Review

Molecular mechanisms regulating myelination in the peripheral nervous system

Jorge A. Pereira, Frédéric Lebrun-Julien and Ueli Suter

Institute of Cell Biology, Department of Biology, Swiss Federal Institute of Technology, ETH Zürich, CH-8093 Zürich, Switzerland

Glial cells and neurons are engaged in a continuous and highly regulated bidirectional dialog. A remarkable example is the control of myelination. Oligodendrocytes in the central nervous system (CNS) and Schwann cells (SCs) in the peripheral nervous system (PNS) wrap their plasma membranes around axons to organize myelinated nerve fibers that allow rapid saltatory conduction. The functionality of this system is critical, as revealed by numerous neurological diseases that result from deregulation of the system, including multiple sclerosis and peripheral neuropathies. In this review we focus on PNS myelination and present a conceptual framework that integrates crucial signaling mechanisms with basic SC biology. We will highlight signaling hubs and overarching molecular mechanisms, including genetic, epigenetic, and post-translational controls, which together regulate the interplay between SCs and axons, extracellular signals, and the transcriptional network.

Introduction

Axon myelination is essential to attain rapid saltatory impulse conduction in the vertebrate nervous system. The remarkable multi-layered myelin sheath structure is achieved by wrapping of the plasma membrane of specialized glial cells, oligodendrocytes in the CNS and SCs in the PNS, around large-caliber axons. This precise arrangement and its integrity are essential, as emphasized by frequent neurological diseases caused by malformation or deterioration of the myelin sheath, including multiple sclerosis, leukodystrophies and peripheral neuropathies. The appearance of myelin was also a major step forward in vertebrate evolution. Plausibly, emergence of the neural crest, a stem cell population giving rise to jaws and most of the PNS including SCs, arose together with myelination, allowing superior predatory and escape behaviors and the efficient construction of large body sizes [1].

The continuous bidirectional dialog between axons and glial cells is fundamental for myelin formation during development, myelin maintenance, remyelination after injury, and in understanding disease etiology. In disease, axon damage is almost invariably observed after myelin damage, suggesting disturbed glia–axon signaling [2]. Many basic mechanisms about the functional roles of glia–axon interactions have been elucidated in the PNS, largely due to the relative anatomical simplicity of peripheral nerves and the consequential experimental opportunities. Although there are significant molecular differences compared to the CNS [3], understanding PNS myelination, in addition to being valuable in its own right and with respect to peripheral nerve diseases [4], will continue to provide important conceptual insights into CNS myelination in health and disease.

In early PNS development, axonal signals are critical for SC migration, survival and proliferation to ensure that SC and axon numbers are matched. Furthermore, axons regulate SC differentiation into myelinating and non-myelinating populations [5]. Reciprocally, SCs provide crucial trophic support for developing neurons and profoundly influence axonal properties, especially through myelination. SC-derived signals guide the sequential assembly of multi-protein complexes, including cell adhesion molecules, ion channels, and scaffolding proteins, into distinct domains at and in the vicinity of the node of Ranvier, a requirement for efficient saltatory impulse propagation [6]. Myelinating SCs also regulate the axon cytoskeleton, organelle content, and rates of axonal transport, all of which are vulnerable in demyelinating diseases.

In this review we will highlight signaling pathways emerging from the axon, the extracellular matrix (ECM), and other extracellular cues that guide PNS myelination. We will focus on molecular mechanisms that integrate signals received by SCs with genetic and epigenetic regulation, together controlling the formation, maintenance and repair of myelinating SC–axon units. Our discussion will be concentrated on the key question: how are myelin formation, maintenance, demyelination, and remyelination controlled? Related issues, including the formation and structure of nodes of Ranvier and the role of glia in eliciting disease and modulating its progression, have been reviewed elsewhere [2,3,6–8].

Myelinating SCs in development and repair

SCs originate from neural crest-derived SC precursors, although this embryonic cell type is not yet fully committed to the SC lineage and also gives rise to melanocytes [9]. Directed by the key regulator neuregulin-1 (NRG1), which is involved in nearly all aspects of SC biology [10], precursor cells develop into immature SCs with a basal lamina, acquire an autocrine survival loop, and surround axon bundles [5]. Next, immature SCs extend processes inside

Corresponding author: Suter, U. (usuter@cell.biol.ethz.ch).

0166-2236/$ – see front matter doi:10.1016/j.tins.2011.11.006 Trends in Neurosciences, February 2012, Vol. 35, No. 2

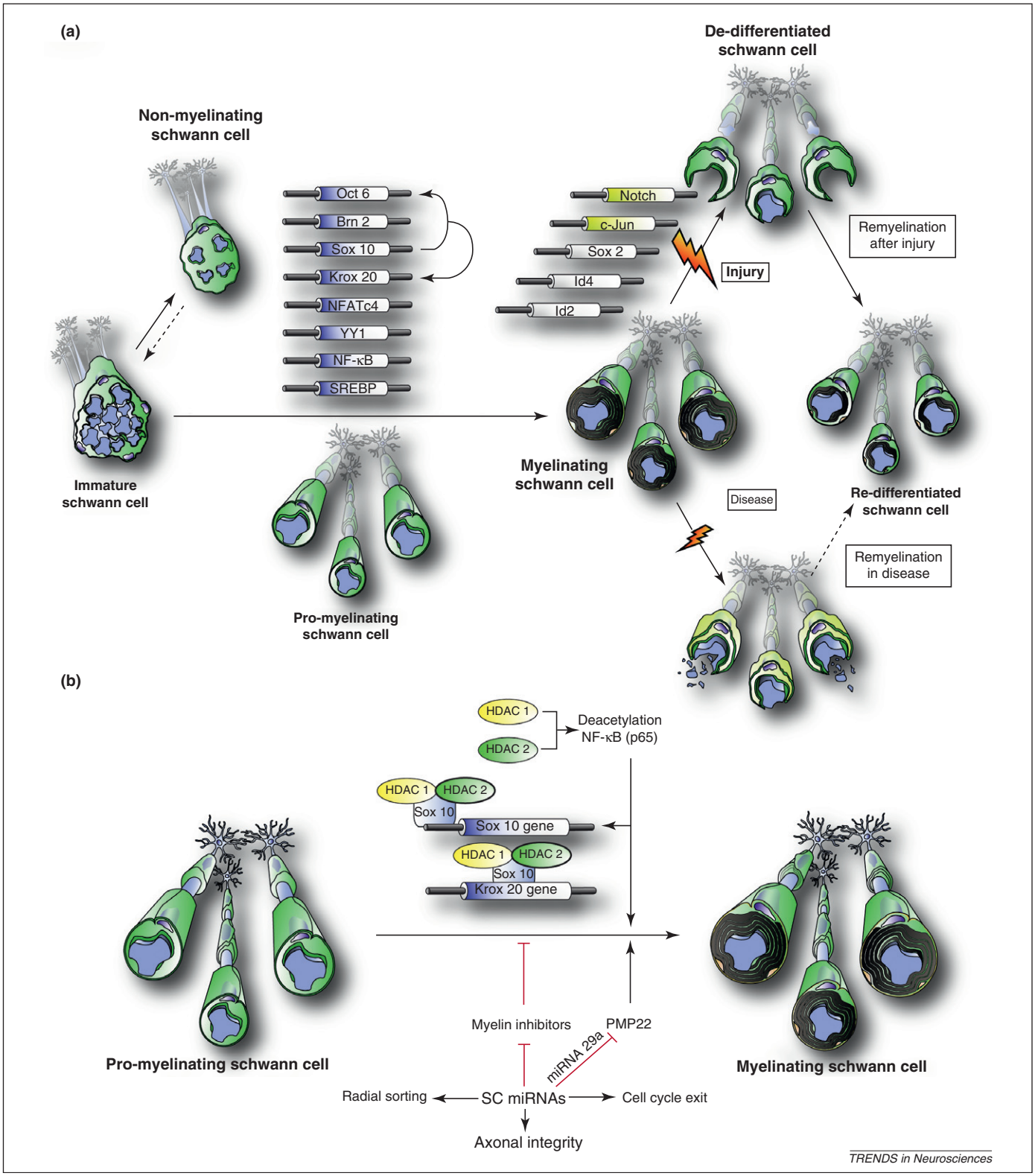

Figure 1. Transcriptional and epigenetic regulation of PNS myelination. **(a)** During late embryonic development and shortly after birth, peripheral nerves are organized in SC–axon families with immature SCs surrounding axon bundles. Subsequently, in a procedure known as radial axonal sorting, SCs extend processes into the bundles, selecting and extracting single axons of large diameters (approx. >1 μm in the adult mouse) to achieve a one-to-one SC–axon relationship termed the pro-myelinating stage. The small axons left behind remain engulfed by a SC but will not be myelinated and form Remak bundles. The main known positive transcriptional regulators of myelination are indicated (purple cylinders). At the heart of the process, Sox10 activates Oct6, and Sox10 and Oct6 together induce Krox20, the main regulator of the ensuing myelination program [14]. Brn2 (Brain-2) is also involved in the regulation of the timing and rate of the pro-myelinating to myelinating transition, with Krox20 as a major target. In addition, Sox10 and Krox20 are required for the maintenance of the myelinated SC state [12,16]. In agreement with the crucial role of these transcription factors, specific Krox20 and Sox10 mutations cause demyelinating diseases in human [13]. In general, myelination inhibitors (white and yellow cylinders) individually play mainly minor roles in regulating developmental myelination because they are typically under the control of the positive regulators. Upon nerve injury, however, the negative regulators direct SC demyelination. Notch and c-Jun definitively control SC de-differentiation, and Sox2, Id4 and Id2 are suspected to play a similar role [12]. After regrowth of peripheral axons, SCs activate a remyelination program that is similar but not an exact match to developmental myelination. Demyelination and incomplete remyelination are also key features in demyelinating peripheral neuropathies. However, current knowledge remains fragmentary about which components and controls are

the bundles to select large caliber axons in a finely tuned multistep process termed radial sorting [11]. This results in individual pro-myelinating SC–axon units, promptly activating a molecular program to generate myelin sheaths. Radial sorting is the decisive step towards a myelinating SC phenotype. We will therefore focus our review on the events from this stage onwards (Figure 1a).

