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# Myelin-based inhibitors of oligodendrocyte myelination: clues from axonal growth and regeneration

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The differentiation of and myelination by oligodendrocytes (OLs) are exquisitely regulated by a series of intrinsic and extrinsic mechanisms. As each OL can make differing numbers of myelin segments with variable lengths along similar axon tracts, myelination can be viewed as a graded process shaped by inhibitory/ inductive cues during development. Myelination by OLs is a prime example of an adaptive process determined by the microenvironment and architecture of the central nervous system (CNS). In this review, we discuss how myelin formation by OLs may be controlled by the heterogeneous microenvironment of the CNS. Then we address recent findings demonstrating that neighboring OLs may compete for available axon space, and highlight our current understanding of myelin-based inhibitors of axonal regeneration that are potentially responsible for the reciprocal dialogue between OLs and determine the numbers and lengths of myelin internodes. Understanding the mechanisms that control the spatiotemporal regulation of myelinogenic potential during development may provide valuable insight into therapeutic strategies for promoting remyelination in an inhibitory microenvironment.

Keywords: differentiation; myelin; nogo-A; LINGO-1; semaphorin; ephrin; netrin-1

## Introduction

The majority of axons in the vertebrate nervous system are wrapped by a lipid-rich membrane known as the myelin sheath, which promotes the rapid saltatory conduction of nerve impulses and provides protection and nutritional support for axons<sup>[1,2]</sup>. In the CNS, oligodendrocyte progenitor cells (OPCs) are specified from neuronal precursor cells and differentiate into myelin-forming oligodendroctyes (OLs)<sup>[3,4]</sup>. In demyelinating diseases such as multiple sclerosis (MS), it is generally accepted that myelin is targeted for destruction by the immune system, disrupting the efficient transmission of action potentials and subsequently depleting the nutritional support and protection of axons<sup>[5]</sup>. Demyelination ultimately results in a loss of neuronal function and axon degeneration. Unfortunately, in demyelinating diseases, remyelination is not an efficient process, even though adult

OPCs and OLs are present around and within the lesion environment<sup>[6-10]</sup>. In short, the supply of newly-formed myelin does not fulfill the requirement set by demyelinated axons. In recent years, much attention has been focused on identifying global determinants (transcription and growth factors) that promote the differentiation of OPCs into myelinating OLs during development<sup>[11-18]</sup>. Based on this view, myelination is an all-or-none event that is controlled in part by transcriptional programs responsible for differentiation. These studies were initiated under the assumption that the rate-limiting step for efficient repair lies in the differentiation of OPCs into OLs. While much evidence clearly demonstrates that the lesion environment is hostile to differentiation, mature OLs can still be identified in lesions<sup>[8,19]</sup>. Is it possible that the lesion itself prevents myelination by OLs? As an alternative approach, OL myelination can be viewed as a graded process, and maximizing the myelinogenic potential of individual OLs (the numbers and lengths of myelin segments they form) may also offer an effective strategy for treatments aimed at remyelination.

Adult OPCs have generated much interest as a reservoir of cells with the potential to self-renew, differentiate, and remyelinate the CNS<sup>[20-24]</sup>. However, it is evident that the CNS is composed of heterogeneous microenvironments that shape its unique architecture and relationships between neurons and glia. Therefore, it is essential to understand the molecular mechanisms and intercellular interactions that modulate the formation and maintenance of the myelin sheath. During development, OPCs differentiate and myelinate axons in a spatiotemporal-specific manner. In order for OLs to myelinate all relevant axons precisely, individual OLs can make numerous myelin segments of variable length and thickness (Fig. 1)<sup>[25]</sup>. The fundamental question proposed in this review is: what mechanisms control the numbers and lengths of myelin internodes formed by OLs? Essentially there are two major possibilities: (1) OLs "decide" how many segments they are supposed to generate solely by intrinsic mechanisms and (2) environmental cues shape myelination. In this review, we will attempt to provide evidence that axon- and myelin-based signals known to regulate axonal growth and regeneration also shape myelin sheath formation, and that identifying these cues may represent a novel and effective approach for remyelination.

