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Advances in myelinating glial cell development

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Abstract

In the vertebrate nervous system, the fast conduction of action potentials is potentiated by the myelin sheath, a multi-lamellar, lipid-rich structure that also provides vital trophic and metabolic support to axons. Myelin is elaborated by the plasma membrane of specialized glial cells, oligodendrocytes in the central nervous system (CNS) and Schwann cells (SCs) in the peripheral nervous system (PNS). The diseases that result from damage to myelin or glia, including multiple sclerosis and Charcot-Marie-Tooth disease, underscore the importance of these cells for human health. Therefore, an understanding of glial development and myelination is crucial in addressing the etiology of demyelinating diseases and developing patient therapies. In this review, we discuss new insights into the roles of mechanotransduction and cytoskeletal rearrangements as well as activity dependent myelination and axonal maintenance by glia. Together, these discoveries advance our knowledge of myelin and glia in nervous system health and plasticity throughout life.

Intrinsic factors guiding oligodendrocyte and SC development

Although both cells produce myelin to insulate and support axons, oligodendrocytes and SCs differ early in their genesis. Oligodendrocytes originate from neuroepithelial precursors, whereas SCs are derived from the neural crest. Furthermore, one oligodendrocyte can myelinate multiple axon segments, but one SC myelinates only a single axon segment (Fig. 1, Fig. 2). This is achieved through a process called radial sorting in which cytoplasmic processes from immature SCs extend into axon bundles and “select” an axon segment [1]. SC development is mediated by a host of transcription factors and signaling molecules, including *Sox10*, which persists throughout development and differentiation, activating other transcription factors [1]. In pro-myelinating SCs, which have radially sorted axons and wrapped 1–1.5 turns around an axon, the G protein-coupled receptor (GPCR) GPR126/ADGRG6 elevates cAMP to promote expression of the transcription factor *Oct6/Pou3f1* [1]. Oct6 and Sox10, along with other factors, activate the master regulator of PNS myelination,

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Krox-20/Egr2, which is essential for expression of critical myelin genes, including *Myelin basic protein* (*Mbp*) [1].

Proliferative and migratory oligodendrocyte precursor cells (OPCs) extend and retract numerous processes during development [2]. Recent work has found that OPCs can migrate along blood vessels in a Wnt-dependent manner involving the receptor-ligand pair Cxcr4-Cxcl12, which are expressed on OPCs and endothelial cells, respectively [3]. Oligodendrocyte differentiation requires some shared SC factors, including *Sox10* and *Yin yang 1* (*Yy1*), in addition to the oligodendrocyte specific regulators *Olig1, Olig2, Nkx2.2* [2] and *Myelin regulatory factor, Myrf*, which plays an analogous role to *Krox-20* [4]. Recent work in SCs and oligodendrocytes has identified novel roles for signaling molecules, including a suite of GPCRs, GPR17, GPR56 and GPR37 in the CNS [5][6][7][8] and GPR44 and the zinc finger Zeb2 in the PNS [9][10][11]. While new myelin regulators remain to be uncovered, elucidating the function of known molecules and pathways is key to understanding myelination in development and repair.

