Myelination: some receptors required

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Feltri et al. (2001, this issue) succeed in disrupting β1 integrin specifically in Schwann cells, and in so doing, demonstrate that it is required for normal myelination. Their results reveal that signaling by an extracellular matrix receptor plays a key role in the differentiation of myelinating Schwann cells.

A series of interactions between axons and Schwann cells govern peripheral nerve development (Mirsky and Jessen, 1999). Axonally derived neuregulin-1 is required for the survival and proliferation of Schwann cell precursors, which, in turn, are required for the survival of neurons. As Schwann cell precursors develop into immature Schwann cells, they surround large bundles of axons and become polarized—the inside facing the axons, the outside depositing a basal lamina. Beginning at this time, and extending for many days thereafter, sheet-like Schwann processes infiltrate these axonal bundles, separating them into ever smaller bundles, and some axons are individually ensheathed (Webster, 1993). The promyelinating Schwann cells, the ones ensheathing axons in a 1:1 manner, subsequently form a myelin sheath within a few days. Unlike the Schwann cells that surround axonal bundles, promyelinating and myelinating Schwann cells are completely surrounded by a basal lamina. In this way, axons that are destined to be myelinated acquire the proper complement of Schwann cells, whereas nonmyelinated axons remain associated with cords of nonmyelinating Schwann cells.

A role for the basal lamina in axonal ensheathment and myelination has long been suspected (Bunge, 1993). The genetic evidence is based on the analysis of *dystrophic* mice and humans with congenital muscular dystrophy (CMD);* both have mutations in the laminin α2 gene (Pegoraro et al., 1998; Xu et al., 1994), resulting in a lack of laminin-2 (the α2β1γ1 isoform). *Lama2/LAMA2* mutations cause muscular dystrophy because laminin-2 is a ligand for dystroglycan, an essential extracellular matrix receptor expressed by skeletal muscle cells. Although myopathy predominates the clinical picture, some CMD patients have abnormal nerve conduction velocities, indicating that myelination is affected, too. Schwann cells express dystroglycan and even several sarcoglycans (Imamura et al., 2000), but the molecular basis of the neuropathy in CMD patients is not known. The finding that the ventral roots of adult *dystrophic* mice contain bundles of unensheathed axons—the persistence of an embryonic phenotype—provides an important clue in this regard.

Despite the known role of laminin-2 in myelination, its receptor and mechanism of action have not been previously elucidated. The report of Feltri et al. (2001) provides important insights into these issues. They conditionally deleted the gene encoding integrin β1, a component of laminin receptors, in immature Schwann cells (β1 integrin was absent by E17.5), before the formation of promyelinating Schwann cells, and found that myelination is markedly delayed. This delay results from the failure of Schwann cells both to subdivide bundles of axons and to progress past the promyelinating stage. Furthermore, the cell membrane of "arrested" promyelinating Schwann cells frequently fails to appose the basal lamina and even retracts, leaving the axon unensheathed. The myelinated axons that do arise, albeit belatedly, appear normal. These anatomical abnormalities likely preclude saltatory conduction and lead to the development of a progressive peripheral neuropathy. Thus, immature Schwann cells require β1 integrin to properly segregate bundled axons during development, and promyelinating Schwann cells may require β1 integrin to adhere to their basal laminae and initiate the formation of a myelin sheath. The earlier observation that antibodies against β1 integrin interfere with myelination in vitro (Fernandez-Valle et al., 1994) is elegantly confirmed and extended.

The findings of Feltri et al. (2001) suggest that the receptor for laminin-2 switches during development. As depicted in Fig. 1, immature and promyelinating Schwann cells express α6β1 integrin, whereas myelinating Schwann cells predominately express α6β4 integrin (Previtali et al., 2001). In epithelial cells, α6β4 integrin links the basal lamina to intermediate filaments via hemidesmosomes, whereas Schwann cells do not have hemidesmosomes. Thus, α6β4 may be linked to the actin cytoskeleton rather than to intermediate filaments. Although dystroglycan appears to be expressed on both promyelinating and myelinating Schwann cells, only the latter express a protein that interacts with dystroglycan, dystroglycan-related protein 2 (DRP2), as well as a protein that interacts with DRP2, periaxin (Sherman et al., 2001). Dystroglycan, DRP2, and periaxin form a macromolecular

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*Abbreviations used in this paper: CMD, congenital muscular dystrophy; DRP2, dystroglycan-related protein 2.