#### Microenvironmental Influence on Myelination

A recent study using a novel transgenic mouse line displaying sparsely-labeled OLs illustrates that a single OL can produce anywhere between 20 and 100 internodes with lengths that vary from 40 to 400  $\mu$ m (Fig. 1)<sup>[25]</sup>. The variations in the numbers and lengths of myelin internodes produced by OLs suggest that endogenous cues should exist to achieve the precise and efficient myelination of axons during development. Are the numbers and lengths of myelin segments solely dependent on cellautonomous mechanisms? If so, this means that OLs are a heterogeneous population, with each cell intrinsically preprogrammed to form a predetermined number of myelin segments with set lengths. The only evidence that OLs are heterogeneous comes from lineage analysis of OPCs during development<sup>[4,26]</sup>. Despite the fact that subpopulations

of OPCs are specified from different domains in a temporalspecific manner, the majority of OPCs differentiate and myelinate axons regardless of their anatomical origin, while the remaining undifferentiated OPCs are distributed throughout the gray and white matter of the adult brain<sup>[27]</sup>. When specific OPC populations are eliminated, OPCs from different regions can replace the lost OPCs, resulting in a normal myelin phenotype<sup>[26,28]</sup>. These results suggest that OLs are most likely not specified for producing predetermined numbers and lengths of myelin segments. Another intrinsic mechanism in oligodendroglia is their ability to repair/remyelinate after demyelination. It is well-established that OLs from younger mice remyelinate more efficiently than those from old mice, and recent evidence attributes the difference to epigenetic changes linked to the recruitment of histone deacetylases (HDACs)<sup>[29-31]</sup>. HDACs are capable of removing acetyl groups from histones to allow for the compaction of chromatin, resulting in transcriptional silencing<sup>[32,33]</sup>. Recent studies suggest that the relatively efficient recruitment of HDACs in young mice corresponds to thr silencing of transcriptional repressors in OLs<sup>[30]</sup>. Therefore, the reduced recruitment of HDACs in older animals leads to the accumulation of repressors, and ultimately hampers differentiation and remyelination<sup>[30]</sup>. However, this viewpoint was established under the assumption that environmental cues are similar in old and young animals, and that HDACs function independently of extrinsic signals. To challenge this hypothesis, old and young OLs were exposed to similar microenvironments, an ideal way to test the role of their intrinsic capacity to remyelinate. Surprisingly, when old OLs are exposed to a youthful systemic environment, their ability to differentiate and remyelinate is revitalized to levels similar to younger cells<sup>[34,35]</sup>. These findings suggest that environmental signals dominate intrinsic mechanisms to modulate the differentiation and myelination of oligodendroglia.

In order to adapt to the heterogeneous microenvironments in the CNS, each OL precisely molds its myelin segments around relevant axons, and the orientation of the segments follows the trajectory of the axons they encase. For example, the corpus callosum contains more aligned axon tracts than the cerebral cortex, and the myelin segments are also mainly parallel (Fig. 2). However, the mechanisms regulating myelin formation remain unclear. The similar appearances of OLs found within defined anatomi-



Fig. 1. Oligodendrocytes in the gray and white matter of adult mouse brain vary in the numbers and lengths of myelin internodes (adapted from Chong et al., Proc Natl Acad Sci U S A, 2012)<sup>[25]</sup>. A: Myelin basic protein staining showing global myelin in a coronal brain section; B–G: Individual oligodendrocytes from the primary somatosensory cortex (B), corpus callosum (C), striatum (D), agranular insular cortex (E), external capsule (F) and anterior commissure (G), visualized using a transgenic mouse carrying mosaic *Mbp*-maEGFP expression (<1% of oligodendrocytes labeled with maEGFP)<sup>[25]</sup>. Scale bars: A, 1 mm; B–G, 20 µm.

cal structures suggest the presence of local environmental control. In addition, even though OLs from one anatomical region appear similar at first glance, they vary in their lengths and numbers of myelin segments (Fig. 2). Based on the fact that only axons are myelinated, it is plausible that axons themselves dictate myelination by providing inductive signals. Recent studies have established that axon diameter may act as an instructive cue to initiate wrapping and myelination<sup>[36,37]</sup>. However, diameter is not the sole factor, as OLs avoid wrapping specific portions of the axon such as the initial segment and terminals, and other types of processes with similar dimensions such as dendrites. Therefore, inhibitory signals are also required to ensure that oligodendroglia wrap axons exclusively. In addition, the fact that not all axons are myelinated in vivo indicates that there may be repulsive signals originating from the axon. Results from recent studies have demonstrated that LINGO-1 (leucine-rich repeat- and Ig domain-containing nogo receptor-interacting protein 1) and polysialylatedneural cell adhesion molecule (PSA-NCAM) act as axonal inhibitory signals that prevent myelination, and that these repulsive signals need to be downregulated prior to wrapping by oligodendroglia<sup>[38-41]</sup>. However, the characterization of potential inductive cues from axons is limited. Nonetheless, is it possible that axonal signals can function as the sole mechanism for the precise formation of myelin during development? Although axonal cues may indicate whether

