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Architecting the Myelin Landscape

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Abstract

Myelin increases the speed and efficiency of action potential propagation. Yet, not all axons are myelinated and some axons are discontinuously myelinated, prompting the question of how myelinating glia select axons for myelination. Whereas myelination by Schwann cells depends on axonal induction, oligodendrocytes can form myelin membrane in the absence of axons. However, oligodendrocytes alone cannot architect the complex myelination patterns of the central nervous system and recent advances have implicated axonal signaling in this process. This review considers how oligodendrocytes and their precursors could be influenced by inductive, attractive, permissive, repulsive, and preventative cues, and discusses recent evidence identifying synaptic activity and membrane-bound adhesion molecules as such cues directing axon selection.

The myelin landscape

Myelin, the insulating membrane concentrically wrapped around axons, accelerates impulse propagation and offloads neuronal energy expenditure. Despite these advantages, not all axons are myelinated and some axons are only intermittently myelinated. In the peripheral nervous system (PNS), Schwann cells (SCs) myelinate solely large diameter axons [1], with individual SCs each myelinating only one axon segment. By contrast, central nervous system (CNS) myelination patterns are more complicated. During development, myelination proceeds in a stereotyped sequence with different regions being myelinated at different times as oligodendrocyte precursor cells (OPCs), which are distributed throughout the CNS, differentiate into myelinating oligodendrocytes (OLs) [2,3]. OPC differentiation and myelination continues into adulthood, albeit at a much slower rate [4–6]. Unlike SCs, each OL extends many processes to myelinate several different axon segments. The smallest caliber CNS axons are never myelinated but there is significant overlap in the diameters of myelinated and unmyelinated axons [7], whereas other CNS structures geometrically similar

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to axons – dendrites, blood vessels, and glial processes – remain unmyelinated, with rare exceptions.

Recent volumetric reconstructions of cortical tissue have further refined our understanding of CNS myelination. Intriguingly, myelination may depend on neuron subtype: a recent study found that parvalbumin-positive basket cells are essentially the only type of GABAergic interneuron with myelinated axons in the adult mouse neocortex [8•]. Another study contested the prevailing dogma of myelination as an all-or-none phenomenon; rather, many pyramidal axons in the adult mouse neocortex are intermittently myelinated, with large unmyelinated gaps between myelinated sections [9], a configuration distinct from nodes of Ranvier that separate individual myelin sheaths (internodes) to permit saltatory conduction.

This partial myelin coverage likely reflects the need to balance the advantages of myelination with overall energy [10] and space constraints, and likely contributes to the precise control of circuit timing [11], underscoring the importance of appropriate myelin localization. In the case of intermittent myelination along a single axon, unmyelinated gaps could provide space for new myelin formation to fine-tune myelination patterns as circuit activity changes in the adult. This review will focus on our current understanding of how these intricate patterns of myelination are established.

The intrinsic nature of OL myelination

Given that sensory and motor axons that pass between the CNS and PNS are myelinated by both OLs and SCs, it seems intuitive that CNS and PNS axons would use similar mechanisms to control myelin formation. In the PNS, axons play a necessary and *inductive* role in their own myelination. Neuregulin-1 type III is required for SC maturation and myelination of PNS axons [12] and its expression level determines myelin sheath thickness [13]. Importantly, its ectopic suprathreshold expression *induces* the myelination of normally unmyelinated axons [12], demonstrating its importance in determining myelination fate.

