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REVIEW

Myelin Biology

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Abstract

Myelin is a key evolutionary specialization and adaptation of vertebrates formed by the plasma membrane of glial cells, which insulate axons in the nervous system. Myelination not only allows rapid and efficient transmission of electric impulses in the axon by decreasing capacitance and increasing resistance but also influences axonal metabolism and the plasticity of neural circuits. In this review, we will focus on Schwann cells, the glial cells which form myelin in the peripheral nervous system. Here, we will describe the main extrinsic and intrinsic signals inducing Schwann cell differentiation and myelination and how myelin biogenesis is achieved. Finally, we will also discuss how the study of human disorders in which molecules and pathways relevant for myelination are altered has enormously contributed to the current knowledge on myelin biology.

Keywords Schwann cell · Myelin · Peripheral nervous system · Peripheral neuropathy

Abbreviations

ADAM17	ADAM metallopeptidase domain 17
Akt	V-Akt murine thymoma viral oncogene-like protein
AMPK	5′-Adenosine monophosphate- activated protein kinase
BAF	Brahma-associated factor
cAMP	Cyclic adenosine monophosphate
Clp	Claw paw
CNS	Central nervous system
Crb3	Crumbs cell polarity complex component 3
c-Jun	Jun proto-oncogene
AP-1	Transcription factor subunit
CADM	Cell adhesion molecule
CMT	Charcot–Marie–Tooth
CX32	Connexin 32
DG	Dystroglycan
Dlg1/SAP97	Discs large 1/synapse-associated protein 97
DRG	Dorsal root ganglia
DRP	Dystrophin-related protein 2
ECM	Extracellular matrix
Egr2	Early growth response 2
Erb-B2	Receptor tyrosine kinase 2
GJB1	Gap junction protein beta 1, the Connexin 32 gene
GPR126	G protein-coupled receptor 126
GPR44	G protein-coupled receptor 44
HDAC	Histone deacetylase
HMN	Hereditary motor neuropathy
HSAN	Hereditary sensory and autonomic neuropathy
HSN	Hereditary sensory neuropathy
IMA	Inner mesaxon
IPL	Intraperiod line
IPN	Inherited peripheral neuropathy
iSCs	Immature Schwann cells
JAG1	Jagged 1
MAG	Myelin-associated glycoprotein
MAGUK	Membrane-associated guanylate like kinase
MAPK	Mitogen-activated protein kinase
MBP	Myelin basic protein
MCT1	Monocarboxylate transporter 1
MPZ	Myelin protein zero gene
MTMR	Myotubularin-related
mTOR	Mechanistic target of rapamycin kinase
MUPP1	Multi-PDZ domain protein
NDRG1	N-Myc downstream regulated 1
Necl	Nectin-like protein
NFATc4	Nuclear factor of activated T cells 4
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells

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NF186	Neurofascin 186
NF2	Neurofibromin
Notch-1	Notch homolog 1, translocation-associated
Nrcam	Neuronal cell adhesion molecule
NRG1	Neuregulin
N-WASP	Wiskott–Aldrich syndrome protein
Lgi4	Leucine-rich repeat LGI family member 4
LKB1	Liver kinase B1
L-PGDS	Prostaglandin D2 synthase
Oct6	(Pou3f1, POU Class 3 Homeobox 1)
OMA	Outer mesaxon
Pals1/MPP5	Membrane palmitoylated protein 5
Par3	Partitioning defective protein
PatJ	PATJ crumbs cell polarity complex component
PGD2	Prostaglandin D2
PLCγ	Phospholipase C gamma
PKA	Protein kinase A
PKC	Protein kinase C
PMP22	Peripheral myelin protein 22
PNS	Peripheral nervous system
PrP	Prion protein
PTEN	Phosphatase and tensin homolog
P0	Myelin protein zero
RBPJ	Recombination signal binding protein for immunoglobulin kappa J region
REDD1	Regulated in development and DNA damage responses 1
PIK3CA	Phosphatidyl-inositol 3 kinase (PI3K) class I
PRX	Periaxin
PTEN	Phosphatase and tensin homolog
SC	Schwann cells
SCPs	Schwann cell precursors
SGK1	Serum/glucocorticoid regulated kinase 1
SHP2	Src homology region 2 (SH2)-containing protein tyrosine phosphatase 2
Sox10	SRY-box transcription factor 10
SREBP	Sterol regulatory element-binding protein
TACE	TNF-alpha convertase enzyme
TAZ	YAP co-activator with PDZ binding domain
TEAD	TEA domain transcription factor
TF	Transcription factor
TSC	Tuberous sclerosis complex
YAP	Transcription co-activator Yes-associated protein 1
YY1	Yin-Yang transcription factor 1
Zeb2	Zinc finger E-box binding homeobox 2
ZO-1	Tight junction protein 1

Organization of Myelinated Fibers in the PNS

In the peripheral nervous system (PNS), myelin is formed by the spiral wrapping of the Schwann cell plasma membrane around the axon [1–3]. In myelinated fibers, both compact and non-compact myelin are distinguished (Fig. 1a, b). Compact myelin represents the "insulating" Schwann cell membrane-based structure along the internode, the portion of the axon between two consecutive nodes of Ranvier. The compaction is realized through the exclusion of the cytoplasm from the Schwann cell intracellular leaflets, where the myelin basic protein (MBP) neutralizes the negative charges of phospholipids (for example of phosphatidylserine) [1, 4]. In addition, the extracellular domains of adjacent consecutive wrapping layers are connected by homophilic and heterophilic interactions of transmembrane proteins such as myelin protein zero (P0) and peripheral myelin protein 22 (PMP22) [5]. Thus, at the ultrastructural analysis, compact myelin appears as an alternation of an electrodense line called the major dense line (MDL), which corresponds to the apposition of the cytoplasmic leaflets, and the intraperiod line (IPL), which is formed by the two apposed extracellular leaflets in the spiral wrap [1] (Fig. 1c).

On the contrary, non-compact myelin refers to specific structures of a myelinated fiber where the cytoplasm is more abundant. Schmidt-Lanterman incisures (SLIs) are cytoplasmic-rich structures interspersed along the internode particularly of large diameter fibers and realize the radial communication between different layers of the Schwann cell membrane [1]. SLIs are formed by autotypic tight, adherens and gap junctions containing, among others, E-cadherin, beta-catenin, p120 catenin, claudins, MUPP1 (multi PDZ domain protein), ZO-1 (tight junction protein 1), and CX32 (connexin 32) [6–8]. Other regions of non-compact myelin include the inner and outer mesaxons (IMA and OMA, Fig. 1b), which correspond to the innermost and outermost layer of the Schwann cell membrane, respectively [9].