an axon is available for myelination, this mechanism alone does not explain how neighboring OLs coordinate myelin generation to fulfill the requirement set by available axons. That is, all axons that should be myelinated become so, with no gaps between myelin internodes, nor aberrant overlap of myelin segments. In addition, the amount of myelin generated by each individual OL should scale according to the number of available oligodendroglia. While the number of OLs generated has been shown to match the number of available axons, there appears to be a variable number of OLs in different anatomical regions (with many more in white matter than in gray matter, for example)<sup>[42-46]</sup>. Furthermore, when specific OPC populations are eliminated, the OPCs from adjacent regions migrate and proliferate to occupy the area<sup>[4,26]</sup>. Together, these findings suggest that OL numbers are constantly in flux. Therefore, dynamic competition between OLs may be a reliable way to coordinate myelin formation, as competition for available axon space is by definition correlated with the number of OLs. Supporting this hypothesis, a high density of OLs has been shown to reduce the numbers and lengths of myelin internodes formed by individual OLs<sup>[25,47]</sup>. On the other hand, at a low OL density relative to a fixed number of available axons, the myelinogenic ability of single OLs increases by approximately three-fold in the number of axons, and two-fold in the length of internodes<sup>[25]</sup>. This inter-OL competition ensures that each individual OL generates a sufficient number of myelin



Fig. 2. Oligodendrocytes in the cerebral cortex (A) and corpus callosum (B) display varying numbers and lengths of myelin segments along similar axon tracts, as visualized using a transgenic mouse carrying mosaic *Mbp*-maEGFP expression (<1% of oligodendrocytes labeled with maEGFP) (adapted from Chong *et al.*, Proc Natl Acad Sci U S A, 2012)<sup>[25]</sup>. Arrows indicate cell bodies. Scale bar: 20 μm.

internodes of appropriate length. These findings, and the fact that OLs never wrap myelinated axons, suggest that inhibitory signals exist between OLs. In the next section, we discuss potential molecular candidates and mechanisms that may mediate OL interactions for regulating myelinogenic potential.

## Myelin-Based Signals of Oligodendrocyte Myelination: Clues from Axonal Regeneration

The inverse correlation between myelinogenic potential and OL density suggests the presence of oligodendroglial cues that can reduce the numbers and lengths of myelin internodes formed by neighboring cells. Supporting a contact-mediated mechanism for repulsion, artificial beads coated with the plasma membranes of OPCs or OLs significantly decrease the numbers of myelin internodes made by individual OLs<sup>[25]</sup>. Similarly, myelin membrane debris has potent inhibitory effects on OPC differentiation and OL myelination<sup>[48,49]</sup>. Together, these findings suggest that membrane-bound cues expressed on the surface of OLs may be responsible for regulating myelinogenic potential. To fulfill their roles in coordinating myelin formation, these candidate molecules should be (1) widely expressed in OLs, and (2) capable of initiating reciprocal intracellular signaling that leads to downstream modulation of myelinogenic potential. The inhibitors of axon regeneration, which are also highly expressed by OLs, appear to satisfy both criteria<sup>[50-55]</sup>. These signaling molecules have been shown to guide axons during development, in addition to their ability to inhibit axon regeneration after injury<sup>[56-58]</sup>. More importantly, the distal ends of OL processes are thought to resemble the molecular structure of axonal outgrowths<sup>[59,60]</sup>, and increasing evidence suggests that both axonal growth cones and the leading edge of OL processes possess similar regulators of actin nucleation<sup>[61]</sup>. Examination and characterization of myelin- and axon-based repulsive factors may provide novel insights into the environmental cues that regulate OL myelination. Here, we review a number of axon- and myelin-based signals that inhibit axonal regeneration and focus on their potential roles in regulating OL myelination.

