Molecular Neurobiology
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ISSN0893-7648/06/33(2): 91–111/$30.00

Targeting Myelin to Optimize Plasticity of Spared Spinal Axons

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Abstract

Functional re-innervation of target neurons following neurological damage such as spinal cord injury is an essential requirement of potential therapies. There are at least two avenues by which this can be achieved: (a) through the regeneration of injured axons and (b) through promoting plasticity of those spared by the initial insult. There are several reasons why the latter approach may be more feasible, not the least of which are the inhibitory character of the glial scar, the often long distances over which injured axons must regrow, and the fact that spared axons are often already in the vicinity of denervated targets. The challenge is to unveil the well-recognized intrinsic plasticity of spared axons in a way that avoids complications, such as pain or autonomic dysfunction. One approach that we as well as others have taken is to target growth-suppressing signaling pathways initiated in spared axons by myelin-derived proteins. This article reviews models used for the study of spinal axon plasticity and describes the anatomical and behavioral effects of interfering with myelin-derived proteins, their receptors, and components of their intracellular signaling cascades.

Index Entries: NogoA; p75; myelin-associated glycoprotein; oligodendrocyte myelin glycoprotein; neurotrophic factors; RhoA; growth cone; spinal cord injury; dorsal rhizotomy; corticospinal tract.

Introduction

After spinal cord injury (SCI), re-innervation of targets rostral or caudal to the lesion can occur through regeneration of injured axons and/or sprouting of spared, intact axons. Although the former process is hindered by the glial scar, which develops at the site of injury *(1,2)*, both regeneration of injured axons and plasticity of those spared by the injury are restricted by myelin and might be enhanced by antagonism of myelin signaling. Additionally, although evidence of limited regrowth of

Received June 6, 2005; Accepted July 18, 2005.
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injured axons in the adult central nervous system (CNS) is convincing, their capacity for long-distance regrowth and re-innervation of appropriate targets is negligible. Therefore, recent work has highlighted the potential for exploiting intrinsic plasticity of CNS axons in the wake of injury *(3,4)*, demonstrating that intact spinal axons are capable of growth, reorganization, and the formation of new, functional connections.

This article reviews injury models used to examine the reaction of uninjured axons in denervated spinal cord, old and new data demonstrating the inhibitory nature of spinal myelin, the components of CNS myelin signaling and relevant antagonists, and data from our laboratory and the laboratories of others demonstrating that intraspinal plasticity can be enhanced by antagonizing individual or multiple components of myelin-signaling pathways. Whereas other plastic processes, such as modificiations of synaptic strength in pre-existing circuits and remodeling of dendritic arbors, are likely to contribute to functional changes, we limit this discussion to sprouting of intact spinal axons. Because such plasticity might have both beneficial and deleterious functional consequences, we also discuss behavioral changes associated with growth of intact spinal axons.

Intraspinal Plasticity After Supraspinal Injury

Unilateral lesions of the cortex *(5–21)* or medullary pyramids *(22–26)* have been used repeatedly to examine injury-induced sprouting of intact corticospinal (CS) axons. In young animals, unilateral cortical ablation or pyramidotomy stimulates sprouting of spared CS axons into denervated spinal gray matter, creating an aberrant and persistent ipsilateral CS projection. Studies using the γ-aminobutyric acid agonist muscimol in cats *(27)* and rats *(28)* have demonstrated that aberrant ipsilateral CS projections also form as a result of unilateral cortical inhibition during development. Interestingly, aberrant ipsilateral projections arose from the active cortex and existed in addition to sustained innervation from the inhibited cortex *(28)*, indicating that activity, and not merely synaptic space, governs the plasticity of CS projections. Hemispherectomy- and pyradmidotomy-induced sprouting of spared CS axons is limited in the adult *(21,24)* and is inversely related to age at the time of injury *(23)*, which is consistent with a significant influence of myelin-derived inhibitors on growth of intact CS axons.

The ipsilateral CS projections stimulated by neonatal hemispherectomy may mediate development of forelimb placing. After a unilateral cortical lesion in adult rats, a subsequent lesion of the intact sensorimotor cortex impaired placement of the forelimb contralateral to the second lesion. In rats that sustained a unilateral cortical lesion as neonates, subsequent lesion of the intact cortex impaired placement of both forelimbs *(15)*. Although the ipsilateral CS projection is well-situated to underlie this differential recovery, these data do not discern between functional contributions of CS tract (CST) axons and supraspinal plasticity induced by neonatal cortical injury, including the formation of aberrant corticothalamic *(29,30)*, corticorubral *(30,31)*, and corticopontine *(32)* projections. The corticorubral projections stimulated by neonatal pyramidotomy have been implicated in a functional reconnection of the motor cortex to the peripheral musculature *(33)*.

Intraspinal Plasticity After Spinal Cord Injury

Plasticity of uninjured CS axons has also been reported in the wake of various incomplete SCIs. Unlike pyramidal lesion, SCI cannot be targeted to a single population of axons; therefore, intraspinal sprouting of intact systems is inferred by the location of aberrant or increased fiber growth relative to the site of the lesion. This approach has been relatively successful for studying sprouting of the CST, which has relatively distinct anatomical projections in the

spinal cord. When SCI occurs shortly after birth caudal to the level of the developing CST, CS axons can grow around the lesion by an anomalous route to terminate in normal patterns in caudal gray matter *(34–37).* Similarly to CS growth stimulated by supraspinal lesion, the propensity for SCI-induced CS growth diminishes rapidly with age *(36).*

In one intriguing demonstration of uninjured CS plasticity following adult SCI, bilateral injury to the dorsal CST in the rat stimulated the growth of ventral CST (vCST) axons *(38).* Then, 6 wk after cervical dorsal column transection, vCST contacts with medial motor neuron pools in lamina IX were significantly increased above intact levels, and biotinylated dextrane amine-labeled axons in the vCST developed new projections to the ventral horn at the level of the lesion.

