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Axonal regulation of Schwann cell ensheathment and myelination

James L. Salzer
Department of Cell Biology, New York University School of Medicine, New York, NY, USA

Abstract

Axons in the vertebrate peripheral nervous system are intimately associated with Schwann cells. Axons regulate the Schwann cell phenotype, determining whether they myelinate individual axons or ensheathe multiple, small axons in Remak bundles. Our current understanding of the axonal signals that drive Schwann cells towards these distinct morphological and phenotypic fates will be briefly reviewed here. Elucidation of these signals, and the intracellular pathways they regulate, may lead to new, rational therapies for the treatment of inherited and acquired neuropathies.

Keywords

myelination; neuropathy; neuregulin; Remak bundle

One of the most striking examples of reciprocal, cell-cell interactions in cell biology is exemplified by the interactions between axons and Schwann cells in the vertebrate peripheral nervous system. These interactions are essential for the formation and function of peripheral nerve fibers. During development, axons promote the generation of Schwann cells via trophic, mitogenic and differentiative effects on precursor cells; Schwann cells, in turn, regulate the integrity and functional organization of axons (Jessen and Mirsky, 2005; Sherman and Brophy, 2005). The critical, mutual dependency of axons and Schwann cells persists into adulthood; it contributes to the vulnerability of myelinated fibers to a variety of clinical disorders as pathology of one partner invariably affects the function of the other (Scherer and Wrabetz, 2008). A major goal remains to elucidate the reciprocal signals that drive formation and maintain the integrity of mature myelinated axons. Elucidation of these interactions, and the intracellular signaling pathways they regulate, may lead to new, rational therapies for the treatment of inherited and acquired neuropathies.

Schwann cells adopt one of two distinct relationships with axons, either myelinating individual axons or ensheathing multiple, small axons in what are termed Remak bundles. In myelinated fibers, Schwann cells form a compact myelin sheath around a large diameter axon, enabling rapid saltatory conduction. In Remak bundles, Schwann cells segregate small diameter axons, such as nociceptive fibers, into separate pockets; these conduct via cable propagation. Remak Schwann cells were a topic of considerable interest in the Griffin lab, which carried out many foundational studies on their biology (Griffin and Thompson, 2008). Myelinating and Remak Schwann cells differ not just in their morphological relationship to the axon - rather, they are fundamentally distinct, binary phenotypes of the Schwann cell characterized by expression of different transcription factors, proteins and lipids (Jessen and Mirsky, 2005). Most peripheral nerves consist of a mixture of myelinated and Remak fibers.

Address correspondence to: James L. Salzer, M.D., Ph.D., Department of Cell Biology, New York University School of Medicine, 550 First Avenue, New York, NY, 10016 USA. Salzer@Saturn.med.nyu.edu.

It has long been known that the axon determines which of these two distinct phenotypes Schwann cells adopt, based on experiments in which nerves of different composition were cross-anastomosed (Langley and Anderson, 1903). The identification of the axonal signals that promote formation of the myelin sheath has remained a topic of considerable interest with clear therapeutic implications. Two alternative hypotheses as to the nature of the axonal signal were originally proposed: either a critical axonal size triggers myelination or, alternatively, distinct biochemical signals presented by the axon dictate its ensheathment fate (Salzer, 1995). These are not mutually exclusive possibilities as larger fibers may express distinct signals and also present them at higher levels to the Schwann cell due to their larger membrane expanse.

Recent data, however, suggests these two types of axons do in fact differ biochemically, and strongly suggests that the key determinant of the ensheathment fate of axons is the amount of the growth factor, neuregulin (NRG) 1 that they express (Nave and Salzer, 2006). NRG1 is a member of the EGF superfamily comprised of a large number of alternatively spliced transmembrane isoforms. Six major classes of NRG1 have been described (types I – VI) which differ in the splicing patterns of the ectodomain; types I-III are the most abundant (Mei and Xiong, 2008).