Despite the remarkable differentiation process of myelination, myelinating SCs are highly plastic. After losing axonal contact in injured nerves, SCs dedifferentiate to an immature SC-like stage, proliferate, and serve as favorable substrate for axon regrowth, followed by remyelination [12]. Similarly, demyelination accompanied by incomplete remyelination occurs in hereditary and acquired peripheral neuropathies [4,13]. It is a current research challenge to differentiate between common regulatory mechanisms and the specific mechanisms that control myelination, demyelination and remyelination in the different settings of nerve development, injury and disease.

Transcriptional and epigenetic control of PNS myelination

SC myelination is under strict transcriptional control [14]. This involves a hierarchy of positive transcription factors, with a central axis that includes Sox10 (SRY-related HMG-box-10) activating Oct6 (octamer-binding transcription factor-6). In a feed-forward loop, Sox10 and Oct6 synergistically induce the expression of Krox20/Egr2 (early growth response-2) [15]. Krox20 takes center stage by activating numerous myelin genes, suppressing myelination inhibitors, and maintaining the myelinated state [12]. Consistent with its crucial role in this regulatory circuit, Sox10 is required for SC progression to myelination and myelin maintenance [16,17]. Other transcriptional regulators implicated in myelination include NFATc4 (nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent-4) that associates with Sox10 to activate the *Krox20* and *P0* (protein-zero) genes [18]. The latter encodes the most abundant PNS myelin protein that is required for myelin lamellae compaction and stability [19]. In addition, the transcription factor Yy1 (Yin yang-1) regulates *Krox20* expression and is required for myelination [20]. Furthermore, NRG1 type III (NRG1-III)-mediated activation of the transcription factor NF-κB (nuclear factor of κ light polypeptide gene enhancer in B cells) in SCs appears to be crucial for myelination [21,22]. In agreement with these findings, deacetylation of NF-κB by the histone deacetylases HDAC1 and HDAC2 promotes activation of the *Sox10* gene and regulates SC myelination [23]. Another study reported that Sox10 recruits both HDAC1 and HDAC2 to regulatory regions of the *Sox10* and *Krox20* loci [24] (Figure 1b). However, only HDAC2, in synergy with Sox10, activates the transcriptional program of myelination, consistent with attenuated myelination in young heterozygous SC-specific HDAC2-deficient mice. SCs deficient in both HDAC1 and HDAC2 cannot myelinate, confirming essential roles of these and probably other histone code regulators in PNS myelination [23–25].

The sterol regulatory element-binding proteins (SREBPs) have also been implicated in transcriptional regulation of myelination [26]. SC-specific deletion of SCAP (SREBP cleavage-activating protein), an activator of SREBPs, causes loss of SREBP-mediated gene expression involved in cholesterol and fatty acid synthesis, accompanied by altered myelin synthesis. Related to these findings, mutant mice lacking SC cholesterol biosynthesis show severe hypomyelination with uncompacted myelin stretches, attributed to disturbed cholesterol-mediated coordination of myelin membrane synthesis and deficient P0 export from the endoplasmic reticulum [27]. Reduced expression of genes involved in cholesterol biosynthesis is also characteristic of animal models of PMP22 (peripheral myelin protein-22)-based inherited peripheral neuropathies with affected myelin sheaths [28], highlighting further the significance of coordinated myelin protein and lipid biosynthesis regulation in health and disease. Mice with SC-specific ablation of *Lpin1* support also a crucial role of lipid homeostasis in myelinating SCs [29]. *Lpin1* encodes phosphatidate phosphatase (PAP1), required for triacylglycerol biosynthesis. In *Lpin1*-deficient SCs, accumulation of the PAP1 substrate phosphatidic acid mediates demyelination and aberrant SC proliferation, probably due to abnormal activation of the MEK (mitogen-activated protein kinase kinase)–Erk (extracellular-signal regulated kinase) pathway after myelination initiation.

In addition to transcriptional regulators promoting SC myelination, negative regulators have also emerged, including the NAB (NGFI-A/Egr-binding) corepressors. NABs interact with Krox20 and are required for coordinating myelin formation [30]. Krox20 and NAB2 associate with Id2 (inhibitor of DNA binding-2), Id4, and Rad (Ras associated with diabetes) promoters when those genes are repressed during the myelination process [31]. Another class of myelination inhibitors is generally inactive in myelinating cells and promotes SC dedifferentiation following injury [12]. The transcription factor AP-1 component c-Jun fits these criteria [32]. Furthermore, analysis of Notch receptor signaling in SCs, regulated by axonal ligands causing proteolytic release of the active transcriptional regulator Notch intracellular domain (NICD), revealed that this pathway also negatively controls myelination [33]. This includes driving demyelination after injury and inducing rapid demyelination in uninjured nerves if ectopically activated. Other candidate transcription factors for negative regulators of myelination include Sox2, Id2 and Id4 [14,34].

Understanding active regulation of demyelination is important in at least two major ways: First, such regulators foster axon regrowth after injury by promoting a

shared between developmental myelination and demyelination/remyelination after injury and in disease. **(b)** HDACs and miRNAs are major epigenetic regulators of PNS myelination. In SCs, HDAC1 and HDAC2 bind to Sox10 and promote the myelination process via Sox10 and Krox20. HDAC1 and HDAC2 can compensate for each other in a level-dependent manner, and both proteins promote deacetylation of NF-κB, which is important for NF-κB-driven myelination via Sox10 [23,24]. SC miRNAs are required for the transition of pro-myelinating to myelinating SCs (and to a minor extent for radial axonal sorting), partly by contributing to silencing of myelination inhibitors and promoting cell cycle exit [35–37]. Furthermore, axonal integrity is dependent on SC-expressed miRNAs [35]. *In vitro* studies showed that miRNA 29a regulates expression of the dosage-sensitive hereditary neuropathy-causing PMP22 [38].

favorable environment. This involves *trans*-differentiation of previously myelinating SCs to cells supporting nerve repair, potentially revealing novel targets to improve this clinically important process. Second, such pathways might become inappropriately activated or modulated in diseased SCs in demyelinating neuropathies. This knowledge may also provide the basis for novel therapeutic strategies [34]. The available information about PNS myelination inhibitors is incomplete, however, in particular with regard to their significance in developmental myelination compared to demyelination and remyelination after injury and in disease.

Micro RNAs (miRNAs) are post-transcriptional regulators with crucial roles in PNS myelination. SC-specific deletion of Dicer in mice disrupts the regulatory miRNA network causing differentiation arrest at the pro-myelinating stage [35–37], closely resembling congenital hypomyelination diseases. Mutant nerves show also mild impairments of radial sorting [35] and increased SC proliferation and apoptosis in late postnatal development [37]. Importantly, compromised axonal integrity indicates that SC miRNAs also regulate gene expression required for axon health, and this is mediated by SC–axon interactions [35]. At the molecular level, myelination inhibitors were increased in SC-Dicer mutants, whereas drivers of myelination were reduced [35–37]. Thus, miRNAs may suppress myelination inhibitors and shift the balance in favor of positive regulators, a model consistent with the modest silencing effects of miRNA-138 on c-Jun, Sox2 and CyclinD1 expression in cell culture [36].

Regulation of myelin protein expression in myelination requires exquisite control. This is well manifested by Charcot–Marie–Tooth disease (CMT) type 1A, the most frequent form of inherited peripheral neuropathies, and hereditary neuropathy with liability to pressure palsy (HNPP). Both are caused by genetic alterations leading to either PMP22 over- (CMT1A) or under-expression (HNPP) [13]. PMP22 is targeted by miRNA-mediated regulation [38] and patients with autoimmunity against GW182, a miRNA pathway key component, are often affected by motor and sensory neuropathies [39]. Thus, studying miRNA regulation and its therapeutical potential may also benefit research in peripheral neuropathies.

Control of myelination by principles of cell polarization

Transcriptional regulation of myelination is well studied, but understanding the cell biology of myelination and its associated signaling pathways remains a challenge. This is partly due to the unique features required to guide the formation of multilayered plasma membrane stacks and to establish and maintain a highly compartmentalized structure, a prerequisite for proper signaling in myelinating SCs (Figure 2). Integration of the continuous dialog with the underlying axon and growth factor- and ECM-derived signaling adds further layers of complexity. The concept of cell polarization, in analogy to epithelial cells, has been useful in this context [40,41]. Myelinating SCs are highly polarized, morphologically and molecularly, both longitudinally from node to node and radially from the axon to the SC basal lamina. Applying the conceptual polarization framework allows testing of whether and how basic principles and molecular players known from polarized epithelia also regulate myelinating SCs. Furthermore, activation, coordination and organization of signaling pathways can be related to the particular qualitative and quantitative protein and lipid compositions of SC membranes in different domains at the various developmental, demyelinating and remyelinating stages. The major intrinsic regulatory complexes in polarized epithelia are Dlg1 (discs, large homolog 1)/scribbled/Lgl (lethal giant larvae) localizing to the basolateral domain, Pals1 (protein associated with lin seven-1)/Patj (PALS1-associated tight junction protein)/crumbs found in the apical domain, and aPKC (atypical protein kinase C)/Par3 (partitioning defective-3)/Par6 associated with adherens and/or tight junctions [42]. Several of these proteins are expressed and distinctly localized in myelinating SCs [41,43–45]. Epithelial basolateral regulators are enriched in the abaxonal domain and apical regulators in the adaxonal domain and Schmidt–Lanterman incisures. This distribution indicates that myelinating SC polarity along the radial axes shares molecular resemblance with epithelial cells and suggests related basic regulatory mechanisms.