In a myelinated fiber, the lateral edges of the Schwann cell membrane open up in finger-like structures called paranodal loops, which flank the node of Ranvier, and in the microvilli, which face the node [1, 3, 9, 10]. Paranodal loops are kept together by autotypic tight, adherens, and gap junctions and are tightly attached to the underneath axolemma through septate-like junctions. Here, Caspr (contactin-associated protein, paranodin) and contactin, both in the axolemma, complex with NF155 (Neurofascin) in the Schwann cell adaxonal membrane apposing to the axon in the periaxonal space. Septate-like junctions generate a physical barrier which impedes the diffusion of juxtaparanodal potassium channels (Kv1.1 and Kv1.2) into

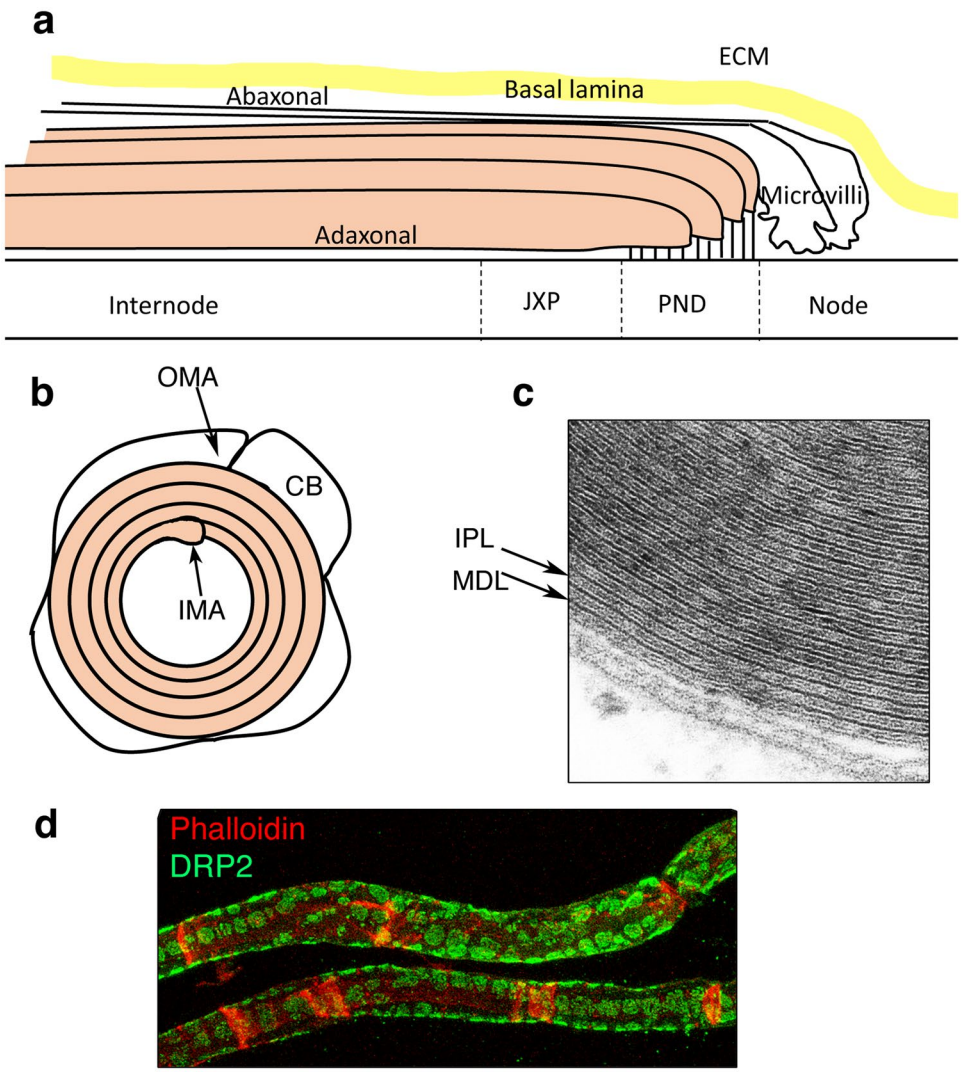

Fig. 1 **a** Schematic representation of a myelinated fiber in a longitudinal view. ECM, extracellular matrix; JXP, juxaparanodal domain; PND, paranodal domain. **b** Schematic representation of a myelinated fiber in a transverse section. CB, Cajal bands; IMA, inner mesaxon; OMA, outer mesaxon. **c** Electron micrograph of a transverse section of a myelinated fiber, which shows at high magnification compact myelin with the alternation of an electrodense line, the major dense line (MDL), and the intraperiod line (IPL). **d** Example of immunofluorescence analysis of teased fibers from quadriceps nerves to detect F-actin (phalloidin staining in red) and appositions in the abaxonal Schwann cell membrane (DRP2 staining in green). Here, phalloidin marks Schmidt–Lanterman incisures and Cajal bands

the paranode. At the node, the clustering of voltage-gated sodium channels ($Na_v1.6$ in the adult) is realized through the interaction with axonal-membrane tethered proteins such as Nrcam and NF186, with glial proteins at microvilli (Gliomedin), and with ECM (extracellular matrix) proteins (phosphocan, tenascin, and versican proteoglycans). The intracellular domains of transmembrane proteins are connected to the underneath F-actin cytoskeleton by scaffolding proteins of the MAGUK (membrane associated guanylate-like kinase) and 4.1 families and by cytoskeleton associated proteins of the ankyrin and spectrin families. For further details on the molecular composition of these domains, we address the reader to seminal reviews on this topic [9–12].

The outermost region of a myelinated fiber is not uniform but interrupted by appositions between the abaxonal Schwann cell membrane (the layer facing ECM, which is opposite to the adaxonal membrane) and the outer layer of the compact myelin [13] (Fig. 1b, d). These contacts are formed by the interaction between the ECM and the βDG (dystroglycan)-DRP2 (dystrophyn-related 2)-PRX (Periaxin) complex, which intracellularly is linked to the F-actin cytoskeleton [14–17]. These membrane appositions thus form longitudinal cytoplasmic channels called Cajal bands, which represent fast tracks for transport of molecules and organelles from the perinuclear region to the periphery [13]. Consistent with this, these channels contain microtubules, intermediate filaments, and F-actin. Cajal bands are also enriched in caveolae-mediating endocytosis from the extracellular environment, thus suggesting that these structures are also relevant for Schwann cell metabolism [1, 4].

A myelinated fiber has a precise geometry with distinct functional domains formed by tightly regulated delivery and assembly of specific glial and axonal molecules. This structure is highly polarized, with both a radial and a longitudinal polarity [1, 10, 18, 19]. Longitudinal polarity is centered along the node of Ranvier and includes paranodal and juxtaparanodal regions moving toward the internode.

Radial polarity instead lies from the axon, to the adaxonal membrane, the compact myelin, and the abaxonal region of Schwann cells. This polarity resembles the epithelial cell polarity, where apical domains are usually facing a lumen and are separated from basolateral regions by tight and adherens junctions. In epithelial cells, a precise distribution of polarity complexes defines and maintains this domain organization with distinct apical (Par3-Par6-aPKC and Crb3-Pals1-PatJ) and basolateral (Scrib-Dlg1-Lgl) complexes separated by tight and adherens junctions [19]. These core complexes contribute to the cell and tissue morphogenesis during development building up distinct functional domains. From these highly ordered domains, signals are initiated and integrated as these core proteins control the precise delivery and trafficking of other proteins and effectors. Trafficking and polarized delivery also depend on the specific distribution of different phosphoinositide signaling species. For example, PtdIns(3,4,5)P_3 phosphoinositide is abundant at basolateral membranes [20].