NRG1 has long been known to have a critical role during the early stages of the Schwann cell lineage (Nave and Salzer, 2006). The first indication that NRG1 is also required for myelination emerged from studies, which demonstrated that genetic inactivation of NRG1's receptors (see below) in late development, results in hypomyelination of peripheral nerves (Garratt et al., 2000). Subsequently, it was shown that the expression levels of type III NRG1 correlate with the ensheathment fate of axons, i.e., axons that will be myelinated express much higher levels of type III NRG1 than do axons in Remak fibers. Importantly, forced expression of type III NRG1 in sympathetic fibers, which are normally unmyelinated, resulted in their myelination (Taveggia et al., 2005). Haploinsufficiency or full genetic inactivation of NRG1, in particular of the type III isoform, resulted in significant PNS hypomyelination (Michailov et al., 2004; Taveggia et al., 2005; Brinkmann et al., 2008). There were also defects in the ensheathment of Remak fibers. Finally, specific overexpression of the type III isoform in neurons results in significant hypermyelination, with substantially reduced *g* ratios (Michailov et al., 2004). Together, these results indicate that type III NRG1 is an instructive signal: threshold levels are required to trigger Schwann cell myelination; above threshold, the amount of compact myelin formed is graded to the levels of type III NRG1.

All NRG1 isoforms, including type III, are cleaved just extracellular to the plasma membrane, by metalloproteinases (Falls, 2003). This cleavage releases most of the ectodomains of the types I and II isoforms, which function as paracrine signals. In contrast, the type III isoform has a second, N-terminal hydrophobic sequence, and is therefore retained on the axon membrane after cleavage, functioning as a juxtacrine signal (Taveggia et al., 2005). Several different metalloproteinases have been implicated in NRG1 cleavage, including BACE (beta secretase). BACE cleavage appears to be required for full NRG1 activation as mice deficient in this enzyme are hypomyelinated in both the PNS and CNS (Hu et al., 2006; Willem et al., 2006); it is also possible that defective cleavage of another, yet to be established BACE substrate, contributes this hypomyelination. Other secretases also cleave NRG1, including tumor necrosis factor-alpha converting enzyme (TACE, also called ADAM 17) (Horiuchi et al., 2005). Recent studies demonstrate that TACE cleavage inactivates NRG1, thereby limiting the extent of myelination (La Marca et al., 2011). Additional secretases, including gamma secretase, have also been implicated in neuregulin cleavage. Together, these results raise the possibility that competition between secretases may regulate the extent of myelination and, further, that modulating NRG1 cleavage with

secretase inhibitors to enhance its activity may be a useful strategy for the therapy of de/dysmyelinating disorders.

While neuregulin (NRG) 1 is currently the best-characterized axonal determinant of Schwann cell myelination, other extrinsic signals are important as well (Fig. 1). Another signaling system recently implicated in axon-Schwann cell interactions is Lgi4, which is secreted by Schwann cells, and binds in a paracrine fashion to Adam (a disintegrin and metalloprotease) 22 on axons. Lgi4/Adam22 interactions are critical for Schwann cells to advance beyond the pro-myelinating stage (Bermingham et al., 2006; Ozkaynak et al., 2010). A Schwann cell G protein-coupled protein receptor (Gpr 126) has also been shown to be required autonomously by Schwann cells for myelination (Monk et al., 2009) and for normal Remak fiber formation (Monk et al., 2011). The ligand for Gpr126 is not yet known, including whether it is expressed by axons or not. Finally, GDNF (glial cell line-derived neurotrophic factor) also has a promyelinating effect (Hoke et al., 2003) although it does not appear to be essential for myelination. Whether these signals are instructive or primarily permissive signals for myelination is not yet clear.

In addition to these signals, the basal lamina, in particular laminin isoforms, have long been known to be a major extrinsic signal required for ensheathment and myelination (Bunge et al., 1986). Laminin, which binds to and signals via integrin and dystroglycan receptors on the outer Schwann cell (abaxonal) membrane, functions as an autocrine signal to drive myelination (Chernousov et al., 2008).

