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Diversity matters: A revised guide to myelination

Giulio Srubek Tomassy^{1,†}, Lori Bowe Dershowitz¹, and Paola Arlotta^{1,†}

¹ Department of Stem Cell and Regenerative Biology, Harvard University, Cambridge, MA, 02138.

Abstract

The evolutionary success of the vertebrate nervous system is largely due to a unique structural feature - the myelin sheath, a fatty envelope that surrounds the axons of neurons. By increasing the speed by which electrical signals travel along axons, myelin facilitates neuronal communication between distant regions of the nervous system. Here, we review the cellular and molecular mechanisms that regulate the development of myelin as well as its homeostasis in adulthood. We discuss how finely tuned neuron-oligodendrocyte interactions are central to myelin formation during development and in the adult and how these interactions can have profound implications for the plasticity of the adult brain. We also speculate how the functional diversity of both neurons and oligodendrocytes may impact the myelination process in both health and disease.

Keywords

oligodendrocytes; myelin; cerebral cortex; neuron-glia interaction; development; brain plasticity

From ‘gluing substance’ to adaptive feature: a 300-year history of myelin

During vertebrate evolution, the formation of a lipid-rich envelope around the axons of neurons, known as the myelin sheath, was a fundamental step that greatly contributed to the expansion of the nervous system and the emergence of complex behaviors. At the beginning of the 18th century, Antonie van Leeuwenhoek was likely the first scientist to observe and describe the myelin sheath [1,2], but 150 years passed before myelin gained its current name; the term myelin was coined by Rudolf Virchow who thought this “substance” was contained within the hollow cavity of axons and thus named it ‘myelin’, an analogy to bone marrow (from the Greek myelos, ‘marrow’) [3]. Now, more than 150 years after Virchow, our knowledge about myelin has dramatically improved, and today the myelin sheath is perceived as a dynamic *functional* unit made by the axon on one end and the myelinating glial cell on the other. Neither side plays a passive role in this interaction – the myelinating

[†] Corresponding Author: Giulio Srubek Tomassy, Ph.D., Harvard University, Department of Stem Cell and Regenerative Biology, 7 Divinity Avenue, room 312, Cambridge, MA 02138, T: 617-495-5371, giulio_tomassy@harvard.edu, Paola Arlotta, Ph.D., Harvard University, Department of Stem Cell and Regenerative Biology, 7 Divinity Avenue, room 305, Cambridge, MA 02138, T: 617-496-9810, paola_arlotta@harvard.edu.

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cells execute a series of complex developmental steps culminating in the generation of large amounts of plasma membrane that wraps around the axon; concurrently, the neuron plays active roles by controlling myelin formation, distribution and maintenance [4,5], as we discuss below.

In the peripheral nervous system (PNS), the myelinating cells are known as Schwann cells, a specialized type of glial cell originating from the neural crest [6]. Likewise, oligodendrocytes myelinate the axons of the central nervous system (CNS); oligodendrocytes originate from multiple pools of oligodendrocyte progenitors (OPCs) that proliferate within the germinal zones of the developing CNS [7].

Although some invertebrate species exhibit glia-derived axonal ensheathment (see Box 1), only in the vertebrate nervous system does myelin reach its full specialization and its most well-recognized role – an “insulator” built around axons to allow action potentials (electrical signals) to travel at greater speeds over long distances [8].

Recently, substantial progress has been made in understanding myelin formation and function. While several questions still remain unanswered, it is clearer than ever that myelin is far more than insulation, playing dynamic roles in the execution of complex CNS functions.

Here, we review current models of myelination, focusing on intrinsic determinants of oligodendrocyte development. Then, we discuss the role of neuron-glia interactions in the context of myelin development, and through this discussion we speculate about the impact of neuronal and glial diversity on myelin formation and maintenance. Finally, we describe some of the most recent theories regarding newly discovered aspects of myelin function in brain plasticity.

