seen major advances in our understanding of how myelination in the CNS is regulated; the use of transgenic and knockout mice in particular has demonstrated clearcut roles for many ligands and transcription factors in the myelination process. More recently, substantial control of oligodendrocyte development by HDACs and microRNAs has also been demonstrated. Increasingly, there will be a need to synthesize these different elements of regulation into a single model. This will require a much better understanding of how these various levels of regulation interact; how the extracellular signals affect intracellular signaling pathways; and how these in turn influence the expression and activity of transcriptional regulators, epigenetic regulators, and microRNAs. Recent work in the peripheral nervous system has made elegant inroads into synthesizing some of these elements in Schwann cells, delineating clearcut pathways between neuregulin signaling, intracellular calcium concentrations, and subsequent activity of transcription factors at myelin gene promoters (*50*). Similar work in the CNS will be of vital importance.

Although we now know that neuronal activity mediates myelination, the exact mechanisms by which this occurs are largely unknown. Moreover, although the existence of synaptic input to OPCs and their depolarization in response were first described a decade ago and have been intensely debated and studied since, the functional importance of these phenomena remains unresolved. Increasingly sophisticated tools such as optogenetics (*51*) are now available to label and manipulate the activity of individual neurons in a tightly controlled manner. Such approaches should be able to determine whether modulation of activity in an individual axon can promote its myelination independently of its neighbors both during development and in the adult, and if so, by what mechanisms. Conversely, genetic approaches manipulating the expression of key receptors or voltage-gated ion channels specifically in OPC populations or manipulating the depolarization of these cells will clarify the role of synaptic inputs onto OPCs and the OPCs' ability to depolarize in response.

A major future challenge will be translating our knowledge of oligodendrocyte development and myelination into therapeutic approaches aimed at promoting remyelination in human diseases such as the leukodystrophies and MS. In early MS, remyelination can occur relatively robustly, but becomes less efficient with disease progression. Given that mature oligodendrocytes are relatively inefficient in initiating new myelin segments (*13*, *52*), it seems likely that strategies promoting remyelination in such diseases will need to be targeted toward promoting the division, recruitment, and differentiation of OPCs and their subsequent myelination. It is not clear whether all mechanisms that regulate developmental myelination will have identical roles in remyelination; for example, unlike in development, Notch signaling does not appear to be a rate-limiting step in experimentally induced remyelination (*53*). Encouragingly, however, many of the mechanisms thus far identified as controlling developmental myelination do have conserved roles in remyelination. For instance, modulation of Lingo-1, known to regulate developmental myelination (*5*), also modulates remyelination in animal models of demyelination (*54*). Similarly, SVZ-derived OPCs receive synaptic input in the white matter in a mouse model of remyelination, indicating that, like developmental myelination, remyelination may be in part mediated by neuronal activity (*26*). We are still a long way from fully applying our understanding of mechanisms of myelin in a therapeutic context; however, the discoveries described here will provide an important basis for such work.

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