Mechanical regulation of myelinating glia during development and differentiation

A unique signaling mechanism in SCs occurs via the basal lamina (BL), and recent evidence points to the molecular mechanisms by which this structure mechanically regulates myelination. In SCs, GPR126 can interact with axonally-derived Prion protein (PrP^c)[12] as well as two SC-derived components of the BL, collagen IV and Laminin-211 [13][14]. Laminin-211 polymerization was proposed to activate GPR126 mechanically, initiating SC myelination (Fig. 1)[13], and SCs respond to mechanical properties of the BL with intracellular molecules such as Focal adhesion kinase (FAK)[15]. Recently, two Hippo pathway signaling molecules, YAP and TAZ (YAP/TAZ), have been implicated as mediators of mechanotransduction during SC development. YAP/TAZ respond to mechanical or chemical stimuli and translocate to the nucleus to regulate gene transcription. *In vitro* culture experiments found nuclear localized YAP/TAZ during SC spreading, plating on stiffer surfaces, plating on Laminin-211, and experimentally applied stretching (Fig. 1). Analysis of mouse mutants demonstrated that YAP/TAZ signaling is required for radial sorting and myelination [16]. YAP also has a role in modulating internode length during development and disease. [17]. In concert with TEAD transcription factors, nuclear YAP activates genes involved in the myelination program, including *Krox-20/Egr2* and *Myelin associated glycoprotein (MAG), Rab11*, and *Laminin* ϒ*1*. The polarity protein Crb3 inhibits YAP nuclear translocation and knock-down of *Crb3* increases the length of SC myelin segments [17]. Crb3 is therefore thought to modulate YAP activity to temper internode length. Interestingly, a dystrophic mouse model of peripheral neuropathy exhibited reduced nuclear YAP with shorter internodes, a phenotype that could be rescued by manual sciatic nerve elongation via femoral distraction to increase nuclear YAP [17]. These data suggest that migration of SCs along axons and/or longitudinal nerve growth could activate YAP/TAZ signaling during development. Perhaps physical maturation of the BL and GPR126 activation is similarly linked to developmental YAP/TAZ signaling, as GPCRs are known upstream regulators of this pathway [18]. Downstream of YAP/TAZ signaling, TEAD1

directly regulates *Peripheral myelin protein 22* (*Pmp22*), mis-regulation of which causes Charcot-Marie-Tooth disease [19].

While a role for YAP/TAZ signaling in oligodendrocytes has not been described, these cells are also responsive to mechanical stimuli. OPC proliferation and migration can be altered by plating on substrates of varying stiffness [20], resulting in differentiation in a density-dependent manner. Plating at high density with polystyrene beads promoted OPC differentiation, demonstrating that this process is mediated by physical space limitations, rather than by extracellular signals [21]. How might external forces drive oligodendrocyte development? A recent report demonstrates that mechanical stimuli interact with the nucleus via the Linker of Nucleoskeleton and Cytoskeleton complex (LINC). One LINC complex component in particular, SYNE1, which binds the nuclear envelope and actin, was shown to link extracellular stimuli, including high density plating with beads and mechanical force using a cell-compression device, to nuclear changes [22]. The switch from primarily euchromatin to heterochromatin is a hallmark of differentiation in oligodendrocytes [23] and requires SYNE1 [22]. Histone modifying complexes, specifically HDAC1 and HDAC2, affect nuclear reorganization by altering chromatin configuration and are essential for oligodendrocyte and SC differentiation. Epigenetic regulation of oligodendrocytes and SCs during development and myelination is reviewed in greater detail elsewhere [1][4].

Producing the myelin sheath

In a feat of cellular morphogenesis, glial cells massively upregulate production of their plasma membrane and spiral it around an axon segment. These dramatic shape changes require extensive cytoskeletal rearrangements, and great inroads have been made in understanding how such rearrangements drive myelin sheath formation. Using zebrafish *in vivo* imaging and 3D electron microscopic reconstruction, Snaidero and colleagues demonstrated that the plasma membrane inner tongue maintains contact with the axon segment as it wraps and progressively spreads out to form the myelin internode. Initial inner tongue movement is aided by the transport of critical material, including mRNA and protein, through nanometer wide channels [24]. How is the inner tongue propelled around the axon? Two elegant studies suggest actin dynamics as a driving force. Nawaz et al. used zebrafish live imaging to determine that F-actin is initially localized to the leading edge, but later excluded from the developing membrane. Culture experiments demonstrated that F-actin depolymerization by drug treatment increased cell spreading, leading to a model in which the force of actin filament disassembly propels the membrane forward (Fig. 2). Interestingly, Zuchero and colleagues found that actin disassembly is driven in part by competition of MBP protein for binding to PI(4,5)P2, which then releases the actin disassembly factors gelsolin and cofilin (Fig. 2). The dynamic interplay between actin assembly during development and disassembly during myelination highlights a potential form of temporal control. Because actin assembly is necessary for OPC development [25], the timing of disassembly must be tightly regulated. What factors could influence timing? One possibility is axonal activity. *In vitro*, vesicular glutamate release from axons in response to electrical stimulation phosphorylates Fyn kinase at the oligodendrocyte membrane, leading to local translation of *Mbp* [26]. Together, these discoveries implicate axons in temporally influencing myelination via actin disassembly.