CS sprouting has also been reported caudal to chronic thoracolumbar lateral hemisection in the adult macaque monkey *(39).* However, a more recent experiment demonstrated that cervical lateral hemisection in macaque monkeys depleted CS axons in the hemicord caudal to the lesion *(40).* In this study, the pattern of CS projections caudal to the lesion did not vary with age at injury (newborn or juvenile) or time following injury (2–150 wk). Furthermore, SCI did not stimulate significant changes in contralateral CS projections, which remained stable over long recovery periods and resembled those in the uninjured monkey. These authors described an important feature of the macaque CST, in which some CS fibers decussate twice—once at the level of the pyramids and once at the level of the spinal cord near the central canal *(40).* Although not widely appreciated, these ipsilaterally terminating fibers exist in significant numbers *(41)* and may confound interpretations of CS plasticity following lateral hemisection in the primate.

Sprouting of intact CS axons following SCI has been reported in association with recovery of motor function. In neonatal cats, CS growth caudal to SCI was correlated with sparing of tactile placing, and cortical ablation abolished tactile placing *(34).* In adult rats, sprouting of the vCST after dorsal column transection paralleled recovery of forepaw reaching for a food pellet: rats with dorsal column injuries recovered forepaw reaching within 4 wk of injury, and this recovery was abolished by subsequent injury to the vCST *(38).* However, macaque monkeys subjected to cervical lateral hemisection as juveniles recovered the ability to reach for and retrieve food pellets within 30 d of injury, despite persistent deficits in movement quality *(42),* in the absence of significant CS remodeling *(40).* Doubly decussating, spared CS fibers may subserve functional recovery following lateral hemisection in the primate *(41,42);* alternatively, the re-establishment of hand representation in the contralateral motor cortex may be the crucial functional substrate *(43).*

For other spinal systems with more diffuse spinal projections, SCI-induced plasticity of intact axons is even more challenging to study, and it is often difficult to determine whether sprouting of intact axons or growth of lesioned axons has occurred. For example, the serotonergic system projects through the dorsolateral, lateral, and ventral funiculi; terminates widely throughout the gray matter, and has dispersed centers of origin in the brain stem that typically preclude anterograde labeling *(44).* Saruhashi et al. *(45)* showed that thoracic lateral hemisection in the adult rat depleted serotonergic projections and terminals caudal and ipsilateral to the injury. Serotonergic fibers were partially reinstated within 3 to 4 wk following injury, but the authors acknowledged that they could not determine whether serotonergic re-innervation arose from growth of injured or spared axons. More recently, serotonergic sprouting was reported rostral to thoracic clip compression injury in rats *(46,47)* and into a thoracic dorsal hemisection in mice *(48),* but contributions of injured and spared axons to sprouting are unclear. Primary afferent sprouting has been reported distal to several types of SCI in the adult rat and cat *(49–55).* Growth of small-diameter primary afferents remote from the site of SCI likely results from collateral sprouting of intact axons; however, several reports have

refuted the occurrence of SCI-induced sprouting of primary afferents *(56–58)* or have suggested that primary afferent sprouting may vary with the level of SCI *(46).* To any extent, SCI-induced plasticity of primary afferents has been associated with both motor recovery *(50)* and autonomic dysreflexia *(54,59).*

Intraspinal Plasticity After Dorsal Rhizotomy

Dorsal rhizotomy is an ideal setting in which to study and manipulate plasticity of intact spinal axons. Rhizotomy reliably induces sprouting of both primary afferents *(60–66)* and descending mono-aminergic axons *(63, 67–73).* Because injury occurs peripherally, rhizotomy-induced intraspinal sprouting can be reliably identified as responses of intact axons. Severing the centrally projecting axons of primary afferent neurons results in both pain and loss of sensory function in affected dermatomes, providing outcome measures to assess the functional consequences of manipulating plasticity of intact spinal axons *(72).*