‘Getting started’: intrinsic programs of oligodendrocyte development

Close-knit neuron-glia interactions are increasingly recognized as key for the formation and maintenance of myelin. For example, Schwann cells require continuous feedback from axons in order to differentiate, produce myelin and express myelin-associated genes [9]; in order to differentiate when cultured *in vitro*, Schwann cells require a medium containing cAMP, a mimic of axonal contribution [10,11]. The readers are referred to [6] for an in-depth review of Schwann cell biology. However, in contrast to Schwann cells, oligodendrocytes can differentiate and produce large amounts of membrane even when cultured alone. Remarkably, when oligodendrocytes are cultured on paraformaldehyde-fixed axons or in the presence of electron-spun nanofibers, these cells are still able to generate a myelin envelope similar to that created *in vivo* on live axons [12-14]. This capacity has recently enabled high-throughput drug screening in a relatively simple, neuron-free culture environment where oligodendrocytes are grown – without neurons – on micropillars made of fused silica [15]. Using this simple and very elegant approach, these authors have tested compound libraries for pro-myelination activity and have identified FDA-approved molecules that enhance oligodendrocyte differentiation [15].

Many laboratories have sought to identify the intrinsic factors that control oligodendrocyte development from early specification through the late steps of maturation and myelination [5,16,17] (Figure 1). During development, waves of oligodendrocyte progenitor cells (OPCs) are generated over time within the germinal zones of the brain and spinal cord. After specification, OPCs spread throughout the CNS while maintaining their proliferative state, and they eventually differentiate into mature oligodendrocytes [7,18].

Several transcription factors that control one or more steps along this process have been identified [16] (Figure 1). For example, the basic helix-loop-helix transcription factor *Olig2* is key for the early specification of the oligodendrocyte lineage but is also important for the subsequent differentiation of oligodendrocytes [19-21]. *Olig2* controls oligodendrocyte differentiation by recruiting the chromatin remodeler Brg1 to regulatory elements of myelin-associated proteins, such as myelin binding protein (Mbp) and *Ugt8a*, and differentiation-promoting genes, such as *Sox10* and *Myrf* [22]. *Myrf*, a membrane-associated protein expressed by postmitotic oligodendrocytes but not by OPCs, is another key determinant of oligodendrocyte terminal differentiation [23]. In conditional *Myrf*-deficient mice, OPCs and pre-myelinating oligodendrocytes are generated normally, but Mbp expression is almost completely absent [24].

Beyond transcription factors, chromatin remodeling may also be required during oligodendrocyte differentiation. Histone deacetylase activity has been detected in the corpus callosum and is important for oligodendrocyte differentiation and myelination [25,26]. For example, two histone deacetylases, HDAC1 and HDAC2, regulate oligodendrocyte differentiation by inhibiting the interaction between β catenin and the transcriptional repressor Tcf7l2. When bound to β -catenin, Tcf7l2 inhibits oligodendrocyte differentiation; conversely, HDAC1 and HDAC2 compete with β -catenin for its binding to Tcf7l2, and the HDAC1/2-Tcf7l2 complex promotes oligodendrocyte differentiation [27].

Recent studies have also highlighted the role of post-transcriptional modifications, regulated by microRNAs, during oligodendrocyte development [28,29]. In particular, three microRNAs (miR-138, miR-219 and miR-338) have been shown to promote oligodendrocyte differentiation by repressing negative regulators such as platelet-derived growth factor receptor α (PDGFR α) and *Sox6* [30,31].

Teamwork I: Neuronal control over myelination

In both the PNS and the CNS, communication between axons and myelinating cells coordinates the formation, repair, thickness and distribution of the myelin sheath [32-34]. Although a role for neurons in myelination was demonstrated several decades ago, our understanding of the interactions between neurons and myelinating cells has increased tremendously during the past few years. Several structural, molecular and electrophysiological properties of neurons have been shown to regulate the process of myelination (Figure 1).