A role for actin dynamics has similarly been described in the PNS. Inhibition of F-actin formation resulted in delayed SC differentiation [27] and SC-specific deletion of neural Wiskott-Aldrich syndrome protein (N-WASp), a mechanical transducer that remodels actin via Arp2/3, inhibits myelination and causes motor deficits [28][29]. Unlike oligodendrocytes, SCs must sort axons prior to myelination. Radial sorting, like myelination, requires dramatic cell shape changes that are mediated by proteins regulating the cytoskeleton, including the Rho family GTPases Rac1 and Cdc42 [30][31]. Although these studies point to the importance of cytoskeletal rearrangements in SC development, less is known about the forces driving myelination. Interestingly, both oligodendrocytes and SCs transport *Mbp* along microtubules to sites of membrane elaboration [32][33]. Whether actin disassembly and local translation of *Mbp* in SCs have roles in driving myelination remains to be determined.

Activity-dependent control of myelination and myelin maintenance

Oligodendrocytes have intrinsic myelinating capacity and can myelinate fixed axons in addition to synthetic nanofibers and micropillars [21][34][35]. What prevents oligodendrocytes from myelinating dendrites or other cells in the CNS? Using a candidate approach, Redmond et al. identified the transmembrane protein JAM2 as a negative regulator of oligodendrocyte myelination (Fig. 2). Overexpression of JAM2 attenuated the ability of plated oligodendrocytes to myelinate micropillars, and loss of *Jam2* in a mouse model caused an increase in myelinated neuronal cell bodies, implicating repulsive cues in modulating myelination [36]. Another study indicates that a component of intrinsic myelination may be hardwired in oligodendrocytes. When plated on nanofibers, spinal cord oligodendrocytes produced more myelin than cortex-derived oligodendrocytes [37]. Are these regional differences due to environmental cues or other factors? One possibility is that there are specific subtypes of oligodendrocytes with distinct myelinating capacities. To this end, single-cell RNA sequencing was used to characterize cell types in the murine hippocampus and cortex. Interestingly, findings from these experiments suggested seven distinct subtypes of oligodendrocytes, including OPCs [38]. Furthermore, a recent study using the same technique to probe oligodendrocyte heterogeneity in more detail proposed 13 distinct populations of oligodendrocytes in the mouse brain [39].

While negative regulators prevent aberrant myelination in the CNS, variation in myelin distribution along single axons of the developing cortex suggests a fine-tuning of myelination capacity beyond an intrinsic program [40]. Indeed, early work implicated electrical signaling as an instructive cue in oligodendrocyte development and myelination [41][42]. How might activity influence myelination? Previous work demonstrated that neurons form functional synapses on OPCs [43]. Recent research suggests, however, that while oligodendrocytes are more likely to myelinate electrically active axons, this occurs independently of synapse formation, instead relying on vesicular release of glutamate and ATP [44]. A critical role for vesicle transport in myelination was confirmed *in vivo* using zebrafish. Mensch and colleagues used tetanus toxin to inhibit vesicular release, resulting in fewer sheaths, while increasing activity led to more sheaths per oligodendrocyte [45]. In a complementary study, Hines et al. found that initial oligodendrocyte axon ensheathment is activity independent, but preferential contact is maintained on axons releasing vesicles.

Processes are either retracted from inactive axons or produce shorter myelin sheaths (Fig. 2) [46]. However, the necessity of vesicular release is differentially regulated in the CNS. This cue is required for myelination by reticulospinal neurons but not by commissural primary ascending (CoPA) neurons [47]. Why there are different regulatory mechanisms depending on neuronal subtype is an area of future investigation.

Rather than a simple static insulator deposited during development, myelin is now recognized as a player in nervous system plasticity. Myelination during development and in adulthood is modulated by an animal's social experience [48][49] and myelin remodeling occurs throughout life [50]. Furthermore, learning new skills, such as juggling and language acquisition, results in changes to myelin [51][52]. How do myelin alterations occur and how do they affect nervous system plasticity? One possibility is that activity stimulates formation of new oligodendrocytes. To this end, it was shown that differentiation of oligodendrocytes from precursors is necessary for mice to learn a new skill effectively [53], and that neuronal activity promotes oligodendrogenesis and concomitant behavior changes [54]. What is the role of new oligodendrocytes? A recent paper examined the timing of oligodendrogenesis in response to learning and found significant formation of new oligodendrocytes in mice learning to navigate a complex wheel within the first 2.5 hours. Furthermore, mice unable to form new oligodendrocytes exhibit learning deficits as early as 2–3 hours after first encountering the wheel. This early necessity for new oligodendrocytes in the learning process indicates a level of active involvement [55]. Whether this occurs through modifying circuits, providing metabolic support or an as yet undetermined mechanism is an area of future investigation.