A key question is what downstream signaling pathways in the Schwann cell mediate the pro-myelinating effects of these extrinsic signals? Given its key role in myelination, substantial attention has focused on how NRG1 mediates its effects. NRG1, like other members of the EGF superfamily, binds to and activates members of the erbB family of tyrosine kinase receptors (Mei and Xiong, 2008). Schwann cells principally express the erbB2/erbB3 heterodimer (Newbern and Birchmeier, 2010). Binding of NRG1 to the erbB2/3 heterodimer activates a series of canonical intracellular pathways, which are downstream of many tyrosine kinases: i.e., PI 3-kinase, PLC gamma, and MAP kinase (Lemmon and Schlessinger, 2010). Each of these pathways has been implicated in Schwann cell development and differentiation (Newbern and Birchmeier, 2010); a consensus on their precise role(s) in Schwann cell differentiation has yet to emerge. Type III NRG1 is the key axonal signal that activates the PI 3-kinase pathway in Schwann cells (Taveggia et al., 2005). This pathway has long been implicated in Schwann cell development (i.e., proliferation, survival, and myelination) based on pharmacological inhibition and overexpression studies (Maurel and Salzer, 2000; Ogata et al., 2006). Recent gain-of-function studies have extended these findings. Thus, activation of the PI 3-kinase pathway by conditional deletion of PTEN, a lipid phosphatase that has opposing effects, results in enhanced Schwann cell wrapping and myelination of axons (Goebbels et al., 2010). In addition, transgenic mice that overexpress activated forms of Akt, a key effector of PI 3-kinase, further support the role of this pathway in driving Schwann cell ensheathment and wrapping (E. Domenech, H. Baloui, and J. Salzer, in preparation). PLC gamma, which is also activated in Schwann cells as the result of NRG1/erbB signaling, is also critical for myelination. PLC activation results in elevated intracellular levels of calcium, activation of the phosphatase calcineurin, and dephosphorylation and translocation of the transcription factor NFAT into the Schwann cell nucleus where it promotes myelination (Kao et al., 2009).

The complexity of elucidating how NRG signaling promotes Schwann cell differentiation is illustrated by studies of the role of the MAP kinase pathway. Initial studies suggested that activation of the MAP kinase pathway was either dispensable (Maurel and Salzer, 2000) or

might even *inhibit* Schwann cell differentiation based on enhanced differentiation of Schwann cells treated with pharmacological inhibitors (Ogata et al., 2004) and dedifferentiation/demyelination when activated forms of MAP kinase were introduced into myelinating Schwann cells (Harrisingh et al., 2004). However, other studies suggest the MAP kinase pathway is important both for the early Schwann cell lineage and for subsequent NRG1-dependent promyelinating signals. For example, p38 MAP kinase has been suggested to be a key promyelinating signal based on pharmacological inhibitor studies *in vitro* (Haines et al., 2008). Compellingly, genetic ablation of pathway components during development impairs Schwann cell differentiation (Newbern et al., 2011). Shp2, a MAP kinase phosphatase required for full MAP kinase activation, is required for normal Schwann cell differentiation and its conditional inactivation in mice phenocopies erbB2 knockout mice (Grossmann et al., 2009). Loss of MAP kinase activity in embryonic Schwann cells impairs their genesis and differentiation. Further, activation of a pro-myelinating transcription factor (Yin Yang) depends on NRG1-mediated activation of the MAP Kinase pathway (He et al., 2010). These recent studies strongly support an important role of MAP kinase signaling. The reasons for the discrepancy between these and older studies are not yet known. Potentially, different experimental preparations, the timing of when MAP kinase is inactivated, and off-target effects of overexpression may account for some of the differences.

The pathways activated by recently identified Schwann cell receptors are even less well defined. Treatment with cAMP analogues rescues myelination in zebrafish with Gpr126 mutations suggesting that this orphan receptor may normally drive synthesis of intracellular cAMP - and correspond to the long sought regulator of this pathway in Schwann cells (Monk et al., 2009). In contrast, the pathways activated by Lgi4 interactions with Adam22 are completely unknown. As Lgi4 is secreted and binds to the axon, signaling may be indirect, via an effect on the axon itself. Finally, morphogenetic changes associated with ensheathment involve remodeling of the actin cytoskeleton via members of the Rho GTPases that are activated by matrix and neuregulin 1 signals (Chernousov et al., 2008; Feltri et al., 2008).