The active role of axonal signals during myelination was initially observed through the relationship between myelin thickness and axon diameter. The caliber of axons in the PNS directly correlates with the thickness of the myelin sheath, and only axons with a thickness

greater than 1 μ become myelinated [35-37]. Interestingly, in the CNS the threshold diameter for myelination is less restrictive, and axons with diameters as small as 0.2 μ are myelinated; also, there is a large overlap in caliber between myelinated and non-myelinated axons [38]. These observations suggest not only that myelinating cells can “measure” the caliber of axons and create myelin layers appropriate for the axon diameter but also that the same rules governing PNS myelination may not fully apply to the CNS.

In the PNS, substantial data suggest that axon-derived molecules “transduce” the thickness of the axon to neighboring Schwann cells. A number of axon-derived molecules, including brain-derived neurotrophic factor (BDNF), Notch 1, cell adhesion molecules and G-protein coupled receptors, can affect myelin thickness in the PNS [5,34,39-41]. One of the most important regulators of myelin thickness is Neuregulin 1 (Nrg1), which is anchored to the membranes of PNS axons and interacts with erbB tyrosine kinase receptors on the surface of Schwann cells [42]. *In vivo*, reduced expression of Nrg1 isoform type III results in severe hypomyelination, whereas its overexpression increases the thickness of the myelin sheath [43]. Levels of Nrg1 type III act as a threshold for myelination, and its overexpression in small, unmyelinated PNS axons can cause myelination of these axons even if their caliber remains below the thickness threshold [44]. One mechanism by which peripheral neurons regulate levels of Nrg1 is through cleavage of the protein by β -site amyloid precursor protein cleaving enzyme 1 (BACE1), a process which seems to be positively regulated by the metallopeptidase Nardylisin [45]. Recently, it has been shown that BACE1 is also expressed in Schwann cells and that Schwann cell-derived BACE1 is as important as axonal BACE1 in controlling myelination [46,47].

In the CNS, the role of axon-associated molecules in myelination is less clear. Removal of *Nrg1* does not have the same effects on CNS myelination as its removal does in the PNS, although overexpression of Nrg1 in the CNS does result in hypermyelination relative to axon size [48,49]. These observations suggest that different molecular mechanisms regulate myelination in the PNS versus the CNS, a discrepancy which is not surprising given the distinct origins of oligodendrocytes and Schwann cells. Furthermore, molecular regulation of myelination in the CNS may vary by region [34,50,51], potentially reflecting the presence of distinct neuronal types. This complicating factor may account for the uncertainty surrounding the roles of various molecules in CNS myelination.

Apart from the somewhat controversial Nrg1-mediated pathway, a few membrane-associated soluble factors and extracellular matrix proteins are involved in the positive or negative regulation of different stages of oligodendrocyte development. These factors include laminins, growth factors (e.g. IGF1, FGF, BDNF), Notch ligands (e.g. Jagged1, F3/contactin), PSA-NCAM and Lingo1 [5] (Figure 1).

Electrical activity of the axon can also coordinate myelination in the CNS. In zebrafish embryos, blocking the release of synaptic vesicles with tetanus toxin causes individual oligodendrocytes to extend fewer myelin processes; conversely, increasing neuronal activity with a GABA receptor antagonist increases the number of myelin processes per oligodendrocyte [52]. Although oligodendrocytes initially wrap processes around many axons, some of these processes are subsequently retracted. Processes that surround

electrically active axons are more likely to be stabilized than are processes that surround silent axons [53], suggesting that active neurons are preferentially myelinated. Several *in vitro* studies have identified mechanisms that may mediate activity-based neuron-oligodendrocyte interactions. Electrical activity influences the expression of cell adhesion molecules (e.g. L1) on axons [54] and stimulates the release of synaptic vesicles that promote the synthesis and localization of myelin proteins by oligodendrocytes [55]. Furthermore, in response to action potentials, astrocytes release the cytokine leukemia inhibitory factor (LIF), which induces myelination by mature oligodendrocytes [56].

Interestingly, electrical activity appears to modulate myelination in the postnatal mammalian brain. Optogenetic stimulation of projection neurons of the mouse motor cortex increases proliferation of OPCs and differentiation of oligodendrocytes not only in the cortex but also in the subcortical white matter; in addition, the thickness of the myelin sheath is increased along the axons of stimulated neurons [57]. These data support a fundamental role for neuronal activity in myelination and suggest that myelination can be a highly dynamic process, even in the adult brain.