Myelin and metabolism

In addition to promoting efficient action potential propagation, myelin is also critical for trophic and metabolic support of axons [56]. To provide metabolites to axons accurately, glia must "know" the metabolic requirements of axons. Could electrical activity by axons function as a means of communication? NMDA glutamate receptors are present on oligodendrocytes [57][58], but were thought to be dispensable for oligodendrocyte development, myelination, and injury response [59][60]. However, recent work has implicated these receptors in mediating calcium influxes in mature oligodendrocytes [61]. Furthermore, NMDA receptors have been shown to link electrical activity in axons to the production of lactate by oligodendrocytes, a critical energy source for axons. By "learning" via NMDA receptor signaling which axons are fast spiking, oligodendrocytes are able to vary lactate production. Loss of NMDA receptors specifically in oligodendrocytes, while not critical during development, causes eventual neurodegeneration from reduced metabolism [62]. Lactate production and metabolic support of axons by SCs is also critical in the PNS [63][64]. The lactate transporter that is used by oligodendrocytes, MCT1, is present in SCs and mediates axonal health [65][66]. However, these studies did not address a role for electrical activity in SC regulation of axonal metabolism. Interestingly, a recent report found that ATP release by electrically active axons mediates mitochondrial signaling to promote energy production in SCs and disruption of this signaling pathway resulted in hypomyelination [67].

Conclusion and Outlook

From static insulating factor to dynamic structure critical in enabling nervous system plasticity, our conceptions about myelin have changed dramatically in recent years. However, although both SCs and oligodendrocytes produce myelin, the mechanisms by which they do so are distinct (Fig. 3). Oligodendrocytes possess an intrinsic ability to myelinate that is fine-tuned by environmental cues, such as mechanical stimulation and electrical activity from axons. New studies suggest the existence of distinct subsets of oligodendrocytes, raising the possibility that such heterogeneity could contribute to differences in innate myelination and re-myelination abilities. It will be exciting to uncover the extent to which interplay between the extracellular environment and oligodendrocyte heterogeneity influences myelination during development and repair. Advances in cellular techniques, including 3D electron microscopic reconstructions and live imaging, have contributed to a better understanding of the physical process of myelination by oligodendrocytes, including a surprising role for actin dynamics. Further research into the cytoskeletal and architectural reorganization of membrane during myelination will help us better understand this feat of morphogenesis and elucidate how to promote re-myelination in disease or injury.

SCs are incapable of myelinating inert structures [37], relying instead on instructive cues. PNS myelination also appears to be less finely tuned compared to the CNS, with stricter correlations between axon diameter and myelin thickness. Whether PNS myelin undergoes dynamic changes similar to CNS myelin has not been well studied. While early work demonstrated a role for axonal activity in modulating SC development and myelination [68], this area of research has lagged behind progress made in the CNS. The mechanisms by which SCs elaborate a myelin sheath are similarly mysterious. One pertinent question is whether actin dynamics, which are vital during CNS myelination, play an analogous role in SCs. A current focus in SCs is on mechanotransduction, and advances in this area are already guiding therapeutic developments through techniques such as optimal matrices for acellular nerve allografts [69].

In summary, the studies highlighted in this review demonstrate that myelination in the CNS and PNS is distinct while sharing some similar processes. Future work would benefit from comparing and contrasting these systems to clarify common or unique aspects of development and myelination. Therapeutic advances will be realized through continued investigation into the mechanisms and controls of myelination from genesis through maturity.

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Highlights

- Schwann cell development is mediated by mechanical signals.
- Some mechanical signals in Schwann cells activate the Hippo signaling pathway.
- Intrinsic oligodendrocyte myelinating capacity is fine-tuned by the environment.
- Lactate made by myelinating glia is critical for axonal metabolism and health.