However, neuregulin-1 type III is largely dispensable for CNS myelination [14,15]. In fact, several aspects of OL myelination proceed successfully without molecular axonal signaling altogether. Cultured OPCs intrinsically differentiate into OLs, which, remarkably, can form compact myelin around inert polystyrene fibers [16]. In fact, certain properties of *in vivo* myelination can be explained by how OL-lineage cells intrinsically interact with axonal geometries. Neither OPCs or OLs will ensheath or wrap synthetic fibers with a diameter smaller than or equal to 0.3 μ m, a similar threshold to that observed *in vivo* [16], indicating that OL-lineage cells directly sense fiber geometries. Geometric sensing by OL-lineage cells may also explain the general correlation between internode length and axon diameter *in vivo* [17,18] as this correlation persists with synthetic fibers [19]. Exactly how OL-lineage cells detect radial axon size remains elusive, but they may utilize properties such as curvature or circumference to do so. Curvature-inducing components could impose a physical limit on OL-lineage cell membrane curvature that prevents wrapping of highly curved, subthreshold diameter axons. Alternatively, OL-lineage cells could sense their own membrane curvature as they wrap (for an example of curvature sensing at a similar scale, see [20]) and avoid

wrapping axons above a threshold curvature. Another approach could be for OL-lineage cells to infer axonal circumference by sensing the length of one wrap of their membrane around an axon (for a potential mechanism of length sensing, see [21]). Upon completing one wrap, an OL-lineage cell process would contact itself. If the process length is subthreshold, the process would retract upon self-contact, preventing wrapping. Retraction of an extending OPC process upon contact with another process of the same OPC has been observed in the adult mouse cortex [6]; the same mechanism could operate in this context as well. To avoid retraction upon self-contact, the OL-lineage process would have to exceed a threshold length. At this threshold, the length sensing machinery would initiate a rapid downregulation of the self-repulsion mechanism locally within the wrapping process (e.g. by internalizing cell adhesion molecules), enabling self-contact and myelination of suprathreshold circumference axons. Similar mechanisms could also be used to correlate internode length with radial axon size.

Regional differences in OL-lineage cells, which likely emerge after OPC specification [22], may explain some differences in myelination between CNS regions. OPCs isolated from developing spinal cord form longer internodes upon differentiation than do those isolated from neocortex in cultures with synthetic fibers or neurons [19], reproducing the differences in internode length observed between these regions *in vivo* [23]. Another study demonstrated that the higher levels of differentiation and myelination in white matter (WM) [24] might be partially explained by differences between WM and grey matter (GM) OPCs. Adult WM OPCs transplanted into either adult WM or GM differentiated more efficiently than adult GM OPCs transplanted into either region [25].

Extrinsic factors regulating OL axon selection

Whereas intrinsic properties of OL-lineage cells might be helpful for setting up some basic features of the myelin landscape, they cannot independently produce the complex and specific myelination patterns observed in the CNS. For example, the relationship between myelin sheath thickness and axonal diameter [26] is not reproduced with synthetic fibers [19], and the ratio of internode length to axon diameter is actually highly variable *in vivo* [17,18,27]. In particular, since OLs are not programmed to myelinate a specific type of axon [28–30] and many suprathreshold diameter axons are not myelinated *in vivo* [7], other factors must contribute to the regulation of axon selection. Indeed, extrinsic factors have an important role in this process. For myelination of the appropriate axons at the appropriate time, OLs must be present and they must know where to form myelin – two components that can be influenced by extrinsic factors. By influencing virtually every aspect of OL development, extrinsic signals can affect the distribution of OLs at any time. Furthermore, extrinsic signals can influence where individual OLs localize their myelin sheaths.

Axons, as the substrates for myelination, are logical candidates for being the source of these extrinsic cues. Axons might precisely regulate the timing of their myelination by expressing dynamic cues. An *inductive* cue could turn on, or a converse *preventative* cue could turn off, in an axon to initiate its myelination. OPCs, which actively survey their environment [6,31] and receive synaptic inputs from axons [32], are well-positioned to integrate such cues from multiple axons. A threshold level of change in these axons could cause OPCs to differentiate

and to myelinate these axons. By utilizing a combined differentiation/axon selection cue (Figure 1A), this system would be extremely efficient in matching the number of OLs and their internodes to the axons requiring myelination at any time.