## Nogo-A

Much of our current understanding of axonal regeneration has been gained from studies of the injured CNS of adult

mammals. As axonal regeneration is severely limited in the adult CNS by inhibitory cues that are also found during development, extensive studies have been devoted to understanding both the injured and the developing CNS environment in order to improve the regenerative capacity of axons. Nogo-A, which is widely expressed by neurons and OLs<sup>[62]</sup>, was initially identified as a potent myelin-based repulsive cue for axons. This molecule has two inhibitory domains: amino-Nogo and Nogo-66<sup>[63,64]</sup>. The Nogo-66 domain in OLs binds to the neuronal Nogo-A receptor (NgR1) to activate small GTPase RhoA, which then mediates actin depolymerization and the subsequent collapse of axonal growth cones<sup>[65,66]</sup>. Conversely, amino-Nogo is predominantly cytoplasmic, but can also be detected on the cell membrane and inhibits axonal outgrowth independent of NgR1<sup>[64,67]</sup>. In a candidate screen for myelin-based inhibitors of myelin internode generation, it was found that amino-Nogo-A-Fc-coated beads designed to mimic OLs significantly reduce the number of myelin internodes formed by individual OLs<sup>[25]</sup>. Moreover, siRNA-mediated silencing of Nogo-A in OLs and genetic knockout of Nogo isoforms both enhance the number of myelin internodes made by individual OLs<sup>[25]</sup>. Notably, knocking down neuronal Nogo-A alone in vitro does not affect the numbers of myelin internodes formed, suggesting that inter-OL interactions are responsible for regulating myelin segment formation through Nogo-A<sup>[25]</sup>. Together, these studies demonstrate that Nogo-A functions in a redundant manner, first as an inhibitor of developmental myelination and axon outgrowth, and later as an inhibitor of axonal regeneration after injury. Furthermore, its function may differ depending on the cell type mediating its action. Interestingly, Nogo-66 does not inhibit myelinogenic potential in OPC-DRG co-cultures<sup>[25]</sup>. In addition, NgR1 is absent from OLs, suggesting the presence of an alternative receptor responsible for the inhibitory effects of amino-Nogo on myelination<sup>[55]</sup>. The divergent roles of Nogo-66 and amino-Nogo present a novel mechanism whereby a single ligand provides context-specific responses depending on its activation domain. Further studies on amino-Nogo may reveal a novel OL receptor or activation pathway for modulating myelinogenic potential<sup>[68]</sup>. As amino-Nogo does not appear to be as potent for inhibiting the number of myelin internodes formed compared with OL membranes, we present additional candidates that may be involved in myelin formation.

## LINGO-1

A Nogo receptor-interacting protein, LINGO-1 is another example of a molecule expressed by OLs and neurons that may modulate both axonal regeneration and myelin formation. LINGO-1 contains the leucine-rich repeat and Ig domain and forms a receptor complex with NgR1 and the effector components p75<sup>NTR</sup>/Troy to inhibit axon regeneration<sup>[69-72]</sup>. It has been suggested that LINGO-1 acts as a negative regulator of OL differentiation and myelination, since functional blocking of LINGO-1 using an anti-LINGO-1 antibody enhances OPC differentiation and OL myelination<sup>[73]</sup>. In addition, LINGO-1 knockout mice display a similar phenotype during development, and improved remyelination after experimental autoimmune encephalomyelitis, lysolecithin treatment and cuprizone-induced demyelination<sup>[73-78]</sup>. Conversely, gain-of-function studies using lentiviral overexpression and transgenic mice demonstrate that LINGO-1 activates the small GTPase RhoA, an important second messenger that negatively regulates OPC differentiation and myelination<sup>[39,74,78]</sup>. However, it is still unclear how LINGO-1 signaling is activated. The fact that overexpression of LINGO-1 in either neurons or OLs is sufficient to inhibit the differentiation and myelination of OLs suggests that LINGO-1 can be activated in multiple ways. A recent study demonstrated that the extracellular and transmembrane domains of LINGO-1 are sufficient to inhibit OPC differentiation in vitro<sup>[39]</sup>. In addition, the extracellular and transmembrane domains of LINGO-1 can bind with LINGO-1 in OLs and activate the small GTPase RhoA. This potential for LINGO-1 to interact with itself makes it an attractive candidate for mediating intercellular interactions between OLs. Also, the activation of small GTPase RhoA, a key cytoskeletal regulator, is consistent with a conserved ability to regulate both axonal and OL processes<sup>[79-81]</sup>. Further investigation of LINGO-1 and its co-receptors may reveal novel mechanisms related to mvelinogenic potential that contribute to its ability to hamper remyelination.

