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Myelination: all about Rac 'n' roll

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During the development of the peripheral nervous system, Schwann cells select individual axons from a nerve bundle and establish a one-to-one relationship through a process termed "radial sorting". Recent findings identify the Rho family GTPase Rac1 as the downstream effector molecule responsible for process extension and lamellipodia formation in Schwann cells, allowing for proper radial sorting and myelination. These findings begin to shed light on our understanding of the distinct and yet essential molecular mechanisms involved in developmental processes preceding myelination.

In the nervous system, neurons and glia share reciprocal interactions in order to establish a functional relationship, and none is more evident than the process by which glia form myelin around axons. During development Schwann cells will proliferate, migrate, and ensheath bundles of axons. Once these axons are completely encircled by Schwann cells, extracellular matrix molecules are deposited and organized into a basal lamina that surrounds each Schwann cell and axonal bundle (Fig. 1 A). Each Schwann cell then selects an individual axon from a nerve bundle through a process called radial sorting, and this ultimately contributes to the initiation of myelination (Fig. 1 B). In recent years the role of laminins, found within the basal lamina, has been studied extensively during peripheral nerve development. Laminins influence multiple developmental processes in Schwann cells including proliferation, migration, and differentiation (for review see Feltri and Wrabetz, 2005). Although the disruption of laminin signaling results in a multitude of peripheral neuropathic conditions, it is widely held that laminin signaling through $\alpha6\beta1$ integrin on Schwann cells is necessary for proper radial sorting of axons (Bradley and Jenkison, 1973; Feltri et al., 2002; Chen and Strickland, 2003; Previtali et al., 2003; Yang et al., 2005; Yu et al., 2005). These studies have stimulated much discussion as to how a basal lamina component, on the outside surface of the Schwann cell, transduces a signal to influence axon sorting, a process that dynamically rearranges the inner and lateral surface of the Schwann cell membrane. In this current issue, two independent laboratories elegantly combine *in vitro* and *in vivo* approaches to demonstrate that laminin signaling

activates the Rho family GTPase Rac1 in Schwann cells, leading to radial sorting and subsequent myelination of axons (Benninger et al., 2007; Nodari et al., 2007).

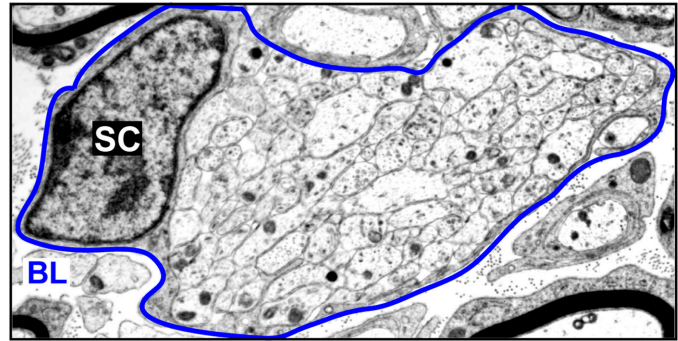
Using tissue-specific conditional gene-targeting technology, Nodari et al. (see p. 1063 of this issue) and Benninger et al. (see p. 1051 of this issue) demonstrate that Rac1 is downstream of $\beta1$ integrin activation. Conditional gene inactivation of Rac1 in Schwann cells results in deficits in axon sorting and myelination of peripheral nerves without affecting Schwann cell proliferation or cell survival (Benninger et al., 2007; Nodari et al., 2007). Importantly, these findings are strikingly similar to the phenotype of the $\beta1$ integrin null mice, suggesting possible cooperation or overlapping mechanisms. Consistent with these results, GTP-bound Rac1 (activated Rac1) is greatly diminished in the $\beta1$ null nerves during postnatal development, without any effect on the Rho family GTPase Cdc42. To examine whether Rac1 is downstream of $\beta1$ integrin, Nodari et al. (2007), using adenoviral-mediated transduction, expresses a constitutively active Rac1 into the Schwann cells of the $\beta1$ integrin null mice. Remarkably, the expression of the enforced Rac1 significantly improves radial sorting in the $\beta1$ null nerves, successfully demonstrating that Rac1 is downstream of $\beta1$ integrin and that it is both necessary and sufficient for axon sorting. Additionally, purified Schwann cells deficient for Rac1 or $\beta1$ integrin display dramatic decreases in the length of radial processes, as well as in the number of lamellipodia, suggesting a possible role for the extension of Schwann cell processes/lamellipodia in the interdigitation and sorting of axons.