Alternatively, differentiation and axon selection could be uncoupled (Figure 1B, C) [33•]. Differentiation could occur either through an actively regulated mechanism or through one that is indiscriminately applied wherein OLs that differentiated in excess of available axons would eventually die [34–36]. Axon selection could be performed by either OPCs (Figure 1B) or OLs (Figure 1C). OPCs could identify axons to myelinate upon their eventual differentiation (Figure 1B), or, once differentiated, OLs could become receptive to axonal cues that regulate either sheath initiation or stability (Figure 1C). The axon selection cues described below could apply to either cell type. *Inductive* or *preventative* axon selection cues could operate in this context (although they are not illustrated in Figure 1B, C). In the case of unregulated OPC differentiation, both the patterns and timing of myelination would be controlled solely by the axons that become available for myelination based on their changing expressions of *inductive* or *preventative* cues. In the case of actively regulated OPC differentiation, the timing of *inductive* (or *preventative*) cue onset (or offset) would have to precisely coordinate with the timing of the regulated differentiation mechanism to be able to initiate myelination of an axon during the seemingly short period between OPC differentiation and the termination of new sheath formation [6,37,38] (although, see [5]). With regulated OPC differentiation, it would instead be simpler for OL-lineage cells to respond to axon selection cues that are not dynamically regulated, perhaps having existed on axons long before differentiation occurs. Such cues would influence myelin localization but not its timing. These cues could be termed *attractive* or *repulsive*, positively or negatively biasing an axon's selection for myelination by either altering the distribution or number of OL internodes (Figure 1B, C).

Finally, regardless of whether differentiation and axon selection are coupled or not, axons must be *permissive* for myelination – a feature that permits their myelination but does not guarantee it (e.g. suprathreshold axon diameters). Axon *permissiveness* may be static or dynamically regulated (e.g. as subthreshold axons grow). An outstanding question in the field is whether structures that are simply *permissive* – lacking any *inductive* or *attractive* cues – are myelinated in the CNS (as illustrated in Figure 1B, C). While the models of axon selection presented here are not mutually exclusive, their conceptual separation is useful for establishing a framework to evaluate research in this field.

A role for axons in OL myelination

Efforts to elucidate the role of CNS axons in their own myelination have greatly benefited from innovations in sparse (low-efficiency recombination), targeted genetic manipulations and live imaging with single-cell resolution. A creative genetic approach generating zebrafish with supernumerary large caliber spinal cord Mauthner axons provided compelling evidence for the influence of axons on an individual OL's myelination patterns. These extra axons caused Mauthner axon-associated OLs to extend more internodes to myelinate more Mauthner axons than normal, and even prompted non-Mauthner axon-associated OLs to

myelinate Mauthner axons. Notably, OL numbers did not change [29], supporting a model wherein axonal cues alter axon selection independent of OPC differentiation (Figure 1B, C).

A recent study in mice demonstrated that axonal cues can have a considerably broader impact on OL development and myelination. Knocking-out *Pten* specifically from cerebellar granule cells, which increased axon caliber to suprathreshold diameters and altered gene expression, caused ectopic proliferation and differentiation of OPCs and myelination of granule cell axons in the normally unmyelinated cerebellar molecular layer [39••]. It is unclear whether all of these effects are mediated through the same or disparate mechanisms – or exactly what those mechanisms are. Could these effects be entirely attributable to increasing axon caliber to a *permissive* level, or are molecular changes also involved? Intriguingly, ectopic myelination was still observed when *Pten* was only sparsely knocked-out [39••]. Identifying whether the axons lacking PTEN were the ones that were myelinated in this sparse manipulation will provide important information on the spatial nature of this change. Moving forward, this genetic model could be a tractable system to investigate the mechanisms by which axons regulate their own myelination.

Axonal cues for axon selection

An axon selection cue must be sufficiently localized to facilitate the distinction between axons as well as geometrically similar substrates in close proximity. Membrane-bound cues or those released at synapses both meet this requirement.