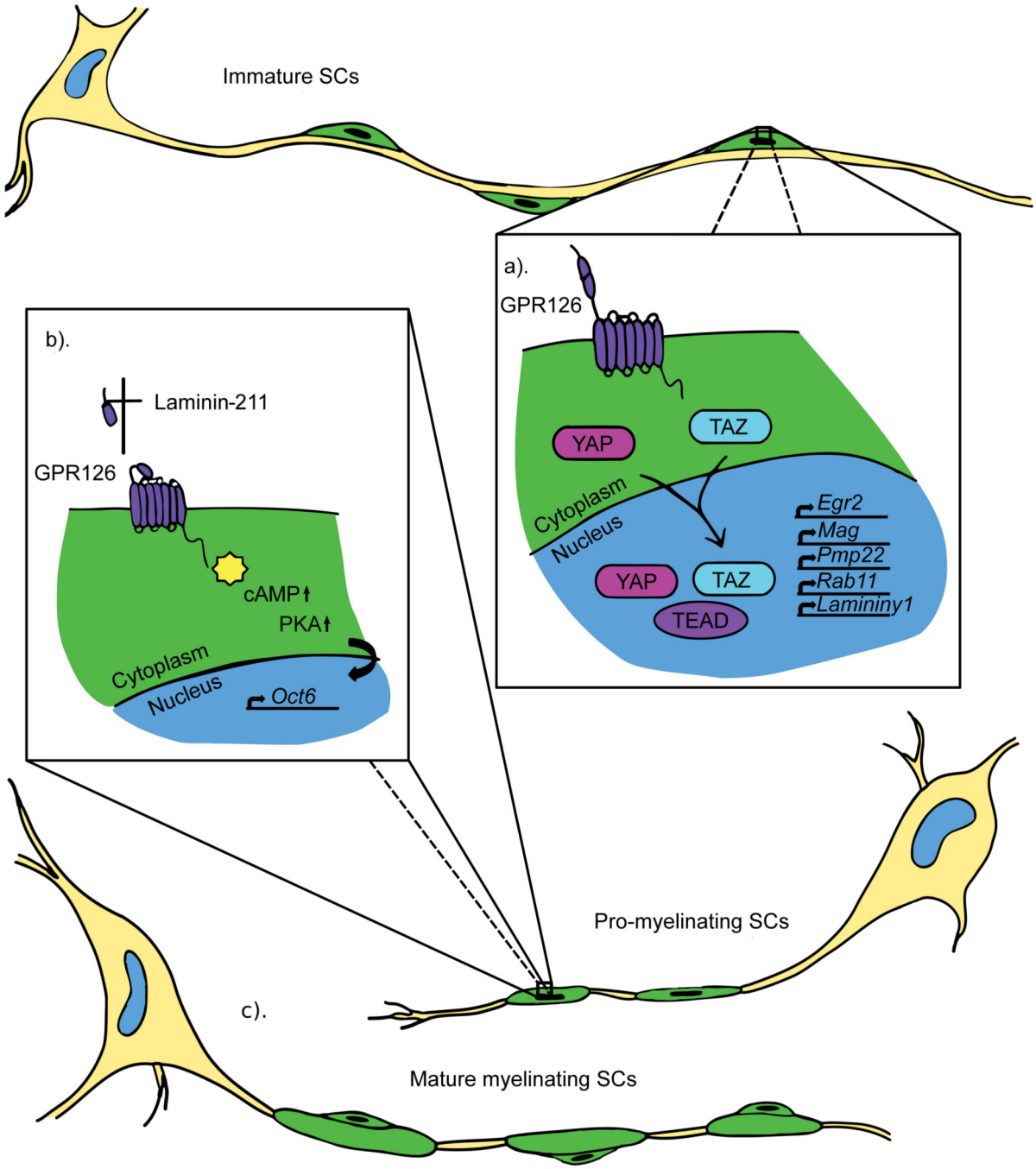


Figure 1.

Mechanotransduction plays a critical role in SC development and differentiation. Immature SCs migrate and divide along growing axons. The forces associated with migration are thought to activate the mechanotransducers YAP/TAZ in SC cytoplasm, which then translocate to the nucleus where they interact with the TEAD family transcription factors to drive expression of important myelin genes (a). After SCs have