Functional testing revealed that Pals1 is essential for radial and longitudinal extension of the myelin sheath and for proper regulation of membrane protein trafficking [43]. Furthermore, reduction of Pals1 disrupted the correct polarized localization of the vesicular markers Sec8 and Syntaxin4, in line with functional roles of polarized vesicular sorting in myelinating SCs.

Par3 is asymmetrically localized at the axon–SC junction at the initiation of myelination [44], and this distinct localization, together with the associated $p75^{NTR}$ (neurotrophin receptor), is crucial to start myelination (these results also relate to the modulatory role of neurotrophins in SC myelination, as reviewed elsewhere [46]) (Figure 3). N-cadherin was suspected to mediate SC polarity by recruiting Par3, by analogy to epithelia, because both proteins colocalize at the SC–axon interface when myelination is initiated [45]. However, SC-specific ablation revealed that N-cadherin is not absolutely required for the initiation of myelination or for myelin maturation, although there was a minor delay in the onset of myelination. Because β-catenin coimmunoprecipitated with N-cadherin, myelination was also assessed in mice lacking SC-expressed β-catenin. A more severe delay in myelination was observed. Thus, N-cadherin may interact with β-catenin to establish SC polarity and the proper timing of myelination, but both proteins are not essential for the formation and maturation of myelin [45]. However, further clarification of the functional roles of Wnt/β-catenin signaling and its interplay with other signaling pathways in PNS myelination is required. Wnt/β-catenin signaling has been described as positive driver of PNS myelination [24,47], and disruption of downstream β-catenin signaling in zebrafish leads to hypomyelination and reduced myelin compaction [47]. By contrast, continuous SC-specific expression of activated β-catenin in transgenic mice does not affect myelination at postnatal day 15 [23].

A function of Dlg1 in myelination was initially suggested by its binding to MTMR2 (myotubularin-related protein-2). MTMR2 is mutated in CMT4B1 that is characterized by

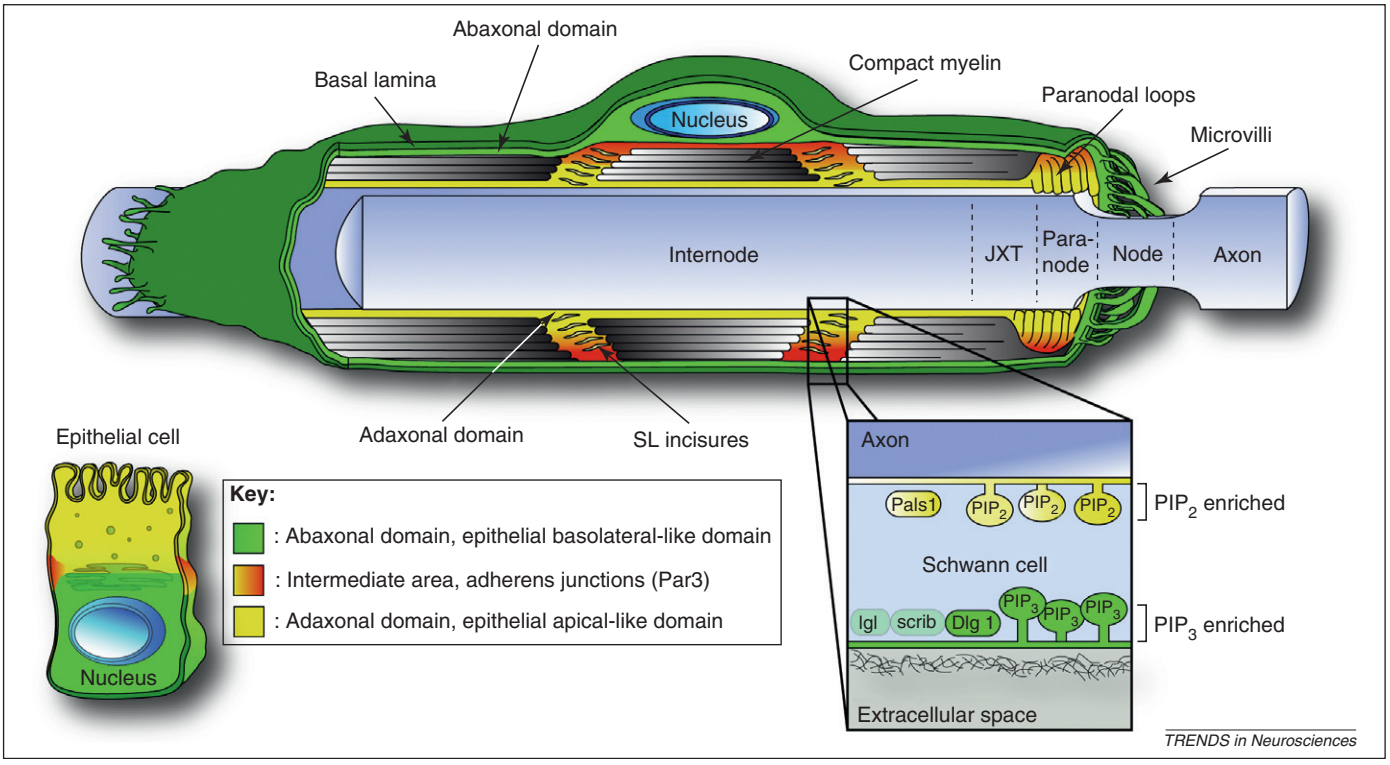

Figure 2. Polarized structure of the adult myelinating SC. Myelinating SCs cover a segment of the axon, designated the internode, and organize their subcellular domains in a polarized fashion, both in the longitudinal and radial axes. Longitudinally, SCs display the nucleus at the center. At the edge of the internode, cytoplasm-filled SC paranodal loops tether the internode to the axon and define the juxtaparanodal region (JXT). SC microvilli project into the nodal area. Radial polarity of SCs is also striking, with the nucleus being localized in the outermost wrap of the myelin sheath (abaxonal domain), followed by compact myelin and the innermost wrap facing the axon (adaxonal domain). Cytoplasm-filled spiral-shaped channels, Schmidt–Lantermann (SL) incisures, connect the adaxonal and abaxonal cytoplasm. The abaxonal domain is in tight contact with the basal lamina, a thin layer of highly organized ECM components synthesized by SCs, whereas the adaxonal domain is in close contact with the axolemma. This radial polarity organization shows similarities to epithelial cell polarization with an apical and a basolateral domain. Adult myelinating SCs show distributions of intrinsic polarity-regulatory proteins similar to those of epithelial cells, with Dlg1 being enriched in the abaxonal domain (basolateral-like), Pals1 concentrated in the adaxonal domain, SL incisures and paranodal loops (apical-like), and Par3 being localized to adherens junctions in outer regions of paranodal loops and SL incisures (between both domains). The asymmetric distribution of polarity proteins is coupled to a polar distribution of phosphoinositides. In mature myelinating SCs, PIP2 is enriched in the adaxonal domain and PIP3 is concentrated at the abaxonal domain. These enriched distributions of polarity proteins and PIPs relate to adult myelinating SCs. Note that when SC polarity is established and further enhanced during the myelination process, localization of these proteins and lipids is dynamic with different effects on signaling, as exemplified by Par3 recruitment to the SC–axon interphase at myelination initiation (Figure 3).

redundant myelin outfoldings [48,49]. SC-specific expression knockdown revealed that Dlg1 acts as a brake on myelination to achieve correct myelin thickness proportional to axon calibers [50]. These findings are consistent with previous suggestions that Dlg1, in concert with MTMR2, Sec8 and the kinesin Kif13b, may regulate vesicular transport and titrate membrane formation during SC myelination [49]. Thus, subtle endosomal trafficking defects might lead to accumulating problems if MTMR2 is absent, culminating in CMT4B. The importance of endocytic pathways in SC myelination has been emphasized by the identification of the probable disease mechanism in demyelinating CMT4C. Here, the mutated SH3TC2 (SH3 domain and tetratricopeptide repeats-2) protein is mistargeted away from the recycling endosome [51,52]. SH3TC2 is strongly enriched in myelinating SCs and acts as an effector of the small GTPase Rab11. Rab11 is a key regulator of recycling endosome functions and is required for SC myelination [52]. Neuropathy-causing SH3TC2 mutations disrupt the Rab11 interaction, probably affecting recycling of cargos essential for SC myelination.