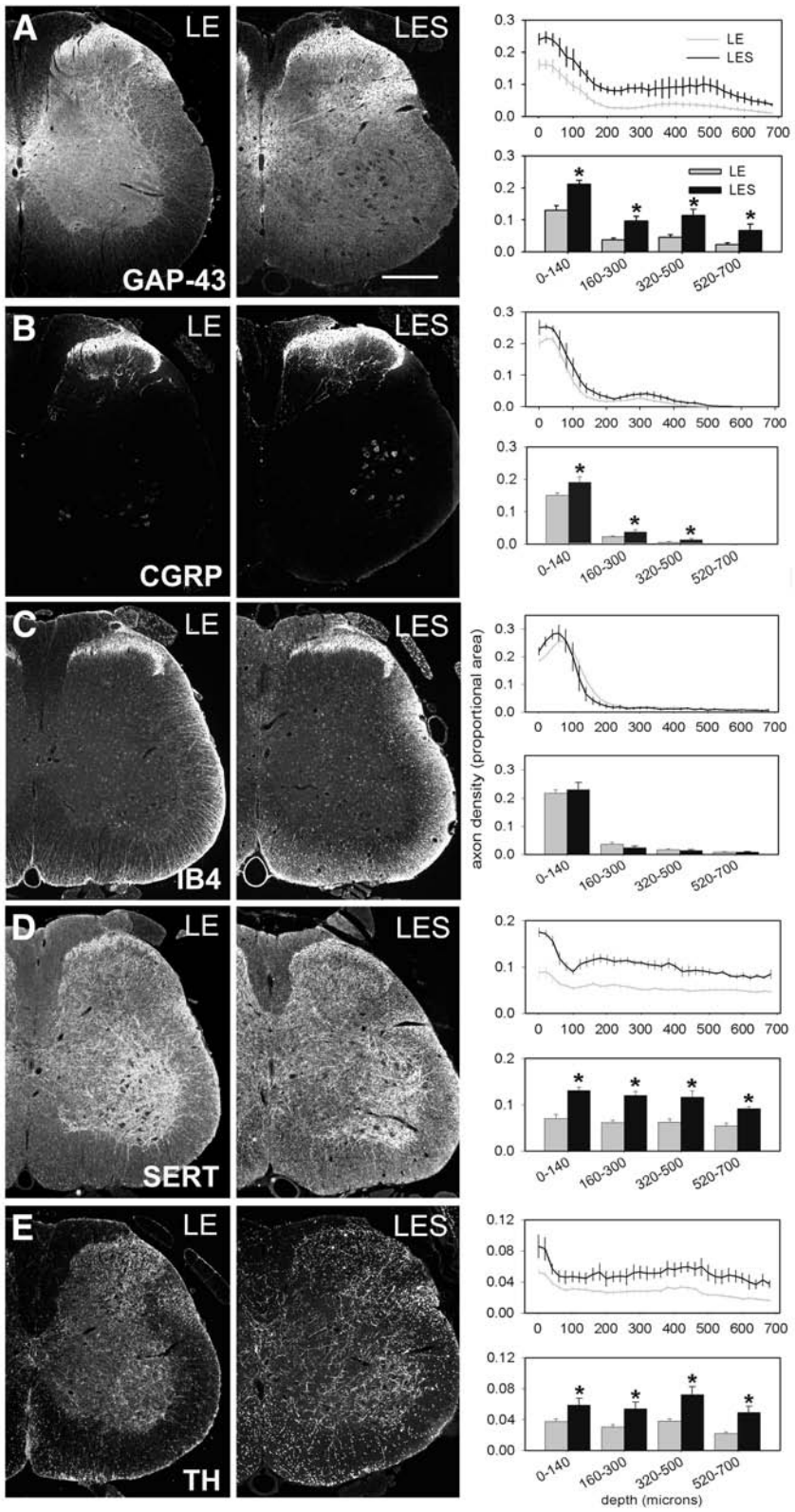
The Inhibitory Nature of Myelin

In the early 20th century, Ramon and Cajal *(74)* observed that axons regenerated in the injured peripheral nervous system (PNS) but not the CNS. An early report by Tello suggested that the differential success of regeneration does not solely result from intrinsic differences between PNS and CNS neurons but, rather, from a consequence of their environment. These findings were later confirmed and extended in a series of seminal transplantation studies by Aguayo and colleagues *(75)* demonstrating that CNS axons grow into peripheral grafts placed in a transected spinal cord. These experiments formed the basis for many subsequent studies that shed light on the constituents contributing to the inhibitory nature of the CNS.

The influence of spinal myelin on axonal growth can be examined in vivo by disrupting myelination experimentally *(76–80)* or by studying spontaneous myelin-deficient animal mutants, such as the Long Evans Shaker (LES) rat *(81–84).* The LES rat has a mutation in the myelin basic protein gene and lacks CNS myelin. Although it has a more severe dysmyelinating phenotype than other myelin mutants, the LES rat has a life-span approaching that of a normal laboratory rat *(85),* permitting studies of the dysmyelinated phenotype in the adult CNS. Previous studies of the uninjured LES rat found evidence of plasticity in the optic nerve, which is indicated by an increase in small axonal profiles without a concomitant increase in retinal ganglion cell numbers *(84).*

To examine the behavior of spinal axons in an environment devoid of myelin, we examined the lumbar spinal cord of uninjured wild-type LE ($n = 7$) and mutant LES ($n = 4$) adult rats (Fig. 1). Axons expressing the 43-kd growth-associated protein (GAP)-43, calcitonin-gene-related peptide (CGRP), isolectin B (IB)4, the transporter for the serotonin neurotransmitter, and tyrosine hydroxylase (TH) were examined at L4/L5 in

Fig. 1. The density of some, but not all, spinally projecting axon populations is increased in the dysmyelinated LES rat. Axons projecting to the lumbar (L4/L5) dorsal horn of LE and LES rats were examined using antibodies against **(A)** GAP-43; **(B)** CGRP, which labels small- to medium-caliber peptidergic primary afferents; **(C)** IB4, which labels small- to medium-caliber nonpeptidergic primary afferents; **(D)** Serotonin neurotransmitter, which labels descending serotonergic axons from the Raphe nuclei; **(E)** TH, which labels noradrenergic axons descending from the locus coeruleus and dopaminergic axons descending from the hypothalamus and substantia nigra pars compacta. Graphs show the density of axons in proportional area as a function of depth in the dorsal horn. Line graphs represent depth profiles of immunoreactivity for each antigen to a maximum depth of 700 μm. Bar graphs illustrate average axon density in specific laminar segments of the dorsal horn, where laminae I and II = 0–140 μm; lamina III = 160–300 μm; lamina IV = 320–500 μm; and lamina V = 520–700 μm. Asterisks (*) indicate significant differences between LE and LES rats ($p < 0.05$; LE rats: $n = 7$; LES rats: $n = 4$). Scale bar = 100 μm.