## Semaphorins/Ephrins

Semaphorins, a large family of secreted and membrane-boundglycoproteins, are expressed widely in the CNS<sup>[56,82,83]</sup>. Class 4–7 semaphorins are transmembrane ligands and were originally identified as potent repulsive axon-guidance molecules in the developing nervous system<sup>[56,84,85]</sup>. A number of membrane semaphorins and ephrins are co-expressed with their receptors, plexins and Eph

receptors in OLs, suggesting the possibility that neighboring OLs compete with each other for axon space through ligand- and cognate receptor-binding<sup>[58]</sup>. Supporting this hypothesis, recent studies showed that semaphorin-4D induces the collapse of OL processes in vitro, and semaphorin-4D-knockout mice exhibit an increased number of OLs in the adult cerebral cortex, indicating its potential role as an inhibitory signal for OL differentiation or myelination<sup>[86-88]</sup>. Similarly, semaphorin-6A-deficient mice exhibit a marked delay in OPC differentiation in vivo and in vitro, suggesting that it may also play other roles in OL development<sup>[89]</sup>. Other semaphorins and ephrins such as semaphorin-5A, 6D and ephrin-B3 may be involved, as they are also highly expressed by OLs<sup>[90-94]</sup>. As classical cues for axon guidance and inhibitors of axonal regeneration, whether semaphorins and ephrins also function in regulating OL myelin formation is an important question for future studies.

## Netrin-1

Netrin-1 is a bifunctional ligand that can either attract or repel axons during development. The Netrin-1 receptor Deleted in Colorectal Cancer (DCC) mediates axonal attraction toward Netrin-1, whereas expression of UNC5 receptors, either solely or in combination with DCC, promotes repulsion<sup>[95,96]</sup>. A recent study demonstrated that Netrin-1 acts as a myelin-associated repulsive factor that inhibits axonal regeneration by binding to DCC and UNC5 in adult animals<sup>[97]</sup>. Interestingly, UNC5 and DCC are both expressed by OLs and the myelin sheath<sup>[98-102]</sup>. The ability of Netrin-1 to manipulate axonal growth cone orientation in a receptor-dependent manner is intriguing if similar mechanisms are present for guiding OL processes prior to the initiation of myelination. For instance, guidance away from axonal contact may result in fewer myelin segments formed by an OL. Mounting evidence indeed proposes a similar mechanism in OLs, as Netrin-1 has been reported to act as a repulsive signal to initiate the dispersal of OPCs from the ventral midline in vitro and in vivo<sup>[99,101]</sup>. In addition, OL development is severely disrupted in Netrin-1-knockout mice<sup>[99]</sup>. The association of Netrin-1 with OL membranes also implicates an involvement in intercellular interactions<sup>[103]</sup>. On the other hand, addition of Netrin-1 to mature OLs in vitro evokes a DCC-dependent increase in process-branching by activating intracellular signaling mechanisms involving Fyn, focal adhesion kinase, neuronal Wiscott-Aldrich syndrome protein and RhoA<sup>[100]</sup>. Furthermore, Netrin-1 and

DCC are co-expressed at paranodal regions in the CNS and contribute to the normal organization of paranodal loops along the axonal surface<sup>[98]</sup>. Together, these results suggest that Netrin-1 plays multiple roles in the development of OLs. However, the precise understanding of Netrin-1 signaling for myelination remains limited because Netrin-1 may also be important for OPC differentiation and migration, and because Netrin-1 and DCC knockout mice both die prior to myelination<sup>[104,105]</sup>. Further studies conducted using conditional knockout mice may overcome this issue and illuminate the Netrin-1 signaling function specific for myelin formation.

## **Other Candidates**

Aside from those previously discussed, some potent myelinbased inhibitors of axon regeneration such as MAG, OMgp and ephrin-B3 have been specifically tested for their effects on myelin formation in vitro, and they do not appear to have a measurable effect on myelin internode number or length<sup>[25]</sup>. However, their involvement in other aspects of myelin formation cannot be excluded, as increasing evidence suggests that the process of myelination is a complex form of cell-cell interaction regulated by multiple signals, and dysfunction of one signal may be compensated by another<sup>[106]</sup>. In addition, a candidate-based screen may exclude novel co-signaling molecules without an assigned known function. This is especially true for lipid and carbohydrate components of the cell membrane, as their biological significance is less well understood than proteins. Furthermore, post-translational modification may significantly affect the function of signaling molecules, and many OL components are heavily glycosylated<sup>[107]</sup>. Hence, complex scenarios should be considered in the search for molecular determinants of myelinogenic potential.