Regulation of myelination by neuregulin

NRG1, in particular the axonal membrane-bound form NRG1-III, is a key regulator of PNS myelination by activating ErbB2–ErbB3 (erythroblastic leukemia viral oncogene homolog-2/3) receptor complexes in SCs [10]. A threshold amount of axonal NRG1-III triggers SC myelination [53], and NRG1-III also controls myelin growth to match myelin thickness to axon caliber [54]. Activation of PI3K (phosphatidylinositol 3-kinase)/PIP3 [phosphatidylinositol (3,4,5)-trisphosphate]/AKT (v-Akt murine thymoma viral oncogene homolog) signaling is a major pathway involved in these processes [53]. PI3K catalyzes the formation of PIP3 from PIP2 [phosphatidylinositol (4,5)-bisphosphate] to foster AKT activation, whereas PTEN (phosphatase and tensin homolog) mediates the opposite reaction. In myelinating SCs, PTEN reduction causes increased levels of PIP3 and hypermyelination [55]. Conversely, silencing of AKT leads to hypomyelination [50]. Activated AKT may act via SREBPs to promote cholesterol biosynthesis which itself is crucial for myelination [56]. Interestingly, the NRG1 signaling program that drives myelination is also involved in stopping the process [50]. During active myelination, NRG1 prevents Dlg1 and PTEN ubiquitination and degradation, which leads to more Dlg1–PTEN complexes. Consequently, accumulating active PTEN reduces AKT activity to terminate myelination. Taken together, the interplay between NRG1, PTEN, and AKT, together with functionally important regulatory accessory proteins including Dlg1, is a

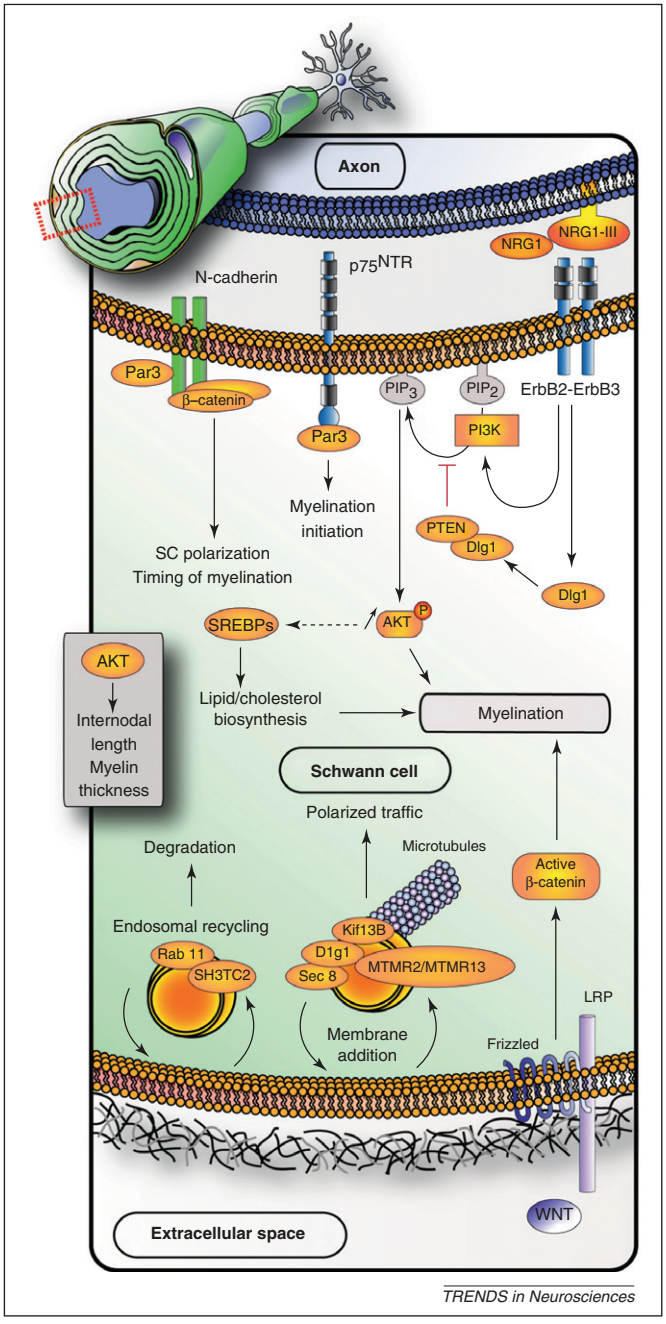

Figure 3. SC-intrinsic polarization mechanisms involved in myelination. Multiple pathways that contain SC-intrinsic polarization regulators and their crucial influence on different steps of myelination are shown. A dotted line from AKT signaling to the induction of SREBPs indicates that this connection is likely, but has not been firmly established in myelination. The local action of WNT/β-catenin signaling on SCs remains to be determined, as do the details of polarized regulation of vesicular trafficking by Sec8, Kif13B, and the Dlg1/MTMR2/MTMR13 complex mediated by the SC microtubule network. The association of MTMR13 with this complex is speculative but likely. MTMR2 or MTMR13 mutations lead to clinically and pathologically indistinguishable forms of demyelinating CMT, and MTMR2 and MTMR13 can also form complexes with regulatory effects [48]. The endosomal recycling regulator Rab11 interacts with the CMT culprit protein SH3TC2, indicating that endosomal recycling is crucial for myelination. This mechanism may affect signaling, or could contribute to regulating the addition of fresh components to the myelin sheath and the recycling of old myelin components by directing them to appropriate degradation pathways.

major regulatory component of PNS myelination. It appears likely that this signaling pathway contributes also to the disease etiology of peripheral neuropathies characterized by hypermyelination and hypomyelination [13].

A second major pathway elicited by NGR1 in SCs triggers increased intracellular Ca^{2+}, mediated by PLC-γ (phospholipase C-γ), and is coupled to calcineurin activation (Figure 4). This process induces dephosphorylation and nuclear translocation of NFATc4, complex formation with Sox10, and activation of the *Krox20* and *P0* genes [18]. The MEK pathway is the third signaling trail activated by NRG1. MEK-dependent Yy1 phosphorylation is crucial for Krox20 induction and myelination [20]. Furthermore, SC cell-specific gene ablation revealed that Erk1/2 are also required for myelination, possibly depending on NRG1 signaling [57]. Reduced Erk1/2 phosphorylation, associated with hypomyelination, was also found in SC-specific tyrosine phosphatase SHP2 (*Ptpn11*; protein tyrosine phosphatase non-receptor type-11)-deficient mice [58], consistent with a critical role of the MEK/Erk signaling cascade in NRG1/SHP2-regulated myelination.

In contrast to developmental myelination, juxtacrine NRG1 signaling is not required for myelin maintenance [59–61]. However, axonal NRG1 is essential for remyelination after injury, axon regeneration, and correct reinnervation of the neuromuscular junction [61].

Post-translational regulation of myelination by secretases

Regulated proteolysis critically regulates PNS myelination. This involves the β-secretase BACE1 [62,63] and the α-secretase TACE/ADAM17 (a disintegrin and metallopeptidase domain-17) [64]. Both cleave NRG1-III at closely spaced sites but have opposite effects on myelination [64,65]. While BACE1 is a positive regulator of myelination [62,63] and remyelination [65], TACE negatively regulates myelination by modulating the amount of functional NRG1-III on axons [64]. It appears that balancing BACE1 and TACE activities is crucial in determining the timing and degree of PNS myelination, and is most likely mediated by PI3K/AKT signaling. Nardilysin (NRD1), a metalloendopeptidase enhancer of protein ectodomain shedding, has also been linked to NRG1 cleavage and is a positive regulator of myelination [66]. How this might relate to the regulation of TACE, BACE1, or other protease activities remains open. Understanding regulation of secretion and processing of different NRG1 isoforms, and how the generated local concentrations of different functional ligands affect myelination, is of continued interest. In SC–neuron cocultures, low quantities of soluble NRG1-III and NRG1-II enhance myelination, whereas high amounts promote SC proliferation [67]. Given these results and the hypomyelination associated with BACE1- and NRD1-deficiencies, paracrine NRG1 signaling remains to be considered in myelination, in addition to the well-established juxtaparacrine effects.

Other ADAM family members are involved in regulating myelination in addition to ADAM17/TACE. Developmental myelination is normal in ADAM19-deficient mice, but there is a delay in remyelination, accompanied by reduced AKT phosphorylation and reduced expression of Krox20 and myelin-related proteins [68]. Mice lacking the catalytically-inactive ADAM22 display PNS hypomyelination [69], most probably due to receptor functions for the SC-secreted Lgi-4 protein (leucine-rich repeat LGI family