A
LE
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B
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SERT
E
LE
LES
TH
LE
LES
0-140
160-300
320-500
520-700
axon density (proportional area)
depth (microns)

both genotypes. Immunoreactivity was measured from the most superficial dorsal horn to a depth of 700 μm. Qualitatively, we observed marked differences between genotypes: spinal axon density was higher in the LES rat, particularly in the superficial layers of the dorsal horn (i.e., laminae I–II). Quantification of the depth profiles revealed statistically significant increases in the density of most axonal populations throughout the dorsal horn in the LES rat ($p < 0.05$). Mono-aminergic and GAP-43-expressing axons exhibited the greatest intergenotype differences; of the populations examined, only the density of IB4-expressing primary afferents in LES rats was equivalent to that in wild-type rats. Our results confirm that CNS myelin can influence the growth of uninjured spinal axons and suggest that manipulation of myelin–axon interaction can enhance the plastic behavior of CNS axons (Fig. 2). These results also illustrate the notion that not all spinally projecting axons are equally susceptible to myelin-associated inhibition *(71).*

Myelin-Associated Inhibitory Proteins

Schwab and colleagues *(86, 87)* were the first to identify and target a source of CNS myelin inhibition. In these experiments, two prominent protein fractions of 250 and 35 kDa were isolated from CNS myelin and were termed NI-250 and NI-35, respectively. Removal of membrane-bound proteins, including NI-250 and NI-35, abolished myelin inhibition, and application of a monoclonal antibody developed against these proteins, IN-1, permitted neurite penetration of sympathetic and sensory neurons into optic nerve explants *(86,87).* Since its discovery, IN-1 has been repeatedly applied in vitro *(88–94)* and in vivo (reviewed in ref. *95* and in Enhancing Injury-Induced Intraspinal Sprouting Via Myelin-Signaling Antagonism) to suppress myelin inhibition.

In 2000, the gene encoding the antigen for the IN-1 antibody was cloned and recognized as Nogo, a member of the Reticulon family *(94, 96,97).* Nogo exists in three isoforms (NogoA, NogoB, and NogoC), which are expressed in all eukaryotes *(98).* All Nogo isoforms share a 118-amino acid sequence at their carboxy-terminus, which contains two hydrophobic domains, as well as a 66-amino acid loop expressed on the surface of the plasma membrane *(96).* Distinct from other reticulon proteins and other Nogo isoforms, NogoA contains a long amino terminus that appears only in higher vertebrates, such as birds and mammals, correlating with regenerative failure in these species *(98).* In the adult mammal, expression of NogoA is localized to oligodendrocytes, and has not been detected in the PNS *(94,96,97).* The interaction of antibodies developed against specific epitopes of NogoA with living, unpermeabilized oligodendrocytes confirmed the external domain of Nogo-66 and uncovered the unexpected extracellular expression of the N-terminal region, suggesting the possible existence of two conformation states *(99).*

The inihibitory nature of NogoA has been verified: growth of retinal ganglion neurites was reduced in stripe assays containing NogoA *(99),* and mouse and rat cerebellar *(100,101)* and chick dorsal root ganglion (DRG) neurons *(102)* grew more successfully on NogoA$^{-/-}$ or NogoA/B$^{-/-}$ CNS myelin extracts. Both the Nogo-66 region and the NogoA-specific N-terminus region appear to be involved in the inhibition of neurite outgrowth. In the presence of a high-affinity IN-1 F_{ab} targeting the N-terminal domain of NogoA, neurite length of neonatal rat cerebellar granule cells grown on a concentrated NogoA substrate was significantly increased *(103).*

Despite the attention devoted to the reticulon family, other inhibitory proteins have also been identified in the CNS. Myelin-associated glycoprotein (MAG) was the first of these molecules to be described *(104).* MAG is a member of the immunoglobulin superfamily and is a sialic acid-binding protein that is expressed on both CNS and PNS myelin sheaths *(105).* It exists in two alternatively spliced isoforms, large and small, dictated by the length of their cytoplasmic domains *(106).* MAG was originally reported to enhance neurite outgrowth, because neonatal DRG neurons displayed enhanced