The analogy between the organization of a myelinated fiber and of epithelial cells is sustained by the specific localization of polarity proteins at different membrane regions of a myelinated fiber. For example, during development, Par3 (partitioning defective protein) is localized at the adaxonal Schwann cell plasma membrane [21], whereas PatJ (PATJ crumbs cell polarity complex component) and Pals1/MPP5 (Membrane palmitoylated protein 5) have been mapped at SLIs and paranodal regions, where also PtdIns(4,5)P_2 is enriched [18, 22]. On the contrary, PtdIns(3,4,5)P_3 is mainly generated at the abaxonal membrane and participates in the integrin-mediated signaling from the ECM [22]. Finally, Crb3 (crumbs cell polarity complex component 3) has been shown to be localized at microvilli and it represents an important negative regulator of internodal myelin growth and extension [23] (see Schwann cell transduction, YAP/TAZ complex). Thus, by analogy with epithelial cell polarity, the abaxonal membrane of myelinated fibers is defined as a basolateral-like region, whereas the adaxonal membrane, SLI, paranodes and microvilli are considered apical-like regions [18, 19].

Schwann Cell Development

During early vertebrate development, neural crest cells delaminate from the neural tube, proliferate, and migrate to generate a broad spectrum of cell types including, among others, Schwann cells, melanocytes, sympathetic neurons, sensory neurons, and skeletal and connective tissues of the head [24–26]. The cell fate largely depends from the region of origin of the neural tube from which neural crest cells migrate. These regions are defined in an anterior–posterior axis direction as cranial, cardiac, vagal, trunk, and sacral. In particular, Schwann cells, dorsal root ganglia (DRG) sensory neurons, sympathetic neurons, and satellite cells associated with sensory neurons, all originate from ventrally migrating trunk neural crest cells [27].

Schwann cells then undergo to a developmental process including two main intermediate stages: Schwann cell precursors (SCPs) and immature Schwann cells (iSCs). SCPs are found among the axons of developing nerves from which they strictly depend for survival and proliferation. At this stage, at E (embryonic stage)12–13 in the mouse and E14–15 in the rat, SCPs and developing axons are not surrounded by connective tissue and do not have blood structures to supply them [24–26]. Surprisingly, SCPs do not influence axons to growth and to reach the target [28, 29]. In mouse mutants lacking SCPs, axons grow normally but are defasciculated at the nerve terminal with altered branching and sprouting [29]. On the contrary, at later stages, DRG sensory neurons and motor neurons die, suggesting that glial cells are crucial to provide trophic support to axons [25]. Similarly to neural crest cells, SCPs maintain an extraordinary multipotency and plasticity as they can generate melanocytes, sensory neurons, parasympathetic neurons, and fibroblasts, which will constitute the "mature" endoneurium [25, 30]. Ultimately, SCPs generate iSCs, which orchestrate radial sorting, a prerequisite for differentiation and myelination [24–26, 31]. Radial sorting is the process by which Schwann cells segregate large caliber axons destined to be myelinated away from small caliber axons. These latter form Remak bundles, where non-myelin forming Schwann cells ensheath multiple axons, contrary to myelin-forming Schwann cells which myelinate a single internode in a 1:1 relationship with the axon. An extensive description of this process is reviewed by Dr. Previtali in this issue. iSCs also communicate with and influence the fate of mesenchymal cells in the endo-, peri-, and epineurium, thus contributing to generate the mature structure of the nerve. At this stage, iSCs become dependent not only from axons but also from the ECM that they contribute to generate and are also capable to respond to their own signals in an autocrine manner.

Main axonal and ECM-derived signaling and pathways promoting the transition through these developmental stages have been recently described in a number of excellent and elegant reviews as well as in this issue [24–26, 31, 32]. Here, we will specifically discuss signaling pathways that promote the transition of iSCs to pro-myelinating and fully differentiated myelin-forming Schwann cells.

Transcriptional Regulation of Myelination

Schwann cell differentiation into a myelin-forming phenotype requires a sequential activation of transcription factors (TFs). In the transition to a pro-myelinating phenotype,

NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells), Oct6 (Pou3f1, POU class 3 homeobox 1), Brn2 (Pou3f2, POU class 3 homeobox 2), Sox10 (SRY-box transcription factor 10), NFATc4 (nuclear factor of activated T cells 4), and YY1 (Yin-Yang transcription factor 1) are all upregulated and activated [33, 34]. Of note, NF-kB is required for Schwann cell myelination in vitro, whereas its role in vivo is unclear [35]. Sox10 activates Oct6, which together with Brn2 promote the expression and activation of Egr2 (early growth response 2/Krox20) [36]. Krox20, the master transcription factor of myelination, is also activated by NFATc4 and YY1, cooperatively with Sox10 [37–39] and by Tead1 (TEA domain) with YAP/TAZ co-activators downstream of the tumor suppressor Hippo signaling pathway [40].

Schwann cells express Sox10 at all stages of development as early as in migratory neural crest cells before lineage specification, thus suggesting that Sox10 is a key determinant of Schwann cell identity [41, 42]. Sox10 is also crucial in terminal differentiation and in myelin maintenance, as it controls the expression of several myelin genes encoding P0, MBP, myelin-associated glycoprotein (MAG), and Cx32 [33]. Conditional deletion in adult nerves showed that Sox10 is also required for myelin homeostasis to maintain myelin integrity [43].

In mutant mice lacking Oct6, myelin genes are repressed and myelination is blocked [44, 45]. A double *Oct6/Brn2* KO model shows a more severe phenotype as compared to single *Oct6* KO, thus suggesting that these factors cooperate to promote the transition to a myelinating phenotype. Even if more severe than the single KO, in *Oct6/Brn2*, double KO myelination is delayed but not completely blocked [46]. This finding led to the hypothesis that another factor such as Brn1 can in part compensate loss of Oct6 in vivo [47].

Egr2/Krox20 is a master transcription factor of myelination whose loss in mice results in the arrest of Schwann cells at the pro-myelinating stage in a 1:1 relationship with the axon and in a-myelinated axons [39, 48]. Krox20 cooperates with Sox10 to promote myelination and activates the expression of myelin genes, encoding structural proteins of compact myelin such as P0 and PMP22 [33]. Myelin biosynthesis also involves the activation of SREBP (sterol regulatory element-binding protein) transcription factors, which promote lipid biosynthesis [49, 50] (see following section on myelin biogenesis).

To induce myelination, inhibitors of myelination must also be repressed at the transcriptional level. Of note, Krox20 itself acts to inhibit *Oct6*, *c-Jun* (Jun proto-oncogene, AP-1 transcription factor subunit) and *Sox2*, which are elevated in iSCs [33, 34, 51]. At the induction of myelination, *c-Jun* and *Sox2* are also repressed by the transcription factor *Zeb2* (zinc finger E-box binding homeobox 2) [52, 53]. Loss of Zeb2 results in the absence of downregulation of these factors and to the arrest of SCs into an immature state that cannot progress toward pro-myelination.