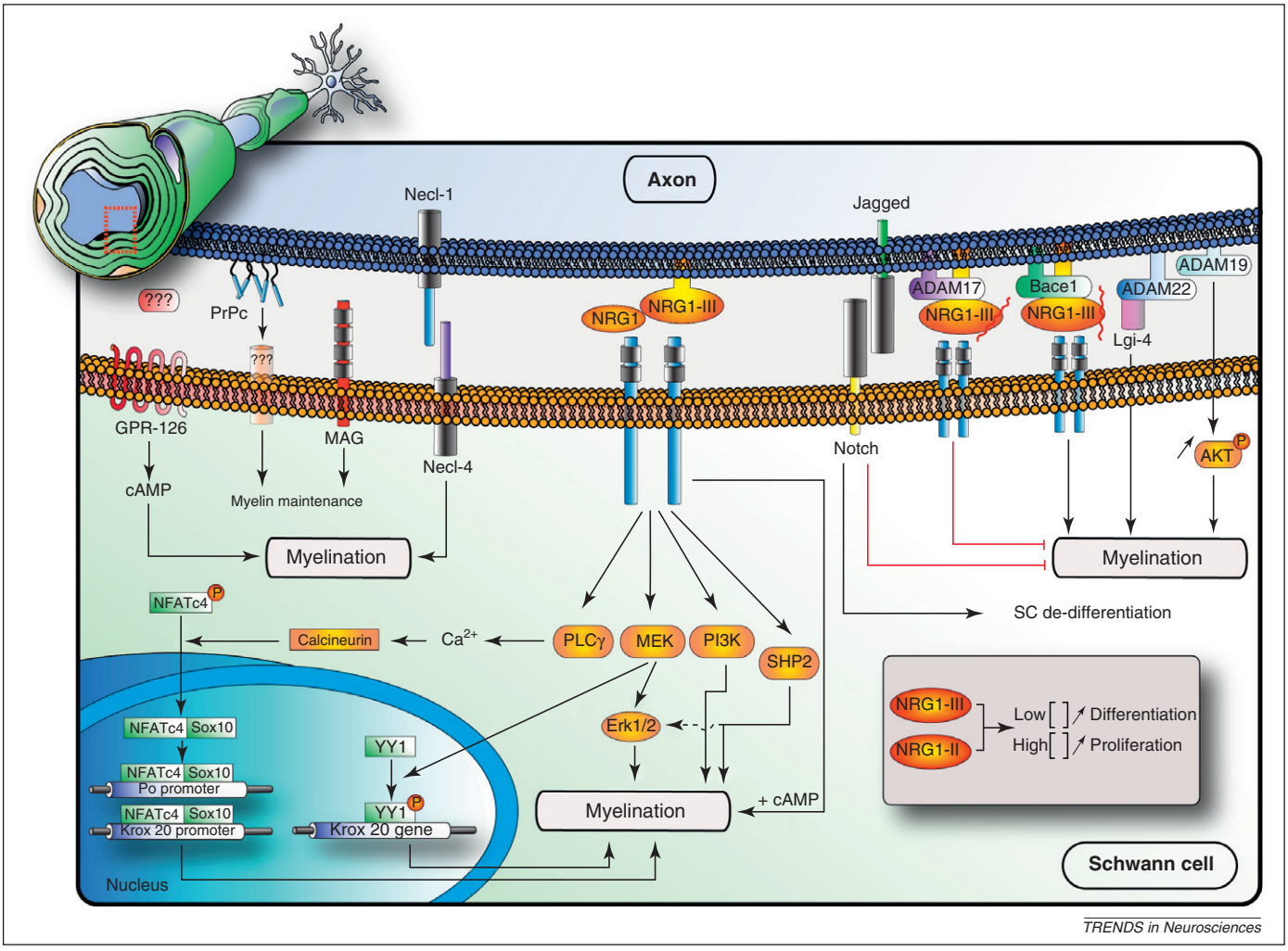

Figure 4. Control of PNS myelination by SC–axon interactions. SC myelination is a process strongly dependent on instructive signals provided by the axons. Well-known mediators of this interaction, together with activated signaling pathways and their influences on myelination are shown. Arguably the most prominent axonal signal regulating myelination is NRG1, which induces a multitude of different responses through several stages of SC maturation and in myelination. Membrane-bound NRG1-III appears to play a dominant role in axon–SC signaling via a juxtacrine mechanism, but there is also evidence for potential paracrine signaling by other NRG1 isoforms, an issue that remains to be explored further. Thus, a schematic membrane-bound form of NRG1-III and a soluble form of NRG1 are depicted here (also in Figures 3,5). Several secretases (members of the ADAM family and BACE1) are present at the axon surface and regulate SC myelination. ADAM17/TACE and BACE1 probably act by regulating NRG1-III signaling via proteolytic processing (wavy red lines), albeit with different effects on myelination. ADAM17/TACE and BACE1 are both shown on the axonal surface, but these proteins are also present in different subcellular compartments where they may already cleave their substrate(s). GPR126 is involved in SC–axon interactions, but further analyses are needed of its precise location within the SC membrane and the identification of the ligand(s) that stimulate GPR126-mediated production of cAMP. On a general note, we depict here (and in Figures 3,5) the signaling events along the internode. Little is known about the individual contributions of spatially and temporally controlled signaling at distinct locations within the SC–axon interface. To complicate matters, these are likely to differ during the different stages of myelination, starting with radial sorting and progressing to homeostasis of the myelinated peripheral nerve. Although it is generally believed that SC paranodal loops are a signaling hotspot, all cytoplasmic regions and the regulated network of their connections within the polarized and compartmentalized SC have to be considered.

member-4) [70]. Lgi-4 is required for PNS myelination as initially revealed by the hypomyelinated spontaneous Lgi-4 mouse mutant *claw paw* [71].

Regulation of myelination by interactions and signaling at the SC–axon interface

In addition to NRG1, other membrane-associated proteins are enriched at the SC–axon interface with impacts on myelination. SC-expressed Necl-4 (nectin-like protein-4) interacts with axonal Necl-1 to promote myelination [72,73]. The relevance of this interaction has been questioned because mice devoid of Necl-1 have no PNS myelination defect [74]. However, compensation effects may explain this result, as is often observed within the large family of related cell-adhesion proteins.

The SC-expressed myelin-associated glycoprotein MAG is required for maintenance of myelin, and MAG-deficient mice show a propensity for axon degeneration [75]. Dependence of axonal integrity on intact myelin sheaths is well known, but whether myelin maintenance relies on axons is less obvious. Surprisingly, axonal expression of the prion protein PrP^c, but not SC-expressed PrP^c, is required for preservation of the adult myelin sheath [76]. This conceptually important finding suggests that adult-onset demyelinating neuropathies might also originate on the axonal side. Thus, elucidating PrP^c binding partners that mediate this protective effect will be instrumental for understanding the myelinating SC–axon unit in health and disease.

GPR126 is a G protein-coupled receptor required for initiation of myelination autonomously in SCs [77,78]. Several G protein-coupled receptors induce production of cAMP, a well-known regulator of SC differentiation that, at least in cell culture, switches NRG1 from a proliferative signal to a myelin differentiation signal [79]. Only if used

together, cAMP and NRG1 upregulate myelin markers. Treatment with forskolin, an inducer of cAMP production, rescued the myelination defect in GPR126-mutant zebrafish, suggesting that GPR126 functions upstream in the cAMP-induced signaling cascade [78]. Determining whether regulation of cAMP by GPR126 is direct, or is possibly indirectly mediated by a G-protein complex, remains important in finding potentially axon-derived ligands.

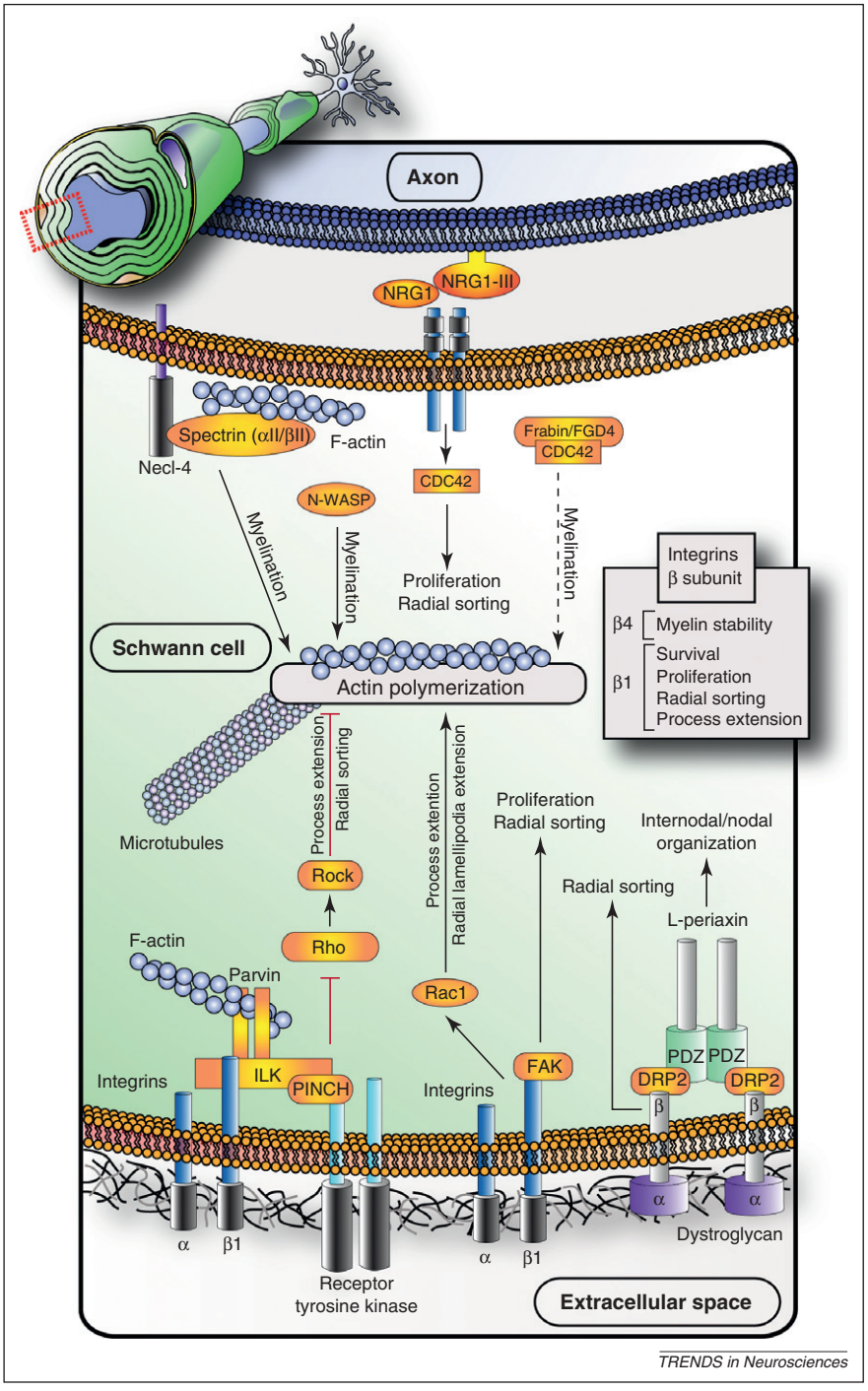

Figure 5. Control of myelination by the ECM and the cytoskeleton. SCs produce and organize a fine layer of highly organized ECM, the basal lamina, which is particularly rich in laminin. Integrins and dystroglycan are shown as crucial SC membrane receptors interacting with the basal lamina, particularly with laminin. Selected intracellular interacting proteins and signal transducers, together with their effects on myelination, are also depicted. Integrins are dimers of α and β chains. Roles for particular isoforms of the β subunit are described on the figure. Although there is evidence that the α6 isoform functions in myelination [88], the precise roles of other α subunits remain to be determined. Dystroglycan associates with various different proteins within different SC compartments. The complex shown is representative of the structures at tight SC–basal lamina appositions in adult myelinating SCs. Integrins signal to the cytoskeleton, and myelination depends on rearrangements of the actin cytoskeleton. One of the best-understood examples is Rac1 activation via integrin β1 signaling that stimulates SC process extension and radial lamellipodia formation. There are also pathways starting at the SC–axon interface, most probably regulated by axonal signals, that direct actin polymerization and myelination. αII/βII spectrins interact with Necl4 and F-actin, thereby promoting myelination [94]. The Rac1-related RhoGTPase Cdc42 is stimulated by NRG1 signaling and induces SC proliferation, but a direct connection to actin dynamics in SCs has not been reported. Several molecules can associate with the intracellular tail of integrins, one of which is FAK (focal adhesion kinase). Signaling via FAK stimulates SC proliferation during radial sorting of axons [108]. At present, the picture concerning molecular mechanisms regulating integrin and growth factor signaling, and their interactions with the cytoskeleton in myelination, is rather sketchy, in particular with regard to the interconnections between the signaling pathways elicited.