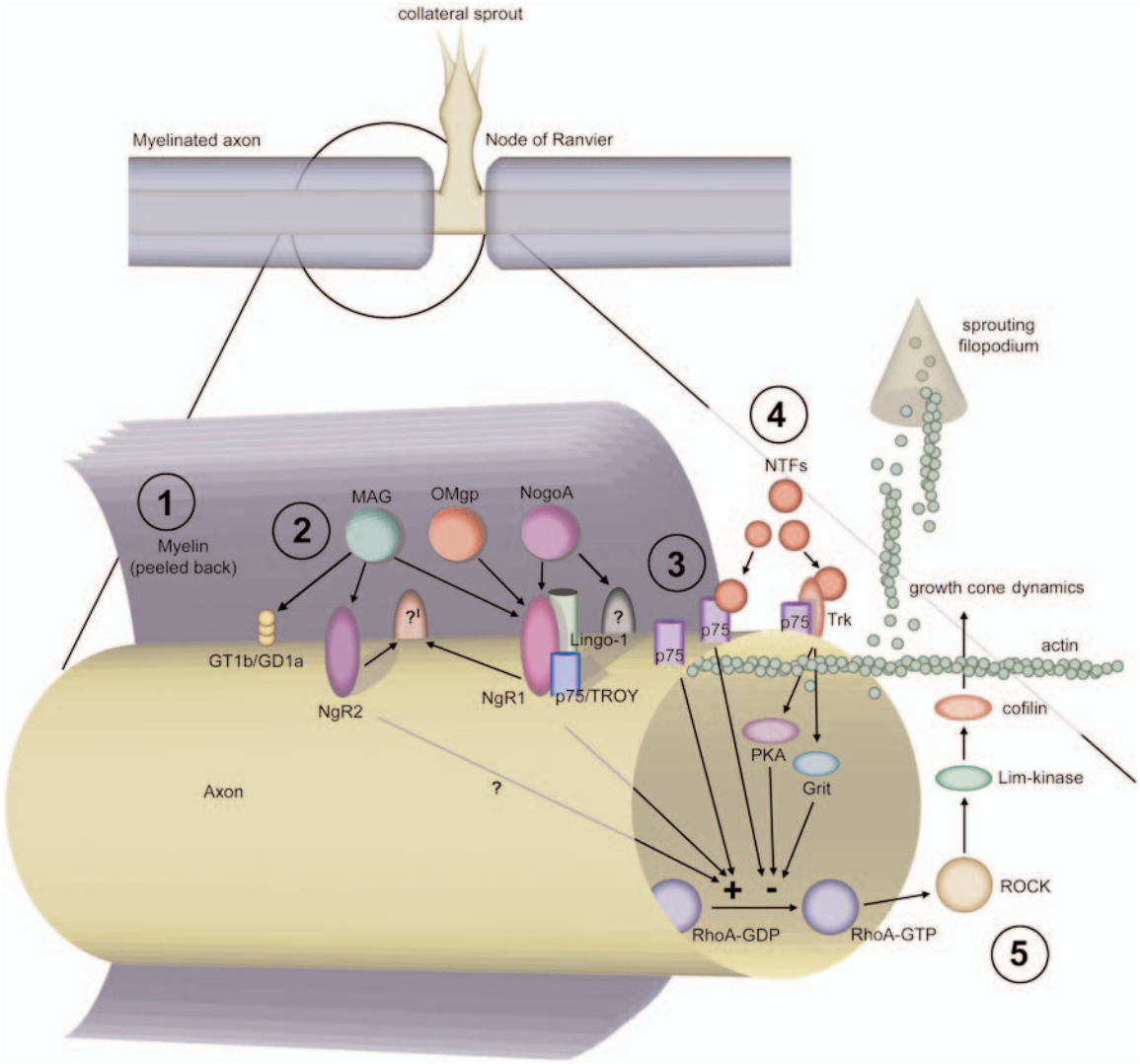

Fig. 2. Sites of potential manipulation of myelin-signaling pathways for promoting axonal plasticity. Myelin-derived inhibitors (MAG, OMgp, NogoA) bind to a growing number of receptors: MAG interacts with the gangliosides GT1b and GD1a as well as the NgR1 and NgR2 receptors. OMgp and NogoA interact with the NgR1 receptor, which requires Lingo-1 and p75 or TROY for signal transduction. The amino (intracellular) terminal of NogoA may also bind to an as yet unidentified receptor (indicated by "?"). Other coreceptors for NgR1 and/or NgR2 may also exist (indicated by "?"). In addition to its interaction with NgR, the p75 receptor binds neurotrophins (NTFs) directly and alters affinity-specificity properties of NTF–Trk interactions. On its own (i.e., in the absence of other receptors or ligands), p75 is involved in the conversion of RhoA-GDP (inactive) to RhoA-GTP (active). The NgR/Lingo-1/p75/TROY complex enhances RhoA activation, whereas NTF binding to p75 inhibits it. MAG/NgR2 complexes probably also enhance RhoA activation. Trk–NTF binding decreases RhoA activation through intracellular messengers such as protein kinase A and Grit. Activated RhoA results in Rho-associated kinase activation. LIM-kinase is directly phosphorylated by Rho-associated kinase to act on cofilin, thus restricting neurite outgrowth. Experimental and potential therapeutic targets include dysmyelinated mutant animals such as the LES rat (1); molecules which interfere with myelin-derived inhibitory molecules and their receptors, such as sNgR1 (2); altering p75 function, as is the case for p75 knockout (exon III deletion) mice (3); promoting Trk-mediated effects with exogenous NTFs (4); and interfering with intracellular small GTPase-dependent signaling with molecules such as C3 or Y-27632 (5).

neurite length when plated on a MAG-containing substrate *(107–109).* The inhibitory action of MAG was revealed independently by two groups, both of which demonstrated that neurite extension of adult DRGs, postnatal cerebellar neurons, and motor neuron-like cells (NG108-15 cells) was significantly diminished when plated on monolayers of MAG-expressing cells *(108, 110).* Experiments using other populations of neurons (including retinal, superior cervical ganglion, spinal, and hippocampal neurons) obtained similar results *(109).* Similarly, adult DRG and neonatal cerebellar axonal growth was enhanced when grown on $MAG^{-/-}$ CNS and PNS myelin *(111)* or on fractionated myelin extract from $MAG^{-/-}$ mice *(112),* and soluble MAG presented in media contributed to growth cone collapse of P3 cerebellar and P6 DRG neurons *(113,114).* MAG is now established as a bifunctional molecule *(115)* that can promote or restrict neurite outgrowth, depending on the neurons involved (immature or mature).

Another inhibitory myelin-associated protein is a glycosylphosphatidylinositol (GPI)-linked oligodendrocyte-myelin glyocoprotein (OMgp). Mikol and Stefansson *(116,117)* identified OMgp as a peanut agglutinin-binding protein in the white matter of the human CNS. Initially described as a myelin-specific protein, OMgp expression was later discovered in diverse populations of neurons, particularly in large projection neurons (motoneurons, dorsal spinal neurons, Purkinjie cells, and pyramidal cells) *(118).* This 110- to 120-kDa GPI-linked protein contains a cysteine-rich amino terminal domain, a series of leucine-rich repeats, a serine/theonine-rich region, and a potential carboxyl-terminal cleavage site *(119).* Similarly to the other myelin inhibitory proteins, OMgp was found to inhibit neurite outgrowth of cerebellar and hippocampal cells, DRG neurons, retinal ganglion neurons, and cell lines NG108 and PC12 *(120)* and was observed to induce growth cone collapse in DRG neurons *(121).*