Epigenetic regulation is also essential for PNS myelination. Chromatin remodeling involves DNA methylation and post-translational modification of histones. For a more comprehensive description of these mechanisms, we refer the readers to an excellent review on this topic [54]. Briefly, the BAF (Brahma-associated factor) complex is recruited by Sox10 to *Sox10* and *Krox20* responsive elements, and enhances the transcription of target genes, including *Oct6*. Consistent with this, loss of BAF blocks Schwann cell development and results in a phenotype similar to *Sox10* mutants. Similarly, HDAC1/HDAC2 (histone deacetylase 1/2) enzymes are induced by Sox10 to activate transcription of *Sox10* target genes. Deletion of *Hdac2* in particular leads to attenuation of myelination, whereas *Hdac1/Hdac2* double deletion results in myelination arrest [55, 56].

Pro-myelinating Signals from the Axon

Neuregulin 1. In the PNS, axons with a diameter bigger than 1 µm are myelinated, whereas axons smaller than 1 µm in diameter are unmyelinated and form Remak bundles [1, 26]. This observation led to the hypothesis that an "axonal determinant" dictates the fate of Schwann cells at the transition from iSCs to myelin-forming or non-myelin forming, but the identity of this factor remained elusive for many decades [26].

NRG1 (neuregulin) signaling influences all developmental stages of Schwann cells, starting from SCPs, when Schwann cells are dependent on axons for their migration, proliferation, and survival [25, 57]. NRG1 is a member of the epidermal growth factor (EGF) superfamily, which comprises several alternatively spliced transmembrane protein isoforms [1]. NRG1 isoforms are classified on six different classes, of which types I–III are the most abundant.

NRG1 type I is a soluble isoform acting as a paracrine signal mainly expressed by Schwann cells. Type I is dispensable for Schwann cells development, but rather crucial for repair and remyelination processes during Wallerian degeneration [58]. On the contrary, overexpression of NRG1 type I specifically in Schwann cells is sufficient to trigger demyelination and onion bulb formation [59]. Consistent with this observation, elevated levels of NRG1 type I are detected in nerves of demyelinating neuropathies in human and mouse [59].

NRG1 type III is tethered on the axonal membrane and interacts with ErbB3 (Erb-B3, receptor tyrosine kinase 3) and ErbB2 tyrosine kinase receptors expressed in Schwann cells (Fig. 2) [1, 32]. Ablation of axonal NRG1 and its receptor ErbB2 provided the evidence that NRG1-ErbB2 signal is one of the main inducer of myelination in the PNS [60–62].

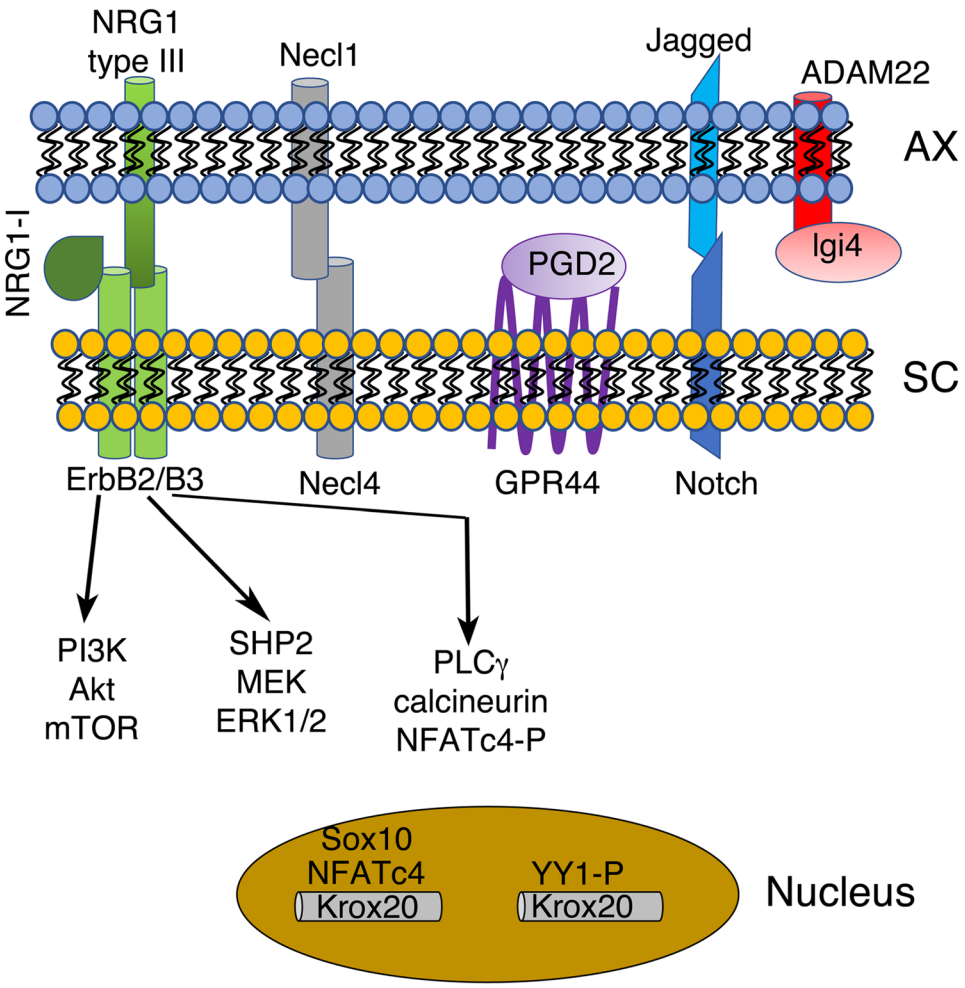

Fig. 2 Interactions at the axon-Schwann cell interface (peri-axonal space) in the internode. AX, axon; SC, Schwann cell. Some signaling pathways in the Schwann cell cytoplasm are also indicated, mainly downstream of the NRG1 type III-ErbB2/B3 interaction. Note that NRG1 is also present as a soluble factor, NRG1 type I, which acts as a paracrine signaling

Elegant experiments in vitro demonstrated that axons that are normally unmyelinated, such as those of superior cervical ganglia, become myelinated following forced ectopic expression of NRG1 type III [61]. Haploinsufficiency of NRG1 type III in mice results in hypomyelination, reduced number of myelinated axons, and defective Remak bundles [61]. Vice versa, overexpression of NRG1 type III in the axon is associated with increased myelin thickness and ectopic myelination, that is myelination of bundles of axons, indicative of a hypermyelinating phenotype [62]. Altogether, these findings suggest that NRG1 type III is an instructive signal for Schwann cell myelination as not only dictates the fate of Schwann cells in the binary choice between myelination and non-myelination but also the amount of myelin that Schwann cells produce. Myelin thickness is a function of the amount of NRG1 type III exposed on the axonal surface and thus of the axonal diameter.