ECM signals regulating myelination

SCs lay down a basal lamina as a crucial prerequisite for myelination. ECM contact, mediated by specific receptors, allows SCs to integrate signaling by growth and differentiation factors with cytoskeleton dynamics and to modulate the strength of matrix attachments. This interplay is pivotal throughout myelination and in myelin maintenance. Laminins are crucial for radial axonal sorting, acting through and being dependent on the β1 integrin subunit and dystroglycan receptors in distinct sequential steps [11,80–82]. At later stages, internodal and nodal organizations depend on SC-expressed dystroglycan [83]. Defects in dystroglycan-deficient mice include abnormal myelin sheath folding, disorganized microvilli, and reduced sodium channel density. Disrupted cytoplasmic compartmentalization of myelinating SCs is a prominent contributing feature [84]. In different SC compartments, dystroglycan acts as an anchor for specific proteins required for myelin stability, including DRP2 (dystrophin related protein-2) and the dysmyelinating CMT4F culprit periaxin [85], which are localized in apposition between the myelin and basal lamina [86]. Cleavage by matrix metalloproteinases 2 and 9 modulates the molecular composition of these complexes and the size of myelinating SC domains [86]. In parallel to myelination, the SC laminin receptor integrin α6-β4 is upregulated by axonal signals and localizes at the abaxonal surface of myelinating SCs, opposite to the basal lamina [87]. SC-deficiency of α6-β4 integrin leads to abnormal myelin sheath folding in aged mice [88], indicating that this integrin receptor pair plays a crucial role in myelin stability, partly in cooperation with dystroglycan. Interestingly, integrin α6-β4 binds to the demyelinating disease-causing PMP22, possibly contributing to the underlying disease mechanism [89]. Consistent with the pivotal role of laminins in PNS myelination, SCs lacking all laminins due to deficiency in the γ1-subunit display a discontinuous basal lamina and radial sorting is blocked [90]. Importantly, these experiments indicated crucial crosstalk between laminin and PI3K signaling. Collagens are also involved in myelination [91]. Collagen XV-deficient mice show a mild peripheral nerve maturation defect and augment laminin4α-deficiency effects, causing permanent blocks in radial sorting compared to a delay in single laminin4α mutants.

Signaling and the SC cytoskeleton

Myelination is a complex mechanical process that depends on rearrangements of the actin cytoskeleton coupled to cross-regulatory synergistic growth factor- and ECM-mediated signaling. Inhibition of actin polymerization [92] or of myosin II activity, a key regulator of actin cytoskeleton dynamics [93], impairs myelination in SC–neuron cocultures (Figure 5). Furthermore, sub-membranous cytoskeletal spectrins act as myelination modulators by linking signals from axons to the SC actin cytoskeleton, probably mediated by polarized Necl-4 enrichment at the SC–axon interface and F-actin stimulation [94]. F-actin rearrangement is also regulated by small RhoGTPases [95]. Cdc42 (cell division cycle-42) acts downstream of NRG1 and stimulates SC proliferation crucial for radial sorting [96]. Mutations affecting Frabin/FGD4, an activator of Cdc42, lead to demyelinating CMT4H [97], consistent with an additional functional role of Cdc42 in later myelination stages [98]. Rac1 (Ras-related C3 botulinum substrate-1) mediates β1 integrin signaling and promotes SC process extension and radial lamellae formation essential for radial sorting [96,99]. During Wallerian degeneration, Rac1 regulates F-actin polymerization and myelin degradation [100]. Downstream of Cdc42, Wiskott–Aldrich syndrome protein (N-WASP) controls F-actin nucleation and branching. Coherent with this notion, SC-expressed N-WASP is required for lamellipodia formation, membrane wrapping, and proper myelination [101,102].

Signaling from integrins and neuregulins can activate RhoGTPases [98], a crucial process for SC myelination, but the molecules that relay the signals in-between are largely unknown. The ILK (integrin-linked kinase)–PINCH (particularly interesting new cystidine-histidine-rich protein)–parvin (IPP) complex forms a hub that physically and functionally bridges growth factor and integrin signals with the actin cytoskeleton, including the regulation of small RhoGTPases [103]. In PNS myelination, ILK negatively regulates Rho kinase (ROCK) to foster SC process extension and to trigger radial axonal sorting, consistent with impaired radial sorting in SC-specific ILK-deficient mice, a phenotype that is ameliorated by ROCK inhibition [104]. ILK is also required for the transition from promyelinating to the myelinating SC phenotype during remyelination, including correct AKT activation, but not for myelin maintenance.

Concluding remarks

We are witnessing exciting progress in PNS myelination research. Genetics has been instrumental in gathering physiologically-relevant data, and an increasing number of studies are investigating molecular aspects of myelin maintenance and SC dedifferentiation and redifferentiation. Further advances will come from comparing the lessons learned from development to the complex processes taking place after injury, including through the study of demyelination/remyelination paradigms that avoid acute damage to axons, as well as assessments of inflammatory and non-inflammatory neuropathy disease models. New fields have emerged that explore overarching regulatory mechanisms such as proteolytic modifiers that probably affect multiple targets, similar to epigenetic mechanisms including histone code regulators and regulatory miRNAs. Recent studies have also revealed how SC mitochondrial metabolism is important for peripheral nerve function and axonal survival [105], and how SC polarity, metabolism, and myelination regulation may be intimately linked [106], and thus deserve further attention. Conceptually, SC polarity with its multiple facets, including the regulation of specific local membranes and signaling complex accumulation and activation, remains a fruitful basis for working hypotheses. This relates further to early SC development, demyelination and remyelination, which all share morphological resemblance with mesenchymal–epithelial and epithelial–mesenchymal transitions. Furthermore, the long-standing question of how the myelin sheath is mechanistically generated still awaits satisfactory answers, as does a thorough

Box 1. Outstanding questions

- What are the similarities and differences between the molecular mechanisms that direct developmental PNS myelination, myelin maintenance, demyelination and remyelination in health and disease? – (note that use of the term 'myelination' within the following points of the text box refers to all of these different settings). To what extent are these control mechanisms modulated by axon damage and inflammatory components after injury and in disease?
- What is the role of non-myelinating SCs (in Remak bundles) in myelination?
- What is the influence of endoneurial fibroblasts in myelination?
- How is the actual myelination process (e.g. membrane wrapping, myelin compaction, and construction of myelin compartments) mechanistically achieved?
- What are the relative physiological contributions of inhibitory mechanisms versus activators in myelination?
- To what extent, and involving which molecular players, does electrical activity regulate myelination [109]?
- How are metabolic processes regulating essential SC–axon interactions [8,105] and what is their relevance for myelination?
- How is polarized (and locally-restricted) protein targeting and secretion achieved, and what are the consequences of such polarization for signaling and myelination?
- What is the spatiotemporal distribution of signaling molecules (membrane-bound and soluble) within the highly compartmentalized myelinating SC, and how is this regulated?
- What is the turnover of individual lipids and proteins within myelinating SCs? How is this process regulated?
- How are different signals integrated by SCs to orchestrate the myelination program? Much is known about the basic receptors and signaling cascades that are involved, however, the relative contributions and crosstalk between individual pathways at given time-points remain to be clarified.
- To what extent is regulated proteolysis involved in the control of myelination? Which proteases and targets are involved?
- How are lipid and myelin protein synthesis molecularly coordinated?
- What is the level of control on myelination by epigenetic mechanisms?
- How important are local concentrations of the various membrane-bound and non-membrane-bound isoforms of NRG1 in the regulation of SC biology and myelination? How is secretion and processing of different NRG1 isoforms regulated?

understanding of mechanisms that are responsible for the maintenance of this structure (Box 1). By extension, elucidating all myelin components [107] and understanding how they are added to myelin membranes through development and in nerve homeostasis remains a challenge, as does, conversely, how old myelin proteins and lipids are shuttled away from myelin through appropriate degradation pathways. It is anticipated that a refined understanding of the molecular basis of myelination will aid in the development of novel treatment strategies for debilitating disorders that involve deregulation of myelination, such as neuropathies in the PNS and multiple sclerosis in the CNS.

Acknowledgments

We apologize to those colleagues whose work we could not cite due to length restrictions. We thank current and past members of the Suter laboratory for fruitful discussions, and the Swiss National Science Foundation and the National Center of Competence in Research (NCCR), Neural Plasticity and Repair for funding support.