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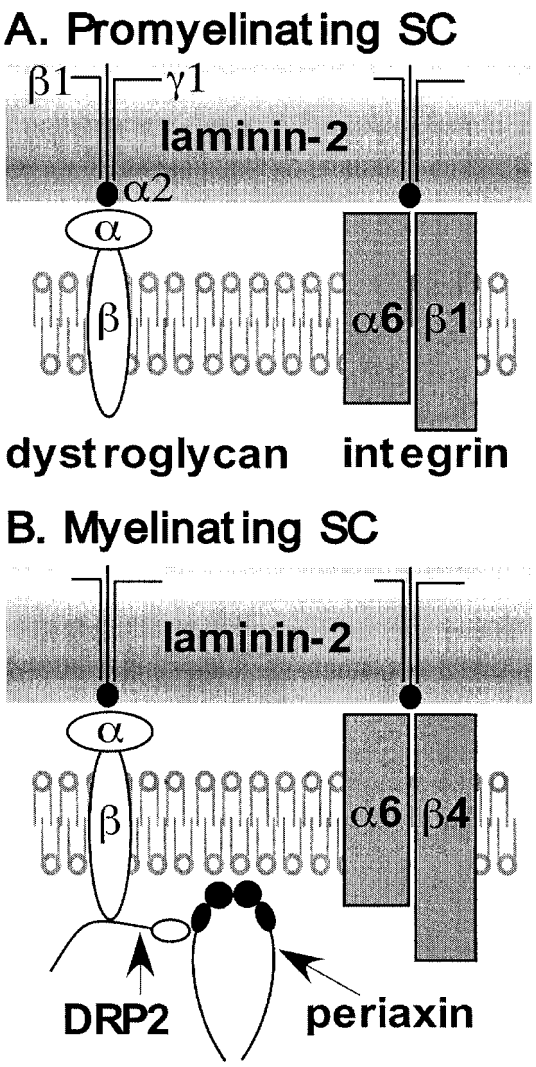

Figure 1. **Laminin-2 receptors of Schwann cells (SC).** This schematic drawing depicts that promyelinating Schwann cells express α6β1 integrin and dystroglycan, both of which bind laminin-2 (A). Myelinating Schwann cells express α6β4 in addition to α6β1, and dystroglycan interacts with periaxin (depicted as a dimmer) via DRP2 (B).

complex with utrophin, Dp116 (an isoform of dystrophin expressed in Schwann cells), and the actin cytoskeleton. One of these components, periaxin, is essential for the stability of myelin sheaths, as mice and humans lacking periaxin develop a demyelinating peripheral neuropathy (Boerkoel et al., 2000; Gillespie et al., 2000; Guilbot et al., 2001). These results suggest that one set of extracellular matrix receptors is required to initiate the formation of the myelin sheath, and another set is required to maintain it.

The developmental switching of laminin-2 receptors also provides a possible explanation for the belated myelination in mice lacking β1 integrin. The two potential candidates, dystroglycan and α6β4 integrin, appear about the day of birth and are expressed by myelinating Schwann cells in wild-type and in β1 integrin–null mice (Feltri et al., 2001). Perhaps the β1-deficient promyelinating Schwann cells that finally form myelin sheaths can do so because they express one of these receptors. It also seems plausible that laminin-2 is not the only ligand for β1 integrin that is relevant for myelination, as myelination is more disrupted in mice lacking β1 integrin than in mice lacking laminin-2. This discrepancy may owe to the versatility of β1 integrin, which has a potentially diverse number of ligands, because it can form heterodimers with a large number of α subunits.

Based on the phenotype of β1 integrin–null mice, Feltri et al. (2001) suggest that the loss of β1 integrin-mediated adhesion to laminin-2 in Schwann cells contributes to the phenotype of CMD caused by *LAMA2* mutations. Peripheral neuropathy likely contributes to the phenotype, as expressing wild-type laminin α2 in skeletal muscle of *dystrophic* mice does not completely reverse hindlimb weakness (Kuang et al., 1998). In the absence of β1 integrin or laminin-2, immature Schwann cells cannot reorganize their cytoskeleton as required to generate the membrane sheets that segregate axonal bundles. Furthermore, promyelinating Schwann cells lacking β1 integrin do not properly adhere to their basal lamina and thus may lack critical signals that are required to form a myelin sheath.