An intriguing notion that has emerged from recent studies is that signaling pathways may be activated during Schwann cell dedifferentiation and contribute to dysmyelination and demyelination in human neuropathies. Indeed, earlier studies demonstrated that growth factors are not only positive regulators of Schwann cells but under some circumstances may inhibit myelination and even result in Schwann cell demyelination in myelinating cocultures (Einheber et al., 1995; Zanazzi et al., 2001). In potential agreement, studies from the Griffin lab have provided compelling evidence that injury signals, released by degenerating myelinated fibers, drive Remak Schwann cell proliferation (Murinson et al., 2005). Emerging evidence strongly supports the notion that aberrant signaling during injury may also negatively regulate Schwann cell differentiation and that dedifferentiation does not simply result from loss of promyelinating signals from the axon (Jessen and Mirsky, 2008). Among the pathways that promote Schwann cell dedifferentiation, and are activated with injury, are Jun-kinase (Parkinson et al., 2008). Jun-kinase antagonizes expression of Krox-20/Egr-2, a key transcription factor with an essential role in the acquisition and maintenance of the myelinating phenotype. Notch has also been implicated in Schwann cell dedifferentiation during the injury response (Woodhoo et al., 2009). These findings raise the intriguing possibility that such injury signals, and their downstream signaling pathways, may contribute to demyelination in various neuropathies.

Our laboratory is investigating the mechanisms of Schwann cell differentiation, using mitogen-activated demyelination as a model. We previously reported that the type II NRG1 isoform has a paradoxical effect on Schwann cell differentiation, resulting in substantial

demyelination of neuron-Schwann cell cocultures (Zanazzi et al., 2001). Subsequent studies suggested that this dedifferentiation was due to activation of the MAP and Jun kinase pathways (Parkinson et al., 2008). Our own findings suggest that inappropriate activation of mTOR (mammalian target of Rapamycin) in myelinating cells by type II NRG1 substantially contributes to demyelination in this model (S. Hagerty, J. Salzer, in preparation). We are currently investigating whether mTOR activation may contribute to the pathology of inherited neuropathies. Ongoing studies from our lab (S. Hagerty, J. Salzer, in preparation) and those from L. Notterpek (Rangaraju et al., 2010), suggest that inhibiting mTOR activity may indeed be useful.

Thus, investigations into the axonal regulation of myelination are providing new insights into pro-myelinating pathways whereas those focused on injury models are elucidating novel dedifferentiative pathways. Together, these studies hold the promise of identifying novel targets for the therapy of acquired and inherited neuropathies.

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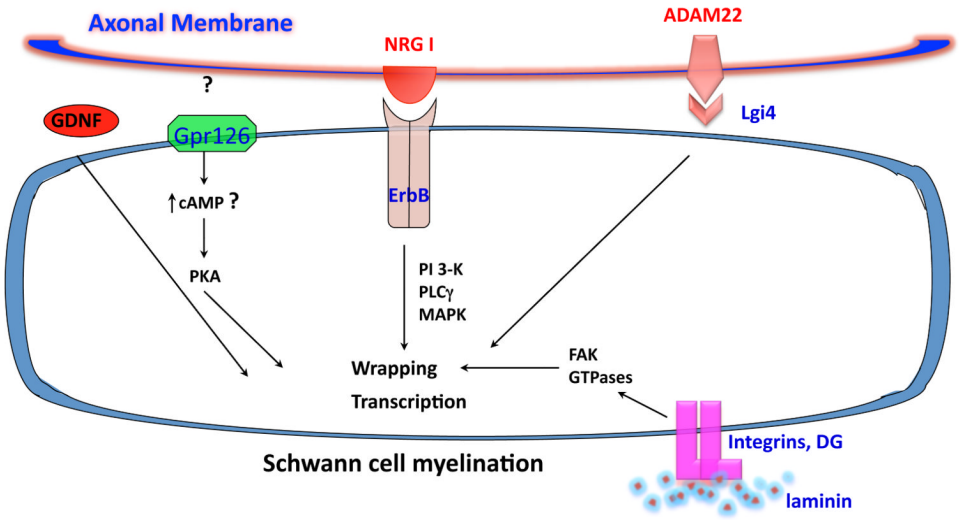

Figure 1. Summary of extrinsic signals that regulate Schwann cell myelination

Signals implicated in promoting Schwann cell myelination are shown schematically and include the axonal signals type III NRG1, which binds to and activates the erbB2/3 co-receptors (and thereby PI 3-kinase, PLC gamma, and MAP kinase) and ADAM22, which binds to Lgi4 secreted by the Schwann cell. GPR126 on the Schwann may function to increase intracellular cAMP levels and activate PKA; its ligand is not known. The extracellular matrix component, laminin binds to integrins and dystroglycan on the Schwann cell (abaxonal membrane) to activate focal adhesion kinase (FAK) and members of the Rho GTPase family. The growth factor GDNF also promotes myelination.