The Nogo Receptor

Fournier et al. *(122)* identified an axon-associated protein later termed the Nogo-66 receptor (NgR), which bound Nogo-66 with high affinity (approx 7 n*M*) and contained a leucine-rich domain, a cystine-rich carboxy-terminal flanking domain, and a GPI-anchoring domain. In this study, retinal ganglion cells (which are normally resistant to Nogo-66) underwent significant growth cone collapse when virally infected with NgR. Subsequent experiments have demonstrated that MAG *(123,124)* and OMgp *(121)* are also functional ligands for NgR, identifying NgR as a point of convergence of myelin signaling and inciting the development of several NgR antagonists. NEP1-40, a competitive antagonist of NgR, enhanced neurite outgrowth of embryonic chick DRG neurons plated on CNS myelin *(125).* Similarly, NgREcto, a soluble, truncated form of NgR, increased outgrowth of embryonic DRG neurons over myelin or Nogo-66 *(126)* and rescued neurite outgrowth of adult DRG neurons over MAG *(124).* Genetic deletion of NgR has had equivocal results. In one case, DRG cultures from mice lacking functional NgR did not undergo growth cone collapse in response to Nogo-66 *(127);* in a second study, deletion of NgR had little effect on DRG neurite outgrowth on myelin inhibitory substrates *(128).*

Two other isoforms of NgR (or NgR1) were recently discovered *(129–131).* Now called NgR2 and NgR3, these share 55% homology with NgR1 and encode the leucine-rich domain, the cystine-rich carboxyl terminal, and the GPI-linkage site. Whereas NgR3 does not interact with any of the known myelin-associated inhibitory proteins, NgR2 binds to MAG with high affinity and is sufficient to confer MAG inhibition in neonatal rat DRG neurons *(132).* MAG is also known to interact with complex gangliosides on the surface of neurons *(133,134);* of these gangliosides, GT1b and GD1a have been implicated in MAG inhibition *(135,136).*

Coreceptors and Transducers

For myelin-associated signal transduction to occur via GPI-anchored receptors, the existence of a signal-transducing coreceptor was evident.

The search for this coreceptor led to the discovery of $p75^{NTR}$, a 75-kDa receptor capable of binding all members of the neurotrophin family. In 2002, two groups independently demonstrated that $p75^{NTR}$ immunoprecipitated with NgR1 and that activation of the second messenger occurred through their interaction *(137, 138).* In vitro, activation of $p75^{NTR}$ by NgR1 ligands inhibited DRG neurite outgrowth, and small interfering RNA directed against $p75^{NTR}$ reduced MAG and myelin inhibition *(137, 139,140).* Additionally, Yamashita et al. *(139)* reported a functional association of $p75^{NTR}$ with GT1b. Mi et al. *(141)* demonstrated that the interaction between NgR1 and $p75^{NTR}$ includes Lingo-1, another transmembrane protein expressed in neurons, therebyforming a trimeric receptor complex. It is unknown whether NgR2 interacts with $p75^{NTR}$ in the same way as NgR1, but the structural homology between NgR1 and NgR2 and the fact that both are GPI-linked to the cell membrane (i.e., they lack intracellular signaling components) suggest this to be true.

$p75^{NTR}$ also binds neurotrophins, interacts with tropomyosin-related tyrosine kinase (Trk) receptors and affects affinity and specificity of neurotrophin binding *(142),* and interacts with sortilin to bind proneurotrophins *(143,144).* Because it participates in signaling for cell growth, survival, and death, the precise contribution of $p75^{NTR}$ to neurite outgrowth is not clear. Recent experiments showed that DRG and cerebellar neurites from mice lacking functional $p75^{NTR}$ had an increased capacity for neurite outgrowth over myelin substrates *(128)* and that prevention of the brain-derived neurotrophic factor–$p75^{NTR}$ interaction promoted cerebellar neurite outgrowth in the presence of myelin inhibitors over MAG *(145).* These data suggest that in the presence of myelin inhibitors, the net influence of $p75^{NTR}$ is to restrict plasticity.

In recent experiments, Park et al. *(146)* and Shao et al. *(147)* independently identified a $p75^{NTR}$ homolog known as TROY, which also forms a receptor complex with NgR1 and Lingo-1. Both groups found that the interaction of TROY with NgR1 was eight times stronger than that of $p75^{NTR}$ and that neurite outgrowth of rodent DRG and cerebellar neurons in the presence of myelin, OMgp, or Nogo-66 was enhanced by the addition of truncated soluble TROY. Because of the restricted expression of $p75^{NTR}$ in the adult CNS, TROY may represent an important target for myelin antagonism; however, the possibility that other undiscovered coreceptors may also participate in myelin inhibition complicates antagonism at the receptor level.

Second Messengers

One family of second messengers involved in the interplay of neurite extension and retraction is the Rho family of small guanine triphosphate (GTP)ases *(148).* Rho GTPases are activated by guanine nucleotide exchange factors, which facilitate the exchange of guanine diphosphate (GDP) for GTP, and are inactivated by GTPase-activating proteins and the Rho-GDP dissociation inhibitor, which interacts with GDP-bound Rho to prevent conversion to the active, GTP-bound form *(149).* One particularly important member of the GTPase family that is involved in myelin signaling is RhoA. RhoA activates Rho-associated kinase, an effector kinase that, in turn, activates LIM-kinase *(150,151).* LIM-kinase phosphorylates cofilin or actin depolymerization factor to reduce actin turnover, thereby inhibiting neurite growth *(152,153)*

Myelin-associated proteins activate RhoA to limit axonal growth. This was demonstrated using the enzyme C3 transferase (C3) from *Clostridium botulinum,* which blocks RhoA function; C3 treatment allowed neonatal retinal, neonatal cerebellar, embryonic cortical, and embryonic and adult DRG neurons to grow on myelin substrates *(139,154–157).* Similar findings were obtained using the Rho-associated kinase inhibitor Y-27632, which alleviated myelin inhibition in neonatal cerebellar, embryonic cortical, and embryonic and adult DRG neurons *(155–157).* RhoA is also activated by $p75^{NTR}$ through a direct association with