Teamwork II: Oligodendrocyte support of neuronal survival

Myelin has undoubtedly provided the nervous system of vertebrates with a critical functional advantage, but this advantage may come at a metabolic cost. The myelin sheath isolates myelinated axons from the surrounding environment, a source of trophic and other support factors. This separation clearly has important consequences for the axonal metabolism and energy requirements of neurons; understandably, problems of axonal metabolism are most evident in the longest axons that connect distant regions of the nervous system (e.g. corticospinal tract) [58, 59].

At the same time, myelin seems to provide fundamental support to axons. Axonal loss is a common feature of many myelin diseases (e.g. Multiple Sclerosis, Pelizaeus-Merzbacher disease), which can lead to chronic and often untreatable deterioration of brain function.

But what is the link between demyelination and axonal degeneration? The answer is not simple. One possibility is that demyelinated axons require more energy than myelinated ones; thus, loss of the myelin sheath may lead to an unsustainable decrease in the overall energy balance of the axon [60]. However, in the *shiverer* mice, oligodendrocytes fail to provide enough myelin to wrap around axons, but this deficiency does not lead to axonal degeneration [58,61]. Additionally, in the Plp1 mutant mouse, a mouse model of human spastic paraplegia, a compact and functional myelin sheath is formed despite signs of axonal degeneration, which occurs following deficiencies in axonal transport [62, 63, 64]. Thus, deficiencies in myelination do not guarantee neuronal degeneration and axonal degeneration can occur even in the absence of any demyelinating event. An alternative hypothesis is that axonal degeneration may arise from defects in oligodendrocyte-to-neuron signaling, which in turn may affect axonal metabolism. Indeed, recent studies have demonstrated that oligodendrocytes support neuronal survival via release of lactate, which myelinated axons may utilize for their energy metabolism [65, 66]. This observation is consistent with findings in the SOD^{G93A} mouse, a classic model of Amyotrophic lateral sclerosis (ALS), in which

dysfunctional oligodendrocytes seem to contribute to the disease phenotype [67, 68]. Thus, metabolic support from oligodendrocytes may be vital for neuronal and axonal metabolism and integrity, a relationship that suggests a crucial role for oligodendrocytes in many human neurodegenerative disorders. Understanding the interplay between myelin and axonal integrity may provide insight into the pathology of these diseases.

A complicated relationship: oligodendrocyte and neuronal diversity in the context of myelination

The nervous system is composed of many different types of cells with specific identities, which are typically defined by structural, molecular and functional traits. It is widely accepted that many classes of neurons exist; these classes populate different regions and connect different areas of the nervous system. The complexity and diversity of these different populations are being extensively investigated around the world [69,70].

Conversely, oligodendrocyte heterogeneity is still an active matter of debate; while some consider all oligodendroglial cells as one structurally and functionally homogeneous population, others support the existence of distinct subtypes (the two groups of “lumpers” and “splitters,” which Freeman and Rowitch fittingly refer to in [71]) (Figure 2). The concept of a heterogeneous population of glial cells is not new; astrocytes are known to be molecularly and functionally diverse [72], and oligodendrocytes may encompass similar heterogeneity. Remarkably, almost a century ago Pio del Rio Hortega proposed the existence of at least four different types of myelinating oligodendrocytes based on their morphologies and the diameters of the axons they myelinated, and his observations have subsequently been confirmed [73,74].