Axonal cues for axon selection: synaptic activity

OPCs receive glutamatergic and GABAergic synaptic inputs from axons and express a myriad of other neurotransmitter receptors [32,40], perhaps to inform OPCs of a myelination need. A model often termed “activity-dependent myelination” posits that changes in synaptic inputs to OPCs could serve as an *inductive* cue, causing OPC differentiation and myelination of the axons providing modified inputs, perhaps even converting axon-OPC synapses into a myelinating sheath (Figure 1A) [41]. This process could shape brain development based on experience or contribute to learning by modifying circuit timing.

Two landmark *in vivo* studies energized this hypothesis. Optogenetic stimulation of neurons in the mouse premotor cortex increased proliferation and differentiation of OPCs [42], which presumably generate new myelin. Similarly, training mice to run on a complex wheel increases OPC proliferation and differentiation in the corpus callosum. In fact, generating new OLs, and presumably new myelin, was required for mice to properly learn the task [43]. Since simply increasing OPC density can enhance differentiation [44], the direct effects of neuronal activity on OPC differentiation in these studies is unclear. A follow-up study using the same motor learning paradigm showed that differentiation occurs from the existing pool of OPCs [45•], suggesting that subsequent OPC proliferation may occur in response to local OPC differentiation, as was observed in live imaging of cortical OPC dynamics [6]. An important next step is to analyze where new myelin is localized in these paradigms; are axons with increased activity *inducing* their own myelination by expressing a combined differentiation/axon selection cue (Figure 1A) or might axonal activity simply act as a differentiation cue without affecting axon selection (Figure 1B)?

A recent study supports the latter. Social isolation of adult mice reduced OPC differentiation, the number of myelinated axons, and myelin thickness in the prefrontal cortex (PFC) and caused social withdrawal, all of which were rescued by oral administration of the pro-differentiation compound clemastine [46]. If the presumably reduced activity of specific sociability-related axons during social isolation prevented these axons from expressing an *inductive* cue that would normally cause OPC differentiation and their selection for myelination (Figure 1A), it's unlikely that the ostensibly indiscriminate upregulation of OPC differentiation by clemastine would rescue these deficits. More plausibly, PFC activity from social interaction upregulates overall OPC differentiation without affecting axon selection, and is important for providing sufficient numbers of OLs to myelinate the relevant axons, which utilize other cues to regulate their selection for myelination (Figure 1B, C).

Notably, other studies have found no [47] or opposite [48] effects of neuronal activity on OPC differentiation, while others have observed differences in properties such as OL internode number [47,49••], length [48,50••,51•], or thickness [42,46,47,52]. Of these, two pioneering studies found a direct role for the synaptic activity of individual axons in regulating their selection for myelination. Treatment of zebrafish with tetrodotoxin (TTX) to block action potentials reduced the myelination of *phox2b*⁺ axons in the spinal cord without affecting total internode or OL numbers, suggesting that these axons use neuronal activity to facilitate their myelination [50••]. Indeed, expressing tetanus toxin (TeNT), which prevents synaptobrevin/VAMP2-mediated synaptic exocytosis, in individual *phox2b*⁺ axons substantially reduced the myelination of these axons [50••]. The same was true for TeNT expression in single reticulospinal axons [49••]. TeNT expression globally or specifically in neurons caused individual OLs to form 30% fewer internodes [49••,50••].

The results with TTX versus TeNT suggest different mechanisms of activity-mediated axon selection, highlighting the importance of elucidating the specific mechanisms involved to resolve the sources of these discrepancies. The TTX data support a model of competition between axons for myelination. When neuronal activity was abolished, *phox2b*⁺ axons lost their competitive advantage, and so other axons were myelinated in their place. Conversely, the TeNT data suggests that the axon selection cue used by these axons promotes their myelination by increasing the number of internodes per OL, perhaps by affecting downstream OL Fyn kinase signaling [37]. Live imaging showed that very early retractions of presumably nascent sheaths [50••] caused a decrease in sheaths per OL 6h after the beginning of sheath formation in the TeNT condition [49••], and that increased sheath retractions continued for many hours [50••]. Despite the reduction in excitatory synaptic input as OPCs differentiate into early OLs, these cells continue to respond to glutamate [53,54] and maintain some glutamate receptor expression [55,56]. The increase in sheath retractions in response to blocking synaptic exocytosis along with the observation that synaptic vesicles preferentially stopped at nascent ensheathment sites [50••] imply that early myelinating OLs do respond to synaptic inputs and that these inputs are important for axon selection (Figure 1C).