Rho-GDP dissociation inhibitor, which is recruited to $p75^{NTR}$ upon binding of myelin-associated proteins to enhance RhoA activation *(158).* The action of myelin-associated proteins is opposed by neurotrophins, which act at $p75^{NTR}$ and Trk receptors and through protein kinase A and the GTPase-activating protein *Grit* to inhibit RhoA activation *(159,160).* Neurotrophin binding to $p75^{NTR}$ may inhibit RhoA activation by preventing $p75^{NTR}$ dimerization *(161).*

Myelin-associated proteins also induce RhoA activation in a $NgR1/p75^{NTR}$-independent fashion. Niederost et al. *(157)* found that NgR was not required for MAG-induced RhoA activation in neonatal cerebellar neurons. More recently, small iinterfering RNA-knockdown of RhoA in adult DRG neurons enhanced neurite outgrowth 30% more than the knockdown of $p75^{NTR}$ and 50% more than the knockdown of NgR1 *(140).* The interaction of MAG with GT1b might be one source of $NgR1/p75^{NTR}$-independent RhoA modulation, because Y-27632 treatment abolished inhibition induced by a GT1b agonist *(135).*

Enhancing Injury-Induced Intraspinal Sprouting Via Myelin-Signaling Antagonism

Characterization of the molecular components of myelin signaling has permitted the development of a host of myelin-signaling antagonists, many of which have been used in vivo to enhance plasticity of intact spinal axons. The critical period for sprouting induced by supraspinal injury of corticospinal axons can be extended by diminishing spinal myelin through neonatal irradiation *(78).* In adult animals, cortical or pyramidal injury stimulates sprouting of spared corticospinal axons when myelin-signaling antagonists are administered. Hybridoma cells secreting IN-1 stimulated sprouting of spared corticospinal axons after unilateral cortical aspiration *(21)* or unilateral pyramidotomy *(24,162).* Emerick and Kartje *(21)* showed that 2 mo after cortical aspiration, animals treated with IN-1 exhibited an increase in the percentage of corticospinal fibers projecting to the medial α-motoneuron cell column in the denervated cervical spinal cord. In this study, IN-1-treated rats exhibited improvements in placement on a horizontal ladder and reaching toward a food pellet but showed no improvement in their ability to successfully grasp food pellets and carry them to the mouth—even at 6 wk after injury. IN-1-induced sprouting was apparent by 1 wk after pyradmidotomy and appeared to be stable, because treated animals exhibited increased CST growth in the denervated spinal cord 6 wk after injury *(162).* In adult rats that received both unilateral pyramidotomy and IN-1, sprouting of intact corticospinal axons was associated with motor recovery in the injury-affected forelimb, indicated by complete recovery of both food pellet retrieval and rope climbing by 6 wk after injury *(24).* IN-1 treatment also stimulated sprouting of rubrospinal axons subsequent to bilateral pyradmidotomy *(3,163,164).* In these experiments, IN-1 treatment increased collateral sprouting from the rubrospinal tract and prompted rubrospinal axons to invade the cervical ventral horn, where they were closely apposed with motoneurons at 2 wk after injury. Rubrospinal plasticity was correlated with recovery of food-pellet reaching by 10 d following injury.

A more clinically relevant model of spinal denervation is ischemic stroke, and myelin-signaling antagonists have also enhanced intraspinal sprouting following unilateral cortical ischemia. Intraventricular infusion of a monoclonal anti-NogoA antibody 7B12 initiated 24 h after ischemic injury enhanced midline crossing of spared corticospinal axons in the cervical spinal cord *(165).* Treated animals exhibited enhanced midline crossing of spared corticospinal fibers in the cervical spinal cord (assessed approx 3 mo after both photothrombotic injury and permanent middle cerebral artery occlusion) as well as recovery of food-pellet retrieval on the Montoya staircase test *(166).* Following ischemic insult, sprouting of spared corticospinal fibers was enhanced in mice lacking NogoA/B and NgR and in rats

treated with NgREcto *(167).* In the latter experiments, although treatment was delayed until 1 wk after middle cerebral artery occlusion, corticospinal sprouting in the cervical spinal cord was enhanced, and treated animals exhibited recovery of staircase food-pellet retrieval and improved performance on a rotorod. These data suggest that myelin-signaling antagonism recruits spared spinal systems to function for those that are lost in supraspinal injury. However, these compounds also stimulate plasticity of corticorubral and corticopontine projections, inducing spared *(167–170)* and injured *(24,171, 172)* corticospinal fibers to sprout into the denervated red nucleus and pons. It seems likely that this supraspinal plasticity also contributes to recovery of function *(24,167,169,170,172).*

The growth triggered by myelin antagonists applied to SCI is more difficult to interpret. Although regenerative growth after anti-myelin treatment of SCI is well-documented *(173,174)*, the extent of plasticity in spared spinal systems is less clear. After thoracic dorsal hemisection in the young adult rat, parietal implants of IN-1-secreting hybridoma cells induced an increase in serotonergic and noradrenergic fiber growth caudal to the lesion; however, the authors acknowledged that they could not reliably distinguish the growth of injured vs uninjured axons *(175).* Other studies of partial SCI face similar difficulties: although anti-myelin treatments clearly stimulate the growth of spinal axons, the relative contributions of injured and spared axons remain open to interpretation.

Myelin-Signaling Antagonism in the Setting of Dorsal Rhizotomy

To further characterize the role(s) of myelin in restricting plasticity of intact spinal axons, our laboratory used several approaches to interfere with myelin signaling by targeting myelin-associated proteins, their receptor complexes, and their intracellular transducers (Fig. 2). Using all of these approaches, we have found that myelin-signaling antagonism differentially enhances rhizotomy-induced plasticity of different populations of intact axons terminating in the dorsal horn. Additionally, myelin-antagonist-induced plasticity correlates with changes in rhizotomy-induced pain.