More recently, high-throughput transcriptional profiling as well as large-scale analysis of the proteome and lipidome of the myelin sheath [23,75-78] have begun to address this issue. For example, single-cell transcriptional analysis of more than 3000 mouse forebrain cells has revealed the existence of six putative subpopulations of oligodendrocytes based solely on gene expression profiles [79]. These data cannot determine whether these clusters correspond to different stages of maturation or if they distinguish functionally unique subtypes, but we are confident that similar approaches will be extremely helpful for resolving the issue in the near future. Interestingly, different combinations of microRNAs have been found in fetal OPCs, adult OPCs and adult oligodendrocytes, suggesting the existence of stage-specific, miRNA-mediated molecular codes that instruct myelination during development and in adulthood [80]. Similarly, different patterns of transcription factors (e.g. Olig2, Nkx2.2) are expressed in different regions of the adult white and grey matter, an observation which again suggests potential heterogeneity within oligodendrocytes [81]. Finally, oligodendrocytes that populate the same tissue are often derived from progenitors arising from distinct brain regions [17,18]. This added complexity suggests another level of specialization that may ultimately produce oligodendrocytes of different classes.

A more complete understanding of oligodendrocyte diversity will be necessary to define the functional roles and evolutionary trajectory of these cells. Ultimately, it will be interesting to

determine if human pathologies of myelination reflect deficiencies in only certain oligodendrocyte subtypes and if these subtypes differ in their abilities to remyelinate the adult brain after pathological insults (see Box 2).

The issue of oligodendrocyte diversity becomes further complicated due to the close association between neurons and oligodendrocytes. Although the role of neuronal diversity in myelination remains poorly defined, it is possible that specific neuronal subtypes differentially control myelination. Also, specific neuronal subtypes may associate with only particular oligodendrocyte partners, a coordinated interaction that would be critical to consider for measuring and modeling circuit behavior.

Neurons actively participate in the myelination process, but neurons are not all alike. For example, the cerebral cortex contains an unparalleled heterogeneity of neuronal subtypes, each of which has specific connectivity and functions. The cortical wall has a laminar structure, typically comprising six adjacent layers (I–VI), each containing distinct neuronal subtypes [70,82]. Recently, it was demonstrated that these layers are not uniformly myelinated; rather, myelin is distributed in a gradient, with a density that is higher in the deep layers (layers V–VI) than in the upper layers (layers II–IV) [83]. This uneven distribution of myelin has been partially explained through reconstructing and tracing single axons of cortical projection neurons; these reconstructions revealed that neurons from different cortical layers have different longitudinal myelination profiles along their axons [83]. Notably, neurons of the upper layers displayed the most heterogeneous set of myelination profiles, including an “intermittent myelin” pattern with alternating long myelinated and unmyelinated tracts along the same axon [83].

A possible explanation for this heterogeneity of myelination profiles is that each subtype of neuron controls its own profile. Indeed, in two mouse models of cortical migration (*Dab1*^{−/−} and *RhoA* conditional knockout), aberrant positioning of deep-layer neurons into the upper layers resulted in an increased distribution of mature oligodendrocytes in the upper layers as well as myelination at levels similar to those normally observed in the deep layers [83].

Because upper-layer and deep-layer cortical projection neurons differ greatly in gene expression, connectivity and function [70,84], a subtype-specific molecular code that is used to communicate with oligodendrocytes could explain the graded distribution of myelin within the cortical wall as well as the different distributions of myelin along the axons of distinct pyramidal neurons. For example, by clustering different sets of membrane-associated proteins along their axons or by locally releasing subtype-specific molecules, each neuronal subtype may uniquely signal to neighboring oligodendrocytes and thus “choose” its own profile of myelination. In the cerebral cortex, such subtype-specific intercellular communication has been demonstrated for projection neurons and GABAergic interneurons [85]. Future studies should investigate whether other processes such as myelination are also regulated by neurons in a class-specific manner.

A “plastic” insulator: myelin remodeling in the adult brain

Several studies highlight the fact that new myelin is continuously generated, even in the adult brain. For example, in the murine optic nerve, OPCs continue to proliferate and

generate new myelinating oligodendrocytes well into adulthood, suggesting that active myelination does occur in the fully developed CNS [86]. In the human brain, myelination continues beyond adolescence and into early adulthood [4,87,88] (Figure 3, Key Figure). However, in contrast to observations in mice, myelination in adult humans seems to be carried out solely by mature oligodendrocytes that were generated during development [89].