NRG1 activity is regulated at post-translational level by secretases, notably β-secretase BACE1 and α-secretase TACE (TNF-alpha convertase enzyme or ADAM17, ADAM metallopeptidase domain 17), whose cleavage results in opposite outcomes [63–65]. BACE1 cleaves NRG1 type III leading to extracellular exposure of the EGF domain, which binds the ErbB3 receptor on Schwann cells. ErbB3 heterodimerizes with ErbB2 thus triggering autophosphorylation and phosphorylation of downstream effectors (see the following section on Schwann cell signaling). On the contrary, TACE inhibits NRG1 type III signal. However, how this opposite effect on NRG1 activity is coordinated during development is not known. Also, the precise subcellular localization of this regulation remains to be clarified. Other secretases such as ADAM19 and ADAM10 have been suggested to regulate NRG1 type I or type III, respectively, but ADAM10 seems to be dispensable in vivo [66].

The NRG1 type III intracellular domain is known to be cleaved in neurons by γ-secretases, following Schwann cell contact. This intracellular cleavage activates a robust expression of the L-PGDS synthase (prostaglandin D2 synthase) in neurons [67]. This enzyme catalyzes the synthesis of PGD2 (prostaglandin D2), which signals to Schwann cells through the GPR44 (G protein-coupled receptor 44) receptor (Fig. 2). The functional role of this interaction

is not completely assessed, but PGD2-GPR44 should be involved in the induction of myelination, thus reinforcing NRG1-ErbB2 signaling, and, at later stages, in myelin maintenance. Consistent with this, nerves from *L-Pgds* KO mice are hypomyelinated, whereas myelin degeneration is observed in adult nerves [67].

Interestingly, the prion protein PrP^C is another axonal membrane-tethered protein that has been shown to have a role in myelin maintenance [68]. Loss of PrP^C specifically in neurons leads to normal myelin development but to a late onset peripheral neuropathy with myelin degeneration [68]. The cognate molecule in the Schwann cell membrane binding to PrP^C remains to be identified. Moreover, it is not known whether the PrP^C-mediated signaling may converge on the NRG1-ErbB2 axis in Schwann cells.

Lgi4 and ADAM22. ADAM22 in the axon has no secretase activity but rather acts as receptor for Lgi4 (leucine-rich repeat LGI family member 4) secreted by Schwann cells (Fig. 2) [69]. Analysis of the spontaneous mutant claw paw (*clp*) carrying a recessive mutation in *Lgi4* revealed a key role for this molecule in promoting myelination during development [70]. Nerves from the claw paw mutant are severely hypomyelinated and present defects in radial sorting. Consistent with this, nerves from conditional mutants lacking ADAM22 are also hypomyelinated [69]. The precise mechanisms of action of Lgi4 and ADAM22 in the PNS, which are not restricted to the axo-glia juxtacrine interaction, remain to be clarified.

Notch-1. Notch-1 (Notch homolog 1, translocation-associated) signaling in Schwann cells, driven by interaction with its axonal ligand Jagged 1 (JAG1) (Fig. 2), promotes Schwann cell development and in particular the transitions from SCPs to iSCs and to mature SCs [24]. During these processes, Notch-1 synergizes the NRG1-ErbB2 axis. Notch-1 signaling pathway is then downregulated during myelination by the Krox-20 transcription factor [71]. Thus, Notch-1 is a negative regulator of myelination in a RBPJ (recombination signal binding protein for immunoglobulin Kappa J region)-dependent manner, in contrast to its role in response to injury driving demyelination, which is RBPJ-independent.

Other axo-glia interactions in the internode. In addition to the molecules and pathways described above, other axo-glia interactions promote myelination in the PNS. Necl-4 (nectin-like protein 4 also known as CADM4, cell adhesion molecule 4) in Schwann cells interacts with Necl-1 (CADM3) in the axon to induce myelination in vitro (Fig. 2) [72, 73]. However, lack of Necl-1 is dispensable for myelination in vivo, whereas conditional KO mutants with Schwann cell specific ablation of *Necl-4* display redundant myelin and myelin outfoldings in the nerve, a pathological hallmark of some recessive forms of Charcot-Marie-Tooth neuropathies [74]. Of note, one of the proposed mechanisms of action of Necl-4 in Schwann cells is the recruitment of the Par3 polarity protein at the adaxonal membrane in the internode following Necl-4/Necl-1 interaction [74].

Pro-myelinating Signals from the Extracellular Matrix

During nerve development, the deposition of the basal lamina by Schwann cells is a well-known prerequisite for myelination. Lack of laminins has been extensively demonstrated to impair myelination both in vitro and in vivo, starting from the orchestration of radial sorting of axons by Schwann cells [31]. This process relies on the complex interactions between ECM components and integrin receptors on the Schwann cell abaxonal surface, transduced by Rho GTPases to the cytoskeleton, and integrated with many signaling pathways controlling differentiation and growth. We refer the readers to seminal reviews on this topic, including this issue [1, 18, 75].

At later stages, Schwann cells express dystroglycan, which is localized at the outer plasma membrane apposing to the basal lamina where it binds laminin 2 and agrin [13, 18]. The intracellular domain of dystroglycan interacts with DRP2 and L-PRX. *DG* (dystroglycan) conditional KO in Schwann cells display a neuropathic phenotype morphologically characterized by irregular folding of myelin, disorganization of microvilli, and consequent altered clustering of Na^+ channels at the node [14]. These features are not typical of laminin mutants and their receptors in development such as β1 integrin, suggesting that this phenotype is not due to altered ECM-Schwann cell communication. One hypothesis is that loss of function of proteins within the DG complex in Schwann cells leads to myelin instability [14]. DRP2 and L-PRX anchor DG in the Schwann cell appositions, which defines the boundaries of the cytoplasm-filled adjacent regions, the Cajal bands (Fig. 1b, d) [13, 15, 17]. Consistent with this, in addition to Cajal bands disruption, loss of either PRX or of DRP2 is associated with myelin abnormalities that share similarities with those observed in the DG mutant.

Other adhesion molecules involved in myelin stability in this region is the integrin α6 β4. Disruption of this complex in mice leads to aberrant folding in older animals [76]. In the abaxonal membrane, the G protein-coupled receptor GPR56 has been found to have a role in myelin maintenance [77]. *Gpr56* mutants display increased myelin thickness, Cajal band disorganization, and progressive defects of myelin maintenance in older mice. The cytoskeletal scaffolding protein Plectin has been identified as an interacting partner of GPR56 to regulate myelin development and homeostasis [77].

Another G protein-coupled receptor, GPR126, on the abaxonal membrane binds collagen IV and Laminin 211 and is required for radial sorting and therefore for differentiation and myelination [78–80]. GPR126 has also a separate role in controlling cAMP (cyclic adenosine monophosphate) levels in Schwann cells through activation of adenylate cyclase. cAMP in turn activates PKA (protein kinase A), which converges on Oct-6 and Krox-20 transcription factors for myelination [79, 81].