Could synaptic activity-mediated axon selection account for CNS myelination patterns?
Different neuronal subtypes utilize different neurotransmitters and have distinct firing rates,

features OL-lineage cells could use to identify specific axonal subtypes to myelinate [8•]. But since these features do not differ within a single neuron, how could synaptic activity produce intermittent myelination along a single axon [9]? Axons could synapse with OPCs unevenly along their lengths. Alternatively, cues from an individual axon could remain consistent but the surrounding environment could affect that axon's competitiveness for myelination.

Axonal cues for axon selection: membrane-bound adhesion molecules

Not surprisingly, not all axons utilize synaptic activity to regulate their selection for myelination. While individual reticulospinal neurons expressing TeNT had reduced myelin coverage, TeNT expression in individual commissural primary ascending axons had no effect on their myelination [51•]. What other cues might axons use to regulate their selection for myelination?

Adhesion molecules, which mediate cell-cell interactions, are logical candidates. In fact, several axonal adhesion molecules negatively regulate OPC differentiation and/or myelination, and seem to downregulate their expression as myelination proceeds (e.g. Jagged1 [57], PSA-NCAM [58], or Lsamp [59]). It is tempting to regard these molecules as potential *preventative* cues for myelination, wherein their removal from an axon would initiate myelination of that axon, potentially in conjunction with causing OPC differentiation. Future studies genetically manipulating these molecules sparsely in axons will elucidate their potential roles in axon selection.

Recently, the adhesion molecule JAM2 was identified as a negative regulator of myelination with no effect on OPC differentiation. It is expressed by the somatodendritic compartment of cultured spinal cord neurons and prevents myelination of this cellular compartment. Oligodendrocytes ectopically myelinate the somata and dendrites of cultured *Jam2* knock-out spinal cord neurons, and increased ectopic myelination of PAX2+ neuronal somata was found in the dorsal spinal cord of *Jam2* knock-out mice [60•]. This study confirms the presence of *repulsive* cues that shape where OLs form internodes. It also suggests either that neuronal somata express sufficiently *attractive* cues such that they become myelinated when inhibition is reduced, or that simply *permissive* structures can be myelinated in the CNS (Figure 1B, C). Intriguingly, JAM2-Fc coated micropillars are *repulsive* to both cultured OPCs and OPC-derived OLs [60•], indicating that OPCs respond to substrate selection cues that influence their eventual internode placement, independent of that cue's ability to affect differentiation (Figure 1B). Likewise, contact-mediated self-repulsion by OPCs [6,31] supports the idea that these cells are well-equipped with adhesion molecules to regulate the placement of their processes.

Could similar *repulsive* cues exist that prevent the myelination of glia or blood vessels? Might there be adhesion molecules, *attractive* or *repulsive*, that distribute unevenly along axons or differentially between different neuronal subtypes, shaping CNS myelination patterns [8•,9]?

Wrapping it up

The question of how axons are selected for myelination has been historically difficult to answer. However, new research efforts utilizing sparse genetic manipulations and high-resolution live imaging have begun to shed light on this complex issue and will be essential moving forward. Despite *in vitro* work establishing the intrinsic nature of OL myelination, current research has clearly demonstrated that axons have a role in their selection for myelination. The extent of their contribution and the molecular players remain to be determined and will be fruitful grounds for future studies.