In summary, although the anatomical aspects of myelination have been known for decades, its molecular underpinnings are only now emerging. Feltri et al. (2001) provide conclusive evidence that signaling through β1 integrin is essential for the first steps of axonal ensheathment. These findings illuminate the earlier observations that axons are required for Schwann cells to assemble a basal lamina, and that a basal lamina is required for myelination (Bunge, 1993). Together, these results indicate that reciprocal interactions govern axonal ensheathment. Axons enable Schwann cells to form a basal lamina, which in turn, enables Schwann cells to interact properly with axons; in both cases, signals originating from one side of the Schwann cell affect the opposite side. How receptor-mediated signaling initiates and maintains the myelin sheath, one of the most spectacular structures in cell biology, is surely a problem worth unwrapping.

References

Boerkoel, C.F., H. Takashima, P. Stankiexicz, C.A. Garcia, S.M. Leber, L. Rhee-Morris, and J.R. Lupski. 2000. Periaxin mutations cause recessive Dejerine-Sottas neuropathy. *Am. J. Hum. Genet.* 68:325–333.

Bunge, M.B. 1993. Schwann cell regulation of extracellular matrix biosynthesis and assembly. *In* Peripheral Neuropathy. Vol. 1. P.J. Dyck, P.K. Thomas, P.A. Low, and J.F. Poduslo, editors. W.B. Saunders, Philadelphia. 299–316.

Feltri, M.L., D.G. Porta, S. Previtali, A. Nodari, B. Migliavacca, A. Cassetti, A. Littlewood-Evans, L.F. Reichardt, A. Messing, A. Quattrini, et al. 2001. Conditional disruption of β1 integrin in Schwann cells impedes interactions with axons. *J. Cell Biol.* 156:199–209.

Fernandez-Valle, C., L. Gwynn, P.M. Wood, S. Carbonetto, and M.B. Bunge. 1994. Anti-β1 integrin antibody inhibits Schwann cell myelination. *J. Neurobiol.* 25:1207–1226.

Gillespie, C.S., D.L. Sherman, S.M. Fleetwood-Walker, D.F. Cottrell, S. Tait, E.M. Garry, V.C.J. Wallace, J. Ure, I.R. Griffiths, A. Smith, and P.J. Brophy. 2000. Peripheral demyelination and neuropathic pain behavior in periaxin-deficient mice. *Neuron.* 26:523–531.

Guilbot, A., A. Williams, N. Ravise, C. Verny, A. Brice, D.L. Sherman, P.J. Brophy, E. LeGuern, V. Delague, C. Bareil, et al. 2001. A mutation in periaxin is responsible for CMT4F, an autosomal recessive form of Charcot-Marie-Tooth disease. *Hum. Mol. Genet.* 10:415–421.

Imamura, M., K. Araishi, S. Noguchi, and E. Ozawa. 2000. A sarcoglycan-dystrophin complex anchors DP116 and utrophin in the peripheral nervous system. *Hum. Mol. Genet.* 9:3091–3100.

Kuang, W., H. Xu, P.H. Vachon, L. Liu, F. Loechel, U.M. Wewer, and E. Engvall. 1998. Merosin-deficient congenital muscular dystrophy - Partial genetic correction in two mouse models. *J. Clin. Invest.* 102:844–852.

Mirsky, R., and K.R. Jessen. 1999. The neurobiology of Schwann cells. *Brain Pathol.* 9:293–311.

Pegoraro, E., H. Marks, C.A. Garcia, T. Crawford, P. Mancias, A.M. Connolly, M. Fanin, F. Martinello, C.P. Trevisan, C. Angelini, et al. 1998. Laminin α2 muscular dystrophy: Genotype/phenotype studies of 22 patients. *Neurology.* 51:101–110.

Previtali, S.C., M.L. Feltri, J.J. Archelos, A. Quattrini, L. Wrabetz, and H.P. Hartung. 2001. Role of integrins in the peripheral nervous system. *Prog. Neurobiol.* 64:35–49.

Sherman, D.L., C. Fabrizi, C.S. Gillespie, and P.J. Brophy. 2001. Specific disruption of a Schwann cell dystrophin-related protein complex in a demyelinating neuropathy. *Neuron.* 30:677–687.

Webster. H.d. 1993. Development of peripheral nerve fibers. *In* Peripheral Neuropathy. Vol. 1. P.J. Dyck, P.K. Thomas, P.A. Low, and J.F. Poduslo, editors. W.B. Saunders, Philadelphia. 243–266.

Xu, H., X.-R. Wu, U.M. Wewer, and E. Engvall. 1994. Murine muscular dystrophy caused by a mutation in the laminin α2 (*Lama2*) gene. *Nat. Genet.* 8:297–302.