Schwann Cell Transduction of Extrinsic Pro-myelinating Signals

Many progresses have been made to decipher signaling pathways that in Schwann cells transduce promyelinating inputs from the extracellular matrix and the axon. However, how these pathways are connected and regulated in time and space during postnatal nerve development is still elusive. Here, we will describe PI3K (phosphatidyl-inositol 3 kinase), MAPK (mitogen-activated protein kinase), and PLCγ (phospholipase C gamma), which have been extensively studied as signaling pathways downstream of axonal-derived signals, particularly NRG1-ErbB2 (Fig. 2).

PI3K-Akt-mTOR. PIK3CA is a class I phosphatidyl-inositol 3 kinase (PI3K) that generates PtdIns(3,4,5)P_3 (also known as PIP_3) from PtdIns(4,5)P_2 (PIP_2) at the plasma membrane [82]. Locally enhanced PIP_3 levels activate a signaling cascade downstream of TKR (tyrosine kinase receptors), which involves the Akt (V-Akt murine thymoma viral oncogene-Like protein)-mTOR (mechanistic target of rapamycin) kinase complex [83]. Several studies highlighted the importance of PI3K in the regulation of Schwann cell proliferation, survival, and the promotion of myelination [84, 85]. In vivo evidence of its involvement in myelin biogenesis has been provided by *Pten* (phosphatase and tensin homolog) conditional deletion in Schwann cells, a phosphatase which dephosphorylates PIP_3 and opposes PI3K function to control lipid homeostasis [86, 87]. PTEN loss results in increased PIP_3 levels and overactivation of Akt-mTOR, leading to ectopic myelination, increased myelin thickness of axons smaller than 2 µm in diameter [86]. Of note, bigger caliber axons carry aberrant myelin such as tomacula and myelin outfoldings, which are ameliorated by rapamycin treatment, a known mTORC1 inhibitor [87].

The relevance of the Akt-mTOR signaling axis in myelination has been then corroborated by other studies. Constitutive activation of Akt in Schwann cells results in hypermyelination and aberrant myelin, which is ameliorated by rapamycin treatment, similarly to *Pten* conditional KO mutants [88]. Overactivation of mTORC1 via conditional Schwann cell ablation of the TSC1/2 (tuberous sclerosis) complex leads to different outcomes, depending on both the promoter driving Cre-mediated recombination and the extent of mTORC1 activation [89, 90]. Overactivation of mTORC1 in *Tsc2 Mpz*-Cre (*Mpz*, myelin protein zero) mutants leads to myelination arrest, as it interferes with Schwann cell proliferation and blocks Krox20 activation at the onset of myelination [89]. On the contrary, moderate activation of mTORC1 in *Tsc1 Mpz*-Cre mutants results in a transient delay in myelination, with increased myelin thickness and aberrant myelin at later stages. Figlia et al. further suggested that the extent and the timing of mTORC1 activation is crucial for myelination, as *Tsc1* deletion in Schwann cells using the *Dhh*-Cre (*Dhh*, Desert hedgehog) transgene, which acts before *Mpz*-Cre during embryonic development, leads to an arrest of myelination similarly to *Tsc2 Mpz*-Cre mutants [90]. Altogether, these studies demonstrated that mTORC1 has a double role in myelination: it is active early during Schwann cell development, to burst cell proliferation and to inhibit precocious Krox20 activation. At the onset of myelination, mTORC1 activation declines but still at sufficient levels to allow lipid and protein synthesis downstream of Krox20 activation and membrane wrapping [91]. To further corroborate this conclusion, moderate mTORC1 activation has been recently shown to be associated with aberrant myelin formation, as observed in mutants with loss of the MTMR2 (myotubularin-related protein 2) phosphatase and its activator Rab35 GTPase [92–94]. MTMR2 is a catalytically active phosphatase, which regulates the turnover of PtdIns(3,5)P_2 in Schwann cells [95]. MTMR2 acts in complex with MTMR13, another myotubularin which instead is catalytically inactive, but potentiates MTMR2 activity also by regulating its subcellular localization [96]. In *Rab35* and *Mtmr2* KO mutants, elevated PtdIns(3,5)P_2 levels overactivate mTORC1 and cause aberrant myelin [93, 94].

YAP/TAZ. Transcription co-activator Yes-associated protein 1 (YAP) and its coactivator with PDZ-binding domain (TAZ) are key promoters of myelination, recently reviewed in Feltri et al. [97]. YAP/TAZ can be phosphorylated and localized in the cytosol, or viceversa, not phosphorylated and translocate in the nucleus, promoting transcription by binding to TEAD (TEA domain transcription factor) transcription factors. Phosphorylation and thus inactivation of YAP/TAZ is mediated by the canonical Hippo pathway, which consists of a cascade of kinases activated by a plethora of extracellular and intracellular biological stimuli. Specifically, in Schwann cells, NF2 (neurofibromin, also called merlin or Schwannomin) activates the Hippo cascade similarly to the Crb3 polarity protein, which is localized at the edge of mature Schwann cell internodes [19, 23]. When final internodal length is achieved, Crb3 is expressed and localizes at microvilli, leading to activation of the Hippo pathway, and inhibition of YAP/TAZ. On the contrary, during longitudinal myelin growth, Crb3 is not expressed and localized at microvilli, Hippo is inactive, YAP/TAZ are not

phosphorylated and localize in the nucleus. During growth, mechanical cues deriving from the acto-myosin cytoskeleton also inhibit Hippo kinases and permit internodal extension via YAP/TAZ localization in the nucleus [98]. Longitudinal elongation is under the control of YAP and its negative regulator Hippo pathway, whereas myelin thickening and wrapping appears to be regulated by NRG1-ErbB2-PI3K-Akt. However, the two pathways seem to be connected, as increasing YAP activity results in Akt stimulation and vice-versa, increasing Akt activity results in YAP expression [23]. However, mice overexpressing NRG1 do not show increased internodal length, suggesting that in this mutant Crb3-Hippo is sufficient to limit longitudinal extension [62].

MAPK. Downstream of NRG1-ErbB2, the SHP2 phosphatase is required for induction of myelination, as loss of its activity phenocopies *ErbB2* KO mutants [99]. SHP2 (Src homology region 2 (SH2)-containing protein tyrosine phosphatase 2) activates ERK1/2 and, consistent with this, loss of ERK1/2 activation in Schwann cells results in hypomyelination [100]. On the contrary, sustained ERK1/2 activation leads to increased amount of myelination [101, 102]. The MEK signaling promotes myelination by activating the YY1 transcription factor [38].

PLCγ. NRG1 also activates PLCγ (phospholipase C) which induces elevation of intracellular calcium concentrations [37]. In turn, calcium-dependent calcineurin B1 phosphatase dephosphorylates NFATc4, which translocates in the nucleus and activates Krox20. This pathway has been found to be also activated downstream of PGD2 and GPR44 receptor in Schwann cells, independently of PI3K-Akt and MAPK [67].