To target myelin-associated proteins, we used a soluble form of NgR1 (sNgR) to sequester Nogo, MAG, and OMgp *(71)* from the endogenous receptors (NgR1 and NgR2). The sNgR was expressed as an IgG of the human NgR extracellular domain (including amino acids 1–457)—that is, it is not the NgREcto–Fc fusion protein previously used by others *(126).* We applied sNgR intrathecally in adult rats and examined spinally projecting axons in the dorsal horn at 2 wk following quadruple rhizotomy. Most axonal populations exhibited plasticity in response to rhizotomy, which was augmented by sNgR. Serotonergic axons both sprouted and increased their transmitter content after rhizotomy, effects that were enhanced by sNgR treatment. TH-expressing axons exhibited less sprouting in response to rhizotomy but responded most vigorously to treatment with sNgR. Rhizotomy induced a modest increase in GAP-43 immunoreactivity, which was further enhanced by sNgR treatment. CGRP-expressing primary afferents responded to sNgR application only contralateral to rhizotomy, whereas noradrenergic/adrenergic (DβH-expressing) axons were least stimulated by both rhizotomy and sNgR treatment. Because NgR1 is not expressed by spinally projecting mono-aminergic axons *(176)*, it appears likely that the effects of sNgR are attributable to its ability to sequester MAG from NgR2.

We have also used $p75^{NTR}$ hypomorphic mice to examine plasticity in the absence of normal receptor complexes for myelin proteins *(73).* Septuple dorsal rhizotomies were performed in mice lacking the extracellular neurotrophin-binding domain of $p75^{NTR}$ ($p75^{-/-}$) as well as in wild-type controls. Before injury, the axon density in the dorsal horn of wild-type mice was either equivalent to (CGRP-expressing axons) or greater than (5-HT- and TH-expressing axons) that of $p75^{-/-}$ mice. This was the first report of reduced spinal

mono-aminergic innervation in intact $p75^{-/-}$ mice. Rhizotomy-induced sprouting of primary afferent and mono-aminergic axons was more prolific in $p75^{-/-}$ mice, and increased density of spinal axons persisted for at least 1 mo after injury. Because the inhibitory character of $p75^{NTR}$ is affected by neurotrophin availability, some animals of both genotypes received exogenous nerve growth factor (NGF) or neurotrophin (NT)-3 at the time of injury. Relative to $p75^{+/+}$ mice, exogenous NGF augmented the sprouting response of mono-aminergic axons in $p75^{-/-}$ mice, whereas NT-3 treatment robustly increased sprouting of both mono-aminergic and primary afferent axons in $p75^{-/-}$ mice. These results are interesting in light of the interactions between $p75^{NTR}$, neurotrophins, and Trk receptors: in the absence of $p75^{NTR}$, the affinity of TrkA for NGF decreases, and NT-3 can bind to all Trk receptors *(177–180).* The surprising increase of mono-aminergic axon sprouting in NGF-treated $p75^{-/-}$ mice may result from an indirect effect, such as NGF-mediated upregulation of primary-afferent-derived brain-derived neurotrophic factor that is released in the spinal cord *(181–185).*

We have also used Y-27632 to antagonize myelin signaling at the intracellular level in adult rats with septuple or double rhizotomy *(72).* We found that rhizotomy alone had a plasticity-inducing effect on serotonergic and, to a lesser extent, TH-expressing axons. We also found that there was a "dose-dependent" relationship between the number of roots injured and the degree of mono-aminergic plasticity in the spinal cord: a septuple rhizotomy (C4–T2) induced more sprouting than a double rhizotomy (C7 and C8). Treatment with intrathecal Y-27632 enhanced the plasticity of both axonal populations, but TH-expressing fibers were preferentially affected. Because descending mono-aminergic axons are intimately involved in pain processing in the dorsal horn, we also investigated the behavioral consequences of dorsal rhizotomy and Y-27632 treatment. We found that C7/C8 rhizotomy induced cold-pain in the ipsilateral forepaw, indicated by an increased duration of withdrawal, biting, or licking in response to acetone application. After C7/C8 rhizotomy, treatment with Y-27632 both accelerated mono-aminergic sprouting and attenuated cold pain. However, similar to most studies of this sort, a causal link between sprouting and behavioral resolution remains to be demonstrated.

Conclusion

Most SCIs in humans are incomplete, and repair strategies should include the optimization of spared systems. This is especially true given that in the absence of regenerative therapy, there is some behavioral recovery in complex motor tasks after SCI *(186,187).* Axonal sprouting has been demonstrated repeatedly, and this response of undamaged axons has been credited not only with producing motor improvements *(188)* but also with the generation of chronic pain and autonomic dysreflexia *(46,59,189).*

Antagonizing myelin signaling has revealed the intrinsic plasticity of numerous spinally projecting systems and, if we can selectively target appropriate axonal populations, may serve as a viable therapeutic approach to improving the quality of life of people living with SCI. One particularly important realization emerging from the work of many groups is that the complexity of interaction between myelin-derived inhibitors and their growing list of receptors and coreceptors suggests that the most reasonable targets are intra-axonal points of convergence of multiple inhibitory signaling pathways.

Acknowledgments

This article is based on work supported by the International Spinal Research Trust, the Christopher Reeve Paralysis Foundation, the Dofasco Employee Donations Fund, the Natural Science and Engineering Research Council of Canada, and the Michael Smith Foundation

for Health Research (MSFHR). M. S. Ramer is a MSFHR scholar.

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