References

1 Zalc, B. *et al.* (2008) The origin of the myelination program in vertebrates. *Curr. Biol.* 18, R511–R512
2 Nave, K.A. and Trapp, B.D. (2008) Axon–glial signaling and the glial support of axon function. *Annu. Rev. Neurosci.* 31, 535–561
3 Taveggia, C. *et al.* (2010) Signals to promote myelin formation and repair. *Nat. Rev. Neurol.* 6, 276–287
4 Dyck, P.J. and Thomas, P.K. (2005) *Peripheral Neuropathy*, Elsevier Saunders
5 Jessen, K.R. and Mirsky, R. (2005) The origin and development of glial cells in peripheral nerves. *Nat. Rev. Neurosci.* 6, 671–682
6 Salzer, J.L. *et al.* (2008) Molecular domains of myelinated axons in the peripheral nervous system. *Glia* 56, 1532–1540
7 Nave, K.A. (2010) Myelination and support of axonal integrity by glia. *Nature* 468, 244–252
8 Nave, K.A. (2010) Myelination and the trophic support of long axons. *Nat. Rev. Neurosci.* 11, 275–283
9 Adameyko, I. *et al.* (2009) Schwann cell precursors from nerve innervation are a cellular origin of melanocytes in skin. *Cell* 139, 366–379
10 Birchmeier, C. and Nave, K.A. (2008) Neuregulin-1, a key axonal signal that drives Schwann cell growth and differentiation. *Glia* 56, 1491–1497
11 Berti, C. *et al.* (2011) Non-redundant function of dystroglycan and β1 integrins in radial sorting of axons. *Development* 138, 4025–4037
12 Mirsky, R. *et al.* (2008) Novel signals controlling embryonic Schwann cell development, myelination and dedifferentiation. *J. Peripher. Nerv. Syst.* 13, 122–135
13 Suter, U. and Scherer, S.S. (2003) Disease mechanisms in inherited neuropathies. *Nat. Rev. Neurosci.* 4, 714–726
14 Svaren, J. and Meijer, D. (2008) The molecular machinery of myelin gene transcription in Schwann cells. *Glia* 56, 1541–1551
15 Jagalur, N.B. *et al.* (2011) Functional dissection of the *Oct6* Schwann cell enhancer reveals an essential role for dimeric Sox10 binding. *J. Neurosci.* 31, 8585–8594
16 Bremer, M. *et al.* (2011) Sox10 is required for Schwann cell homeostasis and myelin maintenance in the adult peripheral nerve. *Glia* 59, 1022–1032
17 Finzsch, M. *et al.* (2010) Sox10 is required for Schwann cell identity and progression beyond the immature Schwann cell stage. *J. Cell Biol.* 189, 701–712
18 Kao, S.C. *et al.* (2009) Calcineurin/NFAT signaling is required for neuregulin-regulated Schwann cell differentiation. *Science* 323, 651–654
19 Giese, K.P. *et al.* (1992) Mouse *P0* gene disruption leads to hypomyelination, abnormal expression of recognition molecules, and degeneration of myelin and axons. *Cell* 71, 565–576
20 He, Y. *et al.* (2010) Yy1 as a molecular link between neuregulin and transcriptional modulation of peripheral myelination. *Nat. Neurosci.* 13, 1472–1480
21 Nickols, J.C. *et al.* (2003) Activation of the transcription factor NF-kappaB in Schwann cells is required for peripheral myelin formation. *Nat. Neurosci.* 6, 161–167
22 Limpert, A.S. and Carter, B.D. (2010) Axonal neuregulin 1 type III activates NF-kappaB in Schwann cells during myelin formation. *J. Biol. Chem.* 285, 16614–16622
23 Chen, Y. *et al.* (2011) HDAC-mediated deacetylation of NF-kappaB is critical for Schwann cell myelination. *Nat. Neurosci.* 14, 437–441
24 Jacob, C. *et al.* (2011) HDAC1 and HDAC2 control the transcriptional program of myelination and the survival of Schwann cells. *Nat. Neurosci.* 14, 429–436
25 Jacob, C. *et al.* (2011) How histone deacetylases control myelination. *Mol. Neurobiol.* 44, 303–312
26 Verheijen, M.H. *et al.* (2009) SCAP is required for timely and proper myelin membrane synthesis. *Proc. Natl. Acad. Sci. U.S.A.* 106, 21383–21388
27 Saher, G. *et al.* (2009) Cholesterol regulates the endoplasmic reticulum exit of the major membrane protein P0 required for peripheral myelin compaction. *J. Neurosci.* 29, 6094–6104
28 Giambonini-Brugnoli, G. *et al.* (2005) Distinct disease mechanisms in peripheral neuropathies due to altered peripheral myelin protein 22 gene dosage or a *Pmp22* point mutation. *Neurobiol. Dis.* 18, 656–668
29 Nadra, K. *et al.* (2008) Phosphatidic acid mediates demyelination in *Lpin1* mutant mice. *Genes Dev.* 22, 1647–1661