Negative Regulators of Schwann Cell Myelination

Myelination must be timely induced in postnatal development. Moreover, Schwann cells wrap and produce myelin so that internodal length and myelin thickness are proportioned to axonal diameter [1, 13]. As described before, the Hippo pathway and their activators such as for instance Crb3 and NF2, limit longitudinal myelin growth and internodal length by YAP/TAZ phosphorylation and inactivation (cytoplasmic retention) [97]. Concerning radial myelin growth and thickness, several negative regulators have been identified most of them converging on the NRG1 pathway [1]. As described before, TACE secretase cleaves NRG1 type III and negatively regulates its activity and myelination [65]. PTEN phosphatase downregulates PIP_3 levels and Akt-mTORC1 activation, thus also negatively regulating myelination [86, 87]. Of note, the Dlg1/SAP97 (Discs Large 1/synapse associated protein 97) is a scaffolding protein of the MAGUK family that has been shown to potentiate PTEN activity and to negatively regulate the Akt-mTORC1 signaling [103]. In turn, Dlg1 is negatively regulated by the Kif13b unconventional kinesin motor protein, that promotes p38γ-MAPK Dlg1 phosphorylation and ubiquitination [104]. Kif13b is thus a positive regulator of myelination. REDD1 (Regulated in development and DNA damage responses 1/*Ddti4*) is another negative regulator of mTORC1, which acts by stimulating TSC1/2. Consistent with this, *Ddit4* KO nerves display increased myelin thickness [105].

Interestingly, ECM signaling transduced by integrins in Schwann cells may also represent negative regulators of myelination. Specifically, α6β4 and downstream effectors such as SGK1 (serum/glucocorticoid regulated kinase 1) and NDRG1 (N-Myc downstream regulated 1) have been proposed to limit myelination [106]. Their function should be to impede precocious myelination.

Finally, HDAC3 has been found as a potent negative regulator of myelination. Deletion of HDAC3 in mice results in hypermyelination that leads to myelin degeneration in adult [107]. HDAC3 should act both by inhibiting transcription of pro-myelinating genes and by activating inhibitors of myelination. Of note, He et al., identified TEAD4 as a novel HDAC3 effector inhibiting myelination in contrast to TEAD1 which cooperates with YAP/TAZ factors to promote myelination [107] (see Schwann cell signaling paragraph). Moreover, Rosenberg et al. suggested that HDAC3 controls the postnatal homeostatic phase of myelination [108]. Conditional inactivation in Schwann cells of HDAC3 using a different Cre recombinase (*Mpz*-Cre) resulted in normal myelination early in postnatal development. Of note, at later stages, a progressive neuropathic phenotype associated with aberrant myelin formation was observed in mutant mice. This study hypothesized that in the absence of HDAC3, HDAC1 and 2 are upregulated postnatally, thus sustaining continuous myelin production, which degenerates at later stages.

Building up the Myelin Membrane: Interplay Between Membrane Synthesis and Cytoskeletal Remodeling

Membrane Synthesis and Schwann Cell Metabolism. Myelin-forming cells must generate an impressive amount of membrane, which in oligodendrocytes in the central nervous system (CNS) has been estimated as approximately 5000 μm^2 of surface area per day and 10^5 molecules per minute [3, 109]. However, recent experiments carried out in zebrafish showed that this amount is underestimated [109]. During radial growth, myelin membrane in the PNS grows around the axon according to a "jelly roll" model of spiral wrapping, where the inner tongue (inner mesaxon) moves and the outer instead does not. This is because in a myelin-forming

Schwann cell, the outer layer contains the nucleus and most of the cytoplasm. Once radial spiral is achieved, this must be coordinated with the lateral longitudinal expansion to form a mature internode. Membrane components are thought to be added at the lateral edges at paranodes and microvilli, and at the abaxonal membrane and then delivered to build up the functional domains of the polarized myelinated fiber [4]. However, how membrane trafficking is regulated in these cells is largely unknown.

In the Golgi compartment, many proteins that are destined to the plasma membrane are glycosylated and sorted. Moreover, the Golgi orchestrates the synthesis and delivery of sphingolipids and the transport from the endoplasmic reticulum of cholesterol, main constituents of the myelin membrane [110, 111]. Recently, Baba et al. investigated the function of PI4KB a kinase associated with the Golgi compartment known to generate PtdIns4*P* from PtdIns [112]. This phosphoinositide and in particular the PI4KB kinase is crucial for the exit of cargos from the Golgi compartment and the recruitment of protein adaptors to generate coated vesicles destinated to the plasma membrane. Consistent with a role for PI4KB at the Golgi and with the relevance of targeted lipid and protein delivery from the Golgi in a myelin-forming cell, conditional *Pi4kb* KO mutants in Schwann cells display thinner myelin and several myelination defects. More importantly, they display altered Golgi-associated functions impairing cholesterol transport and protein glycosylation [112].

The bulk of protein and lipid synthesis is under the control of mTORC1 (see paragraph above on PI3K signaling) [113]. mTORC1 regulates mRNA translation via its targets 4EBP1 and S6K. Moreover, mTORC1 promotes maturation of SREBPs transcription factors that are involved in the expression of several enzymes catalyzing fatty acid and cholesterol synthesis [50, 91]. Several loss-of-function mutants support a central role for mTORC1 in myelination. Ablation of *Raptor* (mTORC1 complex) and of the entire mTOR complex (mTORC1 and mTORC2) results in hypomyelination in mice [50, 114].

mTORC1 is a metabolic hub that controls not only anabolism but also catabolism [113]. In stress conditions and when nutrient levels are low, TSC1/2 GAPs are activated by LKB1 and AMPK (5′ adenosine monophosphate-activated protein kinase), which sense a high AMP/ATP ratio. TSC1/2 in turn inhibit Rheb1 GTPase and therefore mTORC1. Downstream of mTORC1, autophagy and other processes that generate ATP such as fatty acid and glucose oxidation are then activated. Ablation of *Lkb1* in Schwann cells has different outcomes. Pooya et al., found that mutant mice lacking LKB1 (Liver kinase B1) in Schwann cells display hypomyelination, which progresses in a neuropathic phenotype at later stages [115]. Of note, in this mutant hypomyelination is associated with decreased mitochondrial protein expression, which in the TCA cycle leads to decreased levels of citrate, an important intermediate for energy production and lipid synthesis. On the contrary, Beirowski et al. generated another mutant lacking LKB1 in Schwann cells (using the *Mpz*-Cre promoter instead of *Dhh*-Cre), which shows only transient and mild hypomyelination [116]. Interestingly, at later stages these mutants display axon degeneration and loss, together with a neuropathic phenotype, leading to the important conclusion that Schwann cell metabolism also supports axonal maintenance in the PNS. How LKB1 in Schwann cells mediates this function has not been clarified, but one hypothesis is that LKB1-AMPK activates glycolysis and production of lactate, which is supplied to axons. Consistent with this, loss of MCT1 (monocarboxylate transporter 1) specifically in Schwann cells alters SC metabolism and impairs sensory nerve maturation and aging [117]. Similarly, in the CNS, axons uptake lactate from oligodendrocytes using the MCT1 transporter [118].