### Conclusions

The relegation of axon guidance cues as axon regeneration inhibitors after injury is a perplexing, yet pragmatic example of functional redundancy in the CNS. While the reasons behind inefficient repair remain unclear, the employment of repulsive developmental cues to prevent axonal regrowth is consistent with evolutionary adaptation, which would predict the reuse of pre-existing molecular components for contextspecific purposes. In this review, we hypothesize that oligodendroglia may adopt the same cues for determining

the numbers and lengths of myelin internodes formed per cell, because these molecules are also highly expressed by oligodendroglia, and a competitive model necessitates the use of inhibitory cues. Many of these candidates also activate pathways for cytoskeletal regulation, presumably needed for regulating myelin formation as well. Potential mechanisms for signaling specificity include (1) the use of specific activation domains as in the case of Nogo-A, (2) multimeric receptor complexes as in the case of LINGO-1, (3) specific ligand-cognate receptor pairings as in the case of large protein families such as semaphorins and ephrins, and (4) receptor-dependent bifunctionality as in the case of Netrin-1. Oligodendroglial development is inherently complex due to the number of steps involved and the need to interact with multiple cell types. Therefore, the diverse mechanistic possibilities provided by these candidates may be ideal for regulating these processes. However, our hypothesis raises additional questions: for example, why are the molecular cues for myelinogenic potential also redundant? Since Nogo-A-Fc-coated beads are not as potent as oligodendroglial membrane-coated beads in their ability to reduce myelin internode numbers<sup>[25]</sup>, this suggests that multiple cues are necessary for determining these numbers alone. While one may postulate that additional cues provide molecular specificity as previously discussed, perhaps these results also provide clues to novel cellular processes underlying myelination. Does the analogy between axon (re)generation and myelin internode formation extend to include the pruning of excessive outgrowth? During development and after injury, axons undergo a dynamic sprouting and pruning process reliant on guidance cues that ultimately establishes and refines neuronal circuitry<sup>[58,85,108]</sup>. As current technology limits our ability to visualize myelination as it occurs, perhaps a refinement process for myelination also exists but remains scientifically unobserved. Further studies elucidating the transformation of oligodendroglial processes into myelin segments may provide insight into additional mechanisms beyond inter-oligodendroglial competition.

The theme of molecular redundancy applies even more dramatically to intracellular pathways, as cytoskeletal regulation is a highly-conserved component of the molecular machinery that is ubiquitous to most cell types. Most of the molecular candidates discussed in this review inevitably invoke the small GTPase RhoA or other known cytoskeletal regulators<sup>[80,81]</sup>. Supporting the importance of this pathway in oligodendroglia, inhibition of myosin II, a key regulator of actin cytoskeleton dynamics, results in enhanced oligodendroglial branching, differentiation and myelination<sup>[108]</sup>. Will future explorations of other intracellular pathways related to axon regeneration lead to similar insights? For instance, the mTOR pathway has recently been demonstrated to be a potent inhibitor of neural repair<sup>[110]</sup>. Indeed, overexpression of AKT, which activates mTOR, results in hypermyelination as a result of an increased number of myelin wraps<sup>[111]</sup>. Consistent with this result, knocking out PTEN, which negatively regulates AKT, leads to a similar phenotype<sup>[112]</sup>. Together, it appears that the mTOR pathway may demonstrate an alternative analogy between axonal outgrowth and oligodendroglial processes-could the hypermyelination be caused by enhancing the length of oligodendroglial process outgrowth around the axon<sup>[113]</sup>? This intriguing possibility and others such as the regulation of myelin internode length and number remain to be explored, as intracellular pathways often lead to a myriad of outcomes.

In conclusion, current research on axon growth regeneration is highly relevant for understanding oligodendroglial development, and it is our hope that the converse may prove to be true in years to come. However, while molecular redundancy informs us, it also complicates our interpretation of experimental results. Many of these cues affect several aspects of oligodendroglial development. For example, oligodendrocyte precursor cells that cannot proliferate do not reach critical density, and are not be able to differentiate and form myelin segments<sup>[114]</sup>. Therefore, dissecting the intricate processes underlying myelination will require the development of novel questions, and going beyond a mere hunt for molecular candidates.

## ACKNOWLEDGEMENTS

We thank Dr. Sonia Mayoral and Stephanie Redmond for advice and insightful discussions. This work was supported by the US National Multiple Sclerosis Society Harry Weaver Neuroscience Scholar Award (JF 2142-A2/T) and Research Grant (RG 4541A3) and the US National Institute of Health/National Institute of Neurological Disorders and Stroke (NS062796-02).

Received date: 2012-12-06; Accepted date: 2013-02-06

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