Interestingly, gene inactivation of Cdc42 dramatically impairs axon sorting and myelination, to an even greater extent than the ablation of Rac1 (Benninger et al., 2007). Upon further investigation, Cdc42 was shown to be necessary for Schwann cell proliferation, and addition of neuregulin-1 could activate Cdc42, without any effect on Rac1. This finding is reminiscent of a recent report by Grove et al. (2007), demonstrating that focal adhesion kinase is required for Schwann cell proliferation and that the null mice display a similar impairment in axon sorting and myelination. In addition, the expression of the GTPase RhoA is strikingly similar to the Rac1 expression during peripheral nerve development and in the $\beta1$ null nerves (Nodari et al., 2007). Because Rho kinase is a downstream effector of RhoA, and is important for myelination (Melendez-Vasquez et al., 2004), it will be interesting to inactivate RhoA in Schwann cells in similar fashion to Rac1 and Cdc42. Collectively, these findings demonstrate that the Rho family of small GTPases may play distinct and yet essential roles in Schwann cell development.

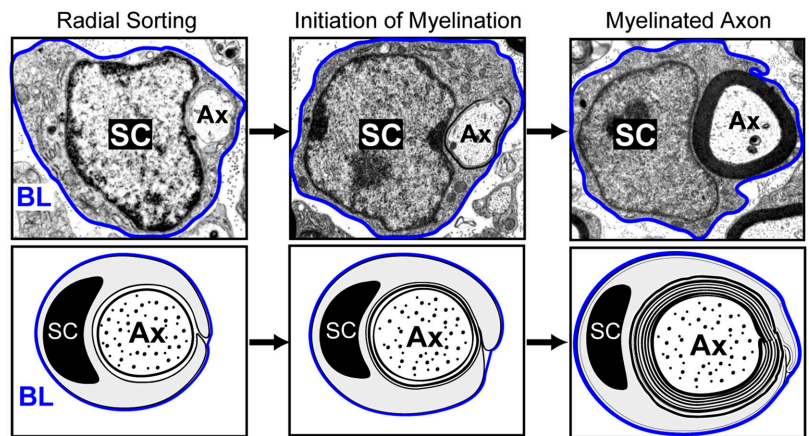
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Figure 1. **Illustration of Schwann cell (SC) development in the mouse sciatic nerve using electron microscopy.** During peripheral nerve development, Schwann cells proliferate, migrate, and ensheath axon (Ax) bundles (A). Schwann cells organize a basal lamina (BL, outlined in blue), which completely surrounds each individual cell and the associated axon(s). Upon receiving the appropriate signals from the local environment, Schwann cells will sort through the axon bundle, isolate an individual axon, and then initiate myelination (B). Bottom panels are schematic representations of the electron micrographs in the top panels, and represent radial sorting, initiation, and myelination of a single axon.

A Schwann cell ensheathment of axon bundles



B Radial sorting of an individual axon and myelination



Although the Rho GTPases unquestionably play essential roles in Schwann cell development, they are ubiquitous proteins, and as such, cannot realistically be targeted for potential therapeutic approaches without altering numerous cellular processes. This fundamental dilemma relates to the question of what intrinsic mechanisms confer the necessary specificity to elicit distinct function? Rho GTPases act as molecular switches and cycle between active (GTP-bound) and inactive (GDP-bound) states to regulate the organization of the actin cytoskeleton. Their activities are controlled positively by guanine nucleotide exchange factors (GEFs), and negatively by guanine nucleotide dissociation inhibitors (GDIs) and GTPase-activating proteins (GAPs), which enhance the endogenous GTPase activity. In recent studies, TrkC activation by neurotrophin-3 in Schwann cells activates the Cdc42 GEF, Dbl's big sister (Dbs), and the Rac1 GEF, Tiam1, leading to Schwann cell migration (Yamauchi et al., 2005a,b). In the case of radial sorting and myelination by Schwann cells, it will be intriguing to identify the specific activating factors for the Rho GTPases and link them to the signals transduced by the basal lamina.

When thinking about Schwann cell development, including myelination, one cannot overlook the importance of signals from the axons. Throughout development, Schwann cells are in constant contact with axons, suggesting that glial/neuronal communication is essential for regulating these processes. Likewise, it is widely accepted that axons control whether they will become myelinated by expressing the appropriate extrinsic signals to either

promote or inhibit this process. A recent series of elegant work provides strong evidence that neuregulin-1 type III acting through the receptor ErbB2 represents an axonal signal necessary for myelination by Schwann cells (Michailov et al., 2004; Taveggia et al., 2005). How are the signals on the opposite sides of the Schwann cell membrane (laminin [outside] and axonal neuregulin-1 [inside]) coordinately transduced to initiate axon sorting and myelination? Recently, the asymmetric localization of the polarity protein Par-3 was identified in Schwann cells at the axon/glia interface and found to be important for the initiation of myelination (Chan et al., 2006). Could these Par proteins aid in the recruitment and assembly of these signaling complexes on opposite sides of the Schwann cell membrane? Future studies examining how these signaling complexes are coordinately organized and established will be essential for furthering our understanding of Schwann cell development and peripheral myelination.

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