Cytoskeletal Remodeling. In the PNS, the generation of several mutants lacking Rho, Cdc42, and Rac1 members of the small Rho GTPase family of proteins revealed a fundamental role of the acto-myosin cytoskeleton remodeling in cell migration and radial sorting of axons, which is a prerequisite for myelination (reviewed in this issue).

During differentiation, myelination requires extensive cytoskeletal dynamics to modify the growing membrane, which wraps radially the axon and expands longitudinally, and to assembly stable clusters of molecules mediating glia-glia, glia-axon, and glia-extracellular matrix interactions [1, 4, 10]. Recently, hypomyelination and impaired actin cytoskeleton rearrangements have been demonstrated in a mutant model lacking the PI4KA kinase, which generates PtdIns4*P* at the plasma membrane [119]. The importance of cytoskeletal dynamics later in myelination has been further supported by other models, which reproduce myelin defects typical of inherited Charcot-Marie-Tooth neuropathies in human. Loss of MTMR2 (Myotubularin-related 2) causes demyelinating CMT4B1 with myelin outfoldings [120]. Recently, Guerrero-Valero et al. found that loss of MTMR2 is associated with increased levels of PdtIns(3,5)P_2 phosphoinositide and overactivation of both mTORC1 and RhoA GTPase pathways, leading to myelin outfoldings [94]. Other models further support the involvement of the F-actin cytoskeletal remodeling in the formation of myelin outfoldings. Loss of function of N-WASP (Wiskott–Aldrich syndrome protein), Cdc42, and of atypical PKC (protein kinase C) have been all associated with myelin outfoldings [121–123]. Moreover, loss of Necl-4/Cadm4, which is localized in the apical-like regions of Schwann cells, results in myelin outfoldings (45). Cadm4 interacts with protein 4.1B and is connected with the actin cytoskeleton underneath the Schwann cell adaxonal membrane. Finally, in the CNS, spatially unrestricted branched F-actin disassembly results

in aberrant myelin membrane growth and myelin outfoldings formation [124, 125]. These findings suggest that lipid-dependent coordinated myelin synthesis and cytoskeletal dynamics are at the basis of myelin growth in Schwann cells.

Concluding Remarks

Many progresses have been made to understand how PNS myelination is promoted and achieved, and which signaling pathways in Schwann cells transduce promyelinating inputs from the extracellular matrix and the axon (listed in Table 1 along with negative regulators). However, how these pathways are integrated in time and space in the nerve is not known. Live imaging analyses to investigate where and how signaling platforms act to regulate myelination and how myelin components are trafficked, delivered, and assembled are limited by the complicated tridimensional geometry and ultrastructure of myelinated fibers. Moreover, the use of rodent models in which signaling pathway components are conditionally inactivated or constitutive activated poses several limitations. Signaling pathways are highly dynamics and tightly regulated and thus constitutive downregulation or overactivation may not recapitulate the physiological mechanism of action. Resulting phenotypes may vary depending on the timing (expression of Cre recombinase) or the extent of downregulation/activation.

The study of human disorders in which molecules and pathways relevant for myelination are altered has enormously contributed to the current knowledge on myelin biology. This is the case for instance of human inherited peripheral neuropathies (IPNs), where the neuropathy is the predominant but not exclusive clinical feature. IPNs represent a broad groups of disorders, which include motor and sensory Charcot–Marie–Tooth (CMT) neuropathies, hereditary motor or predominant motor neuropathies (HMN), and hereditary sensory or predominant sensory and autonomic neuropathies (HSN and HSAN) [126, 127]. CMT neuropathies, with a prevalence of 1 on 2500 individuals, are generally characterized by progressive-length dependent muscular atrophy and weakness, with an age of onset usually comprised between the first and the second decade of life. CMTs are very heterogeneous from the clinical and genetic point of view. Since the advent of next generation sequencing approaches, more than 100 causative genes have been identified as responsible for CMT and IPNs [128] (https://neuromuscular.wustl.edu/time/hmsn.html). CMTs are classified on the basis of clinical and neurophysiological criteria: demyelinating CMT1 are associated with MNCV (motor nerve conduction velocity) values at upper limbs less than 38 m/s; axonal CMT2 with greater than 38 m/s, or slightly decreased values, and finally CMT-I intermediate type, with values ranging between 25–45 m/s. CMT4 refers to demyelinating forms with autosomal recessive inheritance.

Mutations in the genes encoding the EGR2 and SOX10 transcription factors are associated with severe forms of neuropathies, and specifically with demyelination for *EGR2* mutations and with PNS/CNS hypomyelination for *SOX10* mutations.

Genes encoding structural protein of the myelin sheath are also mutated in CMT. CMT1A, the most common form of CMT1, is due to duplication of a 1.4 Mb region on chromosome 17p including the *PMP22* gene. More rarely, point mutations in *PMP22* cause demyelinating CMT1E. The generation and characterization of several animal models for these neuropathies suggested that CMT1A is caused by altered *PMP22* gene dosage, whereas CMT1E by a dominant negative effect of the mutant PMP22 allele on the wild type allele. *MPZ*, the gene encoding myelin protein zero, is mutated in the autosomal dominant demyelinating CMT1B, caused by altered trafficking of P0 and loss of function at the plasma membrane leading to hypomyelination.

Mutations in the *GJB1* gene, encoding Cx32, localized at the gap junctions in non-compact myelin, cause X-linked dominant demyelinating CMT1X.

Other CMT forms are caused by mutations in genes encoding signaling proteins and proteins regulating endosomal trafficking such as for instance MTMR2, MTMR13, and MTMR5 phospholipid phosphatase proteins mutated in autosomal recessive CMT4B1, B2, and B3, respectively, characterized by childhood onset and myelin outfoldings in the nerve. Endosomal regulators are also represented by

Table 1 Positive and negative regulators of myelination mentioned in this review

Positive	Positive	Negative
ADAM22	PI3KCA	Crb3
Akt	PI4KA	DDIT4/REDD1
BACE1	PI4KB	DLG1
Calcineurin B1	PKA	HDAC3
DG	PLCγ	Hippo
DRP2	PrPc	MTMR2
Erb2/B3	Rho GTPases	MTMR13
ERK1/2	SHP2	NDRG1
GPR44	TEAD1	Notch-1
GPR56	YAP/TAZ	Necl-4
GPR126		NF2
HDAC1/HDAC2		PTEN
Integrins		Rab35
KIF13B		SGK1
Laminin 211		TEAD4
Lgi4		TACE
mTORC1		TSC1/2
NRG1		

LITAF mutated in CMT1 and FIG4, mutated in the CMT4J neuropathy. Finally, other CMT proteins interact with the F-actin cytoskeleton such as PRX (CMT4F) or regulates its assembly, such as FGD4, a GEF for Cdc42 GTPase, which is mutated in the autosomal recessive CMT4H.

In conclusion, the generation and characterization of animal models for these neuropathies as well as the increasing number of IPN genes identified using NGS (next generation sequencing) technologies has enormously contributed to expand and deep our knowledge on myelin biology. In turn, the knowledge of the underlying pathogenetic mechanisms allowed to design and validate at the preclinical level promising therapeutical approaches, which can be potentially translated to human in a near future [129–133].

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