Remarkably, recent findings show that myelin production is modulated by neuronal activity not only in the developing brain but also in the adult human brain. Diffusion tensor imaging (DTI) studies have revealed higher mean values of fractional anisotropy (FA) along fiber tracts involved in language circuitry in bilingual children, as compared to monolingual children [90]. Similar effects have been described in English-speaking adults learning Chinese as a second language, suggesting not only that white matter remodeling can continue well after development is terminated but also that brain activity can modulate this process [91,92]. Comparable observations have been made when studying the effects of learning new motor skills such as piano-playing or juggling [93,94] (Figure 3, Key Figure).

These studies suggest that experience can shape myelin, but is the opposite also true? For example, is adult myelination required for learning? In adult rodents, motor learning increases myelination in the white matter [95]; recently, the formation of new myelin was found to be required for motor learning in adult mice [96]. An increased number of newly generated mature oligodendrocytes was observed in adult mice that learned new tasks, and, importantly, mutant mice in which production of new oligodendrocytes was genetically impaired were less capable of learning new motor skills [96]. Interestingly, white matter defects have also been reported for patients affected by a wide range of psychiatric disorders, including schizophrenia and depression [97-99]. Thus, fine coordination between synaptic activity in neurons and myelination may be essential for normal neuronal function and plasticity in the adult brain.

Concluding remarks

A long time has passed since myelin was considered just an inert and static element serving neuronal needs and function. New, unbiased scientific approaches, supported by the acquisition of powerful technological tools like high-throughput electron microscopy, genome-wide transcriptional analysis, and optogenetics to name a few, are revising old concepts and creating a brand-new picture of myelin. Today, myelin is increasingly considered a highly dynamic and metabolically active element of the nervous system, key to the modulation of neuronal circuitry, the plasticity of the adult brain and the computation and execution of the most complex functions of the brain.

Although our understanding of myelin biology has advanced more in the last two decades than in the previous 300 years, many questions remain unanswered (Outstanding questions). Among them is the question of heterogeneity among myelinating cells. How would that diversity impact the process of myelination as well as neuronal function? If multiple subtypes of oligodendrocytes (and their progenitors) exist, are they differentially involved in myelin pathologies?

Another fundamental aspect of myelin biology is how myelin is involved in brain plasticity and, conversely, how brain activity affects myelination. For example, does the distribution of internodes along axons change dynamically upon neuronal activity? This could explain the observation that the most heterogeneous profiles of myelination are found in the upper layers of the cerebral cortex, where the neurons involved in the most elaborate activities of the brain (e.g. associative functions) reside. Further investigation will be necessary to determine if those myelination profiles are a still frame of a more dynamic, frequently changing process or if they represent more static, subtype-specific functional features.

A thorough comprehension of the neural network is not feasible without taking into consideration all of its neuronal and glial components. Whether we aim to create a high-resolution topography (e.g. connectome) or to model complex physiological behaviors (e.g. optogenetically), we must include myelin as a foundational and pivotal element of that network.

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Myelin evolution

As animals populated different and more challenging environments, the rapid conduction of nerve impulses must have constituted a great adaptive advantage, enhancing chances of survival for both predators and prey. Neuronal impulse conduction is classically modeled as a flow of ions through a hollow cylinder. In this model, two physical parameters of the cylinder critically affect the speed of ion flow: axial resistance and capacitance of the surface. Through alterations in either or both of these two parameters, different evolutionary strategies achieved the same goal – increasing the conduction velocity of neuronal signals to make “faster” nervous systems. In some species, axonal diameter was increased in order to decrease the axonal internal resistance and thus speed up signal conduction, an adaptation which resulted in the ‘giant axons’ of many invertebrates; conversely, in vertebrates, development of the myelin sheath increased the axial resistance of the axonal surface in addition to reducing its capacitance [8].

Robust evidence exists for the evolutionary advantage that myelin provides. Myelin repeatedly emerges among species that are phylogenetically distally unrelated; myelin-like structures are found even in some invertebrates, like members of the subphylum Crustacea (some decapods and copepods) and phylum Annelida (e.g. earthworms) [100]. Among myelinated invertebrate species, the structure of the myelin envelope can vary considerably from a loose arrangement of lamellae (e.g. in some decapods) to a “vertebrate-like” compact architecture comprising tightly associated layers (e.g. earthworms). Similarly, biochemical properties, such as content and ratio of proteins and lipids within the myelin envelope, can vary among invertebrate species [101]. In an even more distant example of evolutionary diversity, myelin-like structures with no glial origin were recently described in the nervous system of the copepod *Bestiolina similis* [102].

Myelin found around the axons of gnathostome vertebrates is more homogeneous and structurally similar, even between CNS and PNS, with fine differences observed only at higher magnification [5]. Myelin is present in all vertebrates, from cartilaginous fishes to mammals, with the exception of the class Agnatha, jawless fish; for this reason, it has been hypothesized that appearance of myelin was concomitant with the appearance of a hinged jaw and that the first myelinated gnathostomes may have been the placoderms (among the first jawed fish), whereas other jawless fish (e.g. ostracoderms) may have not been myelinated [103].

Whether loose or compact, produced by Schwann cells, oligodendrocytes, and by yet-to-be-defined mechanisms, myelin is a perfect example of convergent evolution. By increasing the speed of impulse conduction, myelin certainly contributed to the expansion of the vertebrate brain and to the emergence of complex and plastic behaviors.

Myelin disorders

Because myelin plays vital roles in the correct functioning of the nervous system, defects in myelin formation and maintenance result in devastating clinical outcomes. Given that many aspects of myelin biology still remain poorly understood, the limited knowledge of many myelin diseases comes as no surprise. Even the clinical nomenclature for these diseases is inconsistent in the literature. For example, the terms leukencephalopathy and leukodystrophy are sometimes used interchangeably; however, leukencephalopathy refers to any defect of the white matter, whether genetic or environmental (e.g. trauma), but leukodystrophy refers only to myelin disorders that arise from known genetic defects. This lack of consensus recently prompted a panel of experts in the field to achieve common definitions and classifications [104,105]. One of the major obstacles to a clear definition is the fact that, for a large proportion of pathologies, the triggering cause is unknown, and many of these disorders still lack clinical categorization; often, magnetic resonance image analysis is the only tool that clinicians can use to provide a diagnosis [106,107].

Myelin diseases can be broadly sorted into three categories: myelin loss (demyelination), abnormal myelin production (dysmyelination) or reduced myelin production (hypomyelination). The incidence and prevalence of many of these diseases are poorly defined, and onset can range from prenatal to adult. One aspect that has been almost completely ignored is whether specific glial cell subtypes are involved in myelin diseases. It is well known that several neurodegenerative disorders primarily affect specific types of neurons, often located in restricted areas of the brain, while sparing other neuron types (e.g. Huntington disease affects medium spiny neurons of the striatum, whereas amyotrophic lateral sclerosis affects motor neurons of the cortex and spinal cord). Conversely, no clear links have been made yet between Schwann cell or oligodendrocyte subtypes and a specific myelin disorder; indeed, even the existence of structurally and/or functionally distinct subtypes of Schwann cells and oligodendrocytes is not yet accepted (see main text). We speculate that this possibility exists; if multiple Schwann cell and oligodendrocyte types are identified, unique features of each cell type may help characterize different myelin disorders. For example, NG2⁺ OPCs with elongated or stellate shape have been found in the lesions of patients with multiple sclerosis; interestingly, elongated OPCs express the p75 neurotrophin receptor, which is involved in cell survival [108], while stellate NG2⁺ OPCs in the same lesions are p75-negative [109]. This observation suggests that these two types of OPCs may have different functions within the same lesions and may therefore differentially contribute to the pathology of multiple sclerosis. Discovery of functionally distinct subtypes may lead to a brand new understanding of many myelin pathologies and may lead to better-targeted therapeutic approaches and more effective treatments. Cell subtype-based clinical markers may also be identified, and these molecules could help classify one myelin disease versus another.