This review has focused primarily on the mechanisms through which axons might communicate with OL-lineage cells to regulate their initial myelin coverage. While myelin sheath retractions have been observed in early OLs, it is not yet clear how ongoing communication between axons and OLs might alter myelin coverage in the long term. In addition to affecting axon selection, evidence suggests that axons can regulate internode length and sheath thickness, properties that – like axon selection – affect conduction velocity and energy usage. It remains a beautiful mystery as to how these properties are regulated in concert with one another, and to what extent axons are active players in this coordination, functioning as grand architects of the ever-changing myelin landscape.

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Highlights

- Not all axons are myelinated and some axons are discontinuously myelinated.
- Oligodendrocytes do not require molecular axonal signals to form myelin membranes.
- Axon selection can occur at various stages of oligodendrocyte development.
- Axons can express various cues to regulate their selection for myelination.
- Synaptic activity and membrane-bound adhesion molecules influence axon selection.

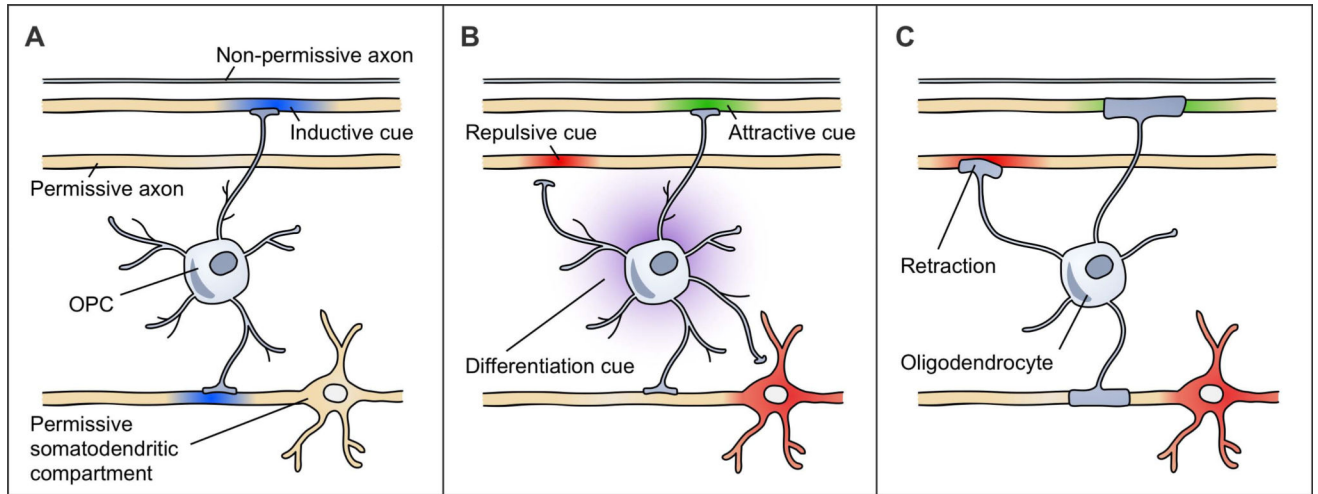


Figure 1. Different mechanisms of axon selection could produce the same CNS myelination patterns

These three models are non-exhaustive and not mutually-exclusive. Structures with suprathreshold diameters are shown in yellow as permissive. The first axon has a subthreshold diameter, rendering it non-permissive. **(a)** An inductive cue (blue) turns on in axons to initiate their myelination. Shown here, an OPC senses a threshold myelination need from the second and fourth axons that causes the OPC to differentiate and myelinate these axons. These axons are among the permissive structures. **(b)** OPCs respond to attractive (green), permissive (yellow), and repulsive (red) cues on axons and other cellular compartments that regulate the contacts that OPCs make and the eventual placement of myelin sheaths. The OPC processes retract from repulsive cues on the third axon and the somatodendritic compartment. Upon differentiation, this cell will myelinate the second and fourth axons. The differentiation cue (purple) is uncoupled from axon selection. **(c)** OLs respond to attractive (green), permissive (yellow), and repulsive (red) cues that affect sheath initiation or stability. Retraction of an early sheath in response to a repulsive cue on the third axon is shown. This OL myelinates the second and fourth axons.