30 Le, N. *et al.* (2005) Nab proteins are essential for peripheral nervous system myelination. *Nat. Neurosci.* 8, 932–940
31 Mager, G.M. *et al.* (2008) Active gene repression by the Egr2.NAB complex during peripheral nerve myelination. *J. Biol. Chem.* 283, 18187–18197
32 Parkinson, D.B. *et al.* (2008) c-Jun is a negative regulator of myelination. *J. Cell Biol.* 181, 625–637
33 Woodhoo, A. *et al.* (2009) Notch controls embryonic Schwann cell differentiation, postnatal myelination and adult plasticity. *Nat. Neurosci.* 12, 839–847
34 Jessen, K.R. and Mirsky, R. (2008) Negative regulation of myelination: relevance for development, injury, and demyelinating disease. *Glia* 56, 1552–1565
35 Pereira, J.A. *et al.* (2010) Dicer in Schwann cells is required for myelination and axonal integrity. *J. Neurosci.* 30, 6763–6775
36 Yun, B. *et al.* (2010) MicroRNA-deficient Schwann cells display congenital hypomyelination. *J. Neurosci.* 30, 7722–7728
37 Bremer, J. *et al.* (2010) Ablation of Dicer from murine Schwann cells increases their proliferation while blocking myelination. *PLoS ONE* 5, e12450
38 Verrier, J.D. *et al.* (2009) Peripheral myelin protein 22 is regulated post-transcriptionally by miRNA-29a. *Glia* 57, 1265–1279
39 Bhanji, R.A. *et al.* (2007) Clinical and serological features of patients with autoantibodies to GW/P bodies. *Clin. Immunol.* 125, 247–256
40 Salzer, J.L. (2003) Polarized domains of myelinated axons. *Neuron* 40, 297–318
41 Poliak, S. *et al.* (2002) Distinct claudins and associated PDZ proteins form different autotypic tight junctions in myelinating Schwann cells. *J. Cell Biol.* 159, 361–372
42 Mellman, I. and Nelson, W.J. (2008) Coordinated protein sorting, targeting and distribution in polarized cells. *Nat. Rev. Mol. Cell Biol.* 9, 833–845
43 Ozcelik, M. *et al.* (2010) Pals1 is a major regulator of the epithelial-like polarization and the extension of the myelin sheath in peripheral nerves. *J. Neurosci.* 30, 4120–4131
44 Chan, J.R. *et al.* (2006) The polarity protein Par-3 directly interacts with p75NTR to regulate myelination. *Science* 314, 832–836
45 Lewallen, K.A. *et al.* (2011) Assessing the role of the cadherin/catenin complex at the Schwann cell–axon interface and in the initiation of myelination. *J. Neurosci.* 31, 3032–3043
46 Xiao, J. *et al.* (2009) The role of neurotrophins in the regulation of myelin development. *Neurosignals* 17, 265–276
47 Tawk, M. *et al.* (2011) Wnt/beta-catenin signaling is an essential and direct driver of myelin gene expression and myelinogenesis. *J. Neurosci.* 31, 3729–3742
48 Suter, U. (2007) Phosphoinositides and Charcot–Marie–Tooth disease: new keys to old questions. *Cell. Mol. Life Sci.* 64, 3261–3265
49 Bolis, A. *et al.* (2009) Dlg1, Sec8, and Mtmr2 regulate membrane homeostasis in Schwann cell myelination. *J. Neurosci.* 29, 8858–8870
50 Cotter, L. *et al.* (2010) Dlg1–PTEN interaction regulates myelin thickness to prevent damaging peripheral nerve overmyelination. *Science* 328, 1415–1418
51 Roberts, R.C. *et al.* (2010) Mistargeting of SH3TC2 away from the recycling endosome causes Charcot–Marie–Tooth disease type 4C. *Hum. Mol. Genet.* 19, 1009–1018
52 Stendel, C. *et al.* (2010) SH3TC2, a protein mutant in Charcot–Marie–Tooth neuropathy, links peripheral nerve myelination to endosomal recycling. *Brain* 133, 2462–2474
53 Taveggia, C. *et al.* (2005) Neuregulin-1 type III determines the ensheathment fate of axons. *Neuron* 47, 681–694
54 Michailov, G.V. *et al.* (2004) Axonal neuregulin-1 regulates myelin sheath thickness. *Science* 304, 700–703
55 Goebbels, S. *et al.* (2010) Elevated phosphatidylinositol 3,4,5-trisphosphate in glia triggers cell-autonomous membrane wrapping and myelination. *J. Neurosci.* 30, 8953–8964
56 Quintes, S. *et al.* (2010) Neuron–glia signaling and the protection of axon function by Schwann cells. *J. Peripher. Nerv. Syst.* 15, 10–16
57 Newbern, J.M. *et al.* (2011) Specific functions for ERK/MAPK signaling during PNS development. *Neuron* 69, 91–105
58 Grossmann, K.S. *et al.* (2009) The tyrosine phosphatase Shp2 (PTPN11) directs Neuregulin-1/ErbB signaling throughout Schwann cell development. *Proc. Natl. Acad. Sci. U.S.A.* 106, 16704–16709
59 Atanasoski, S. *et al.* (2006) ErbB2 signaling in Schwann cells is mostly dispensable for maintenance of myelinated peripheral nerves and proliferation of adult Schwann cells after injury. *J. Neurosci.* 26, 2124–2131
60 Fricker, F.R. *et al.* (2009) Sensory axon-derived neuregulin-1 is required for axoglial signaling and normal sensory function but not for long-term axon maintenance. *J. Neurosci.* 29, 7667–7678
61 Fricker, F.R. *et al.* (2011) Axonally derived neuregulin-1 is required for remyelination and regeneration after nerve injury in adulthood. *J. Neurosci.* 31, 3225–3233
62 Willem, M. *et al.* (2006) Control of peripheral nerve myelination by the beta-secretase BACE1. *Science* 314, 664–666
63 Hu, X. *et al.* (2006) Bace1 modulates myelination in the central and peripheral nervous system. *Nat. Neurosci.* 9, 1520–1525
64 La Marca, R. *et al.* (2011) TACE (ADAM17) inhibits Schwann cell myelination. *Nat. Neurosci.* 14, 857–865
65 Hu, X. *et al.* (2008) Genetic deletion of BACE1 in mice affects remyelination of sciatic nerves. *FASEB J.* 22, 2970–2980
66 Ohno, M. *et al.* (2009) Nardilysin regulates axonal maturation and myelination in the central and peripheral nervous system. *Nat. Neurosci.* 12, 1506–1513
67 Syed, N. *et al.* (2010) Soluble neuregulin-1 has bifunctional, concentration-dependent effects on Schwann cell myelination. *J. Neurosci.* 30, 6122–6131
68 Wakatsuki, S. *et al.* (2009) Roles of meltrin-beta/ADAM19 in progression of Schwann cell differentiation and myelination during sciatic nerve regeneration. *J. Biol. Chem.* 284, 2957–2966
69 Sagane, K. *et al.* (2005) Ataxia and peripheral nerve hypomyelination in ADAM22-deficient mice. *BMC Neurosci.* 6, 33
70 Ozkaynak, E. *et al.* (2010) Adam22 is a major neuronal receptor for Lgi4-mediated Schwann cell signaling. *J. Neurosci.* 30, 3857–3864
71 Bermingham, J.R., Jr *et al.* (2006) The claw paw mutation reveals a role for Lgi4 in peripheral nerve development. *Nat. Neurosci.* 9, 76–84
72 Maurel, P. *et al.* (2007) Nectin-like proteins mediate axon Schwann cell interactions along the internode and are essential for myelination. *J. Cell Biol.* 178, 861–874
73 Spiegel, I. *et al.* (2007) A central role for Necl4 (SynCAM4) in Schwann cell–axon interaction and myelination. *Nat. Neurosci.* 10, 861–869
74 Park, J. *et al.* (2008) Disruption of Nectin-like 1 cell adhesion molecule leads to delayed axonal myelination in the CNS. *J. Neurosci.* 28, 12815–12819
75 Schachner, M. and Bartsch, U. (2000) Multiple functions of the myelin-associated glycoprotein MAG (siglec-4a) in formation and maintenance of myelin. *Glia* 29, 154–165
76 Bremer, J. *et al.* (2010) Axonal prion protein is required for peripheral myelin maintenance. *Nat. Neurosci.* 13, 310–318
77 Monk, K.R. *et al.* (2009) A G protein-coupled receptor is essential for Schwann cells to initiate myelination. *Science* 325, 1402–1405
78 Monk, K.R. *et al.* (2011) Gpr126 is essential for peripheral nerve development and myelination in mammals. *Development* 138, 2673–2680
79 Arthur-Farraj, P. *et al.* (2011) Mouse Schwann cells need both NRG1 and cyclic AMP to myelinate. *Glia* 59, 720–733
80 Feltri, M.L. and Wrabetz, L. (2005) Laminins and their receptors in Schwann cells and hereditary neuropathies. *J. Peripher. Nerv. Syst.* 10, 128–143
81 Feltri, M.L. *et al.* (2002) Conditional disruption of beta 1 integrin in Schwann cells impedes interactions with axons. *J. Cell Biol.* 156, 199–209
82 Yang, D. *et al.* (2005) Coordinate control of axon defasciculation and myelination by laminin-2 and -8. *J. Cell Biol.* 168, 655–666
83 Saito, F. *et al.* (2003) Unique role of dystroglycan in peripheral nerve myelination, nodal structure, and sodium channel stabilization. *Neuron* 38, 747–758
84 Court, F.A. *et al.* (2009) A laminin-2, dystroglycan, utrophin axis is required for compartmentalization and elongation of myelin segments. *J. Neurosci.* 29, 3908–3919
85 Sherman, D.L. *et al.* (2001) Specific disruption of a Schwann cell dystrophin-related protein complex in a demyelinating neuropathy. *Neuron* 30, 677–687

86 Court, F.A. *et al.* (2011) MMP2-9 cleavage of dystroglycan alters the size and molecular composition of Schwann cell domains. *J. Neurosci.* 31, 12208–12217
87 Feltri, M.L. *et al.* (1994) Beta 4 integrin expression in myelinating Schwann cells is polarized, developmentally regulated and axonally dependent. *Development* 120, 1287–1301
88 Nodari, A. *et al.* (2008) Alpha6beta4 integrin and dystroglycan cooperate to stabilize the myelin sheath. *J. Neurosci.* 28, 6714–6719
89 Amici, S.A. *et al.* (2006) Peripheral myelin protein 22 is in complex with alpha6beta4 integrin, and its absence alters the Schwann cell basal lamina. *J. Neurosci.* 26, 1179–1189
90 Yu, W.M. *et al.* (2005) Schwann cell-specific ablation of laminin gamma1 causes apoptosis and prevents proliferation. *J. Neurosci.* 25, 4463–4472
91 Rasi, K. *et al.* (2010) Lack of collagen XV impairs peripheral nerve maturation and, when combined with laminin-411 deficiency, leads to basement membrane abnormalities and sensorimotor dysfunction. *J. Neurosci.* 30, 14490–14501
92 Fernandez-Valle, C. *et al.* (1997) Actin plays a role in both changes in cell shape and gene-expression associated with Schwann cell myelination. *J. Neurosci.* 17, 241–250
93 Wang, H. *et al.* (2008) Myosin II has distinct functions in PNS and CNS myelin sheath formation. *J. Cell Biol.* 182, 1171–1184
94 Susuki, K. *et al.* (2011) Schwann cell spectrins modulate peripheral nerve myelination. *Proc. Natl. Acad. Sci. U.S.A.* 108, 8009–8014
95 Feltri, M.L. *et al.* (2008) The function of RhoGTPases in axon ensheathment and myelination. *Glia* 56, 1508–1517
96 Benninger, Y. *et al.* (2007) Essential and distinct roles for cdc42 and rac1 in the regulation of Schwann cell biology during peripheral nervous system development. *J. Cell Biol.* 177, 1051–1061
97 Stendel, C. *et al.* (2007) Peripheral nerve demyelination caused by a mutant Rho GTPase guanine nucleotide exchange factor, Frabin/FGD4. *Am. J. Hum. Genet.* 81, 158–164
98 Krause, S. *et al.* (2008) Small Rho GTPases are key regulators of peripheral nerve biology in health and disease. *J. Peripher. Nerv. Syst.* 13, 188–199
99 Nodari, A. *et al.* (2007) β1 Integrin activates Rac1 in Schwann cells to generate radial lamellae during axonal sorting and myelination. *J. Cell Biol.* 177, 1063–1075
100 Jung, J. *et al.* (2011) Actin polymerization is essential for myelin sheath fragmentation during Wallerian degeneration. *J. Neurosci.* 31, 2009–2015
101 Novak, N. *et al.* (2011) N-WASP is required for membrane wrapping and myelination by Schwann cells. *J. Cell Biol.* 192, 243–250
102 Jin, F. *et al.* (2011) N-WASp is required for Schwann cell cytoskeletal dynamics, normal myelin gene expression and peripheral nerve myelination. *Development* 138, 1329–1337
103 Legate, K.R. *et al.* (2006) ILK, PINCH and parvin: the tIPP of integrin signalling. *Nat. Rev. Mol. Cell Biol.* 7, 20–31
104 Pereira, J.A. *et al.* (2009) Integrin-linked kinase is required for radial sorting of axons and Schwann cell remyelination in the peripheral nervous system. *J. Cell Biol.* 185, 147–161
105 Viader, A. *et al.* (2011) Schwann cell mitochondrial metabolism supports long-term axonal survival and peripheral nerve function. *J. Neurosci.* 31, 10128–10140
106 Beirowski, B. *et al.* (2011) Sir-two-homolog 2 (Sirt2) modulates peripheral myelination through polarity protein Par-3/atypical protein kinase C (aPKC) signaling. *Proc. Natl. Acad. Sci. U.S.A.* 108, E952–E961
107 Patzig, J. *et al.* (2011) Quantitative and integrative proteome analysis of peripheral nerve myelin identifies novel myelin proteins and candidate neuropathy loci. *J. Neurosci.* 31, 16369–16386
108 Grove, M. *et al.* (2007) FAK is required for axonal sorting by Schwann cells. *J. Cell Biol.* 176, 277–282
109 Stevens, B. and Fields, R.D. (2000) Response of Schwann cells to action potentials in development. *Science* 287, 2267–2271