Outstanding questions

- What are the molecular signals that CNS neurons utilize to support myelination? Many studies have revealed molecules involved in neuron-glial cell signaling in the PNS, but corresponding molecular cues that instruct myelin wrapping around the axon have yet to be identified in the CNS.
- Do structurally and functionally distinct subtypes of Schwann cells/oligodendrocytes exist? Novel tools for high-throughput transcriptional profiling will help to define subtypes at the molecular level, but additional studies are necessary to define structural and functional differences and resolve questions about the existence of subtypes.
- If multiple subtypes do exist, are they differentially affected in myelinopathologies? If specific subtypes of myelinating cells are indeed involved in myelin pathologies, a better understanding of subtype function will be critical for understanding the pathobiology of these disorders. This understanding could allow for the development of better-targeted and more effective therapeutic approaches and could also provide novel diagnostic tools for clinicians.
- How do neurons and Schwann cells/oligodendrocytes affect each other's integrity? Secondary axonal loss is a common clinical feature of many myelin diseases, and, in many neurodegenerative diseases, demyelination also occurs even at later stages of the disease. Thus, understanding how either of the two components of the myelin unit is affected by each other dysfunction, may help reveal novel aspects of disease and find new therapeutic approaches.

Trends Box

- New myelin is continuously generated, even in the adult brain. More importantly, novel findings have shown that myelin production is modulated by neuronal activity. This observation changes our classic view of myelin as a static insulator and suggests that myelination may be essential for neuronal function and plasticity in the adult brain.
- Typically, myelinating cells have been considered a structurally and functionally homogeneous population. However, recent observations suggest that these cells may encompass greater diversity with more subtypes than previously acknowledged.
- Neurons actively support myelination, yet the role of neuronal diversity in myelination remains poorly defined. In the neocortex, distinct subtypes of neurons display different myelination profiles along their axons, suggesting that specific neuronal types may differentially control myelination.

Figure 1. Intrinsic and neuron-derived factors controlling oligodendrocyte development

Oligodendrocytes originate from pools of progenitors (OPCs) located in different regions of the developing CNS. After specification, OPCs spread throughout the CNS and eventually differentiate into pre-myelinating oligodendrocytes (Pre-OLs). Pre-OLs then produce large amounts of cell membrane, which wraps around multiple axons to form the myelin sheath (Myelinating oligodendrocytes). Several cell-autonomous factors that control one or more steps along this process have been identified; these include transcription factors, chromatin remodeling proteins and non-coding RNAs. In addition to these intrinsic factors, neuron-

derived signals also play an active role in oligodendrocyte development and myelination. Among them, membrane-associated proteins, soluble factors and extracellular matrix proteins are involved in the positive or negative regulation of different stages of development, including proliferation, differentiation and initiation of myelination. Recent studies have also demonstrated that electrical activity of the axon can dramatically affect oligodendrocyte development and myelination in the CNS.

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Figure 2. The “lumpers” and “splitters” dichotomy of oligodendrocyte cellular diversity

It is widely accepted that the nervous system is composed of many different classes of neurons, each with specific identities typically defined by structural, molecular and functional traits; these classes populate different regions and connect different areas of the nervous system. Conversely, oligodendrocytes are still considered by many as one homogeneous population (**A**, the lumpers); however, it is possible that structurally and functionally distinct subtypes exist (**B**, the splitters); these subtypes may have different myelinogenic potential and may also interact differently with neighboring neurons. Further investigation of oligodendrocyte diversity will be critical to better understand subtype-specific functions and neuron-glia interactions in the context of myelin formation and maintenance.

Figure 3. Developmental and adaptive myelination in the human brain

(A) Human myelination is mostly a postnatal process that peaks during childhood and can continue until early adulthood. (B) Once myelination of all brain regions is completed, production of new myelin is still possible; adults who actively learn complex tasks like studying a second language, juggling or piano-playing, show increased myelination in specific regions of the brain. These observations suggest that brain activity can impact the production of new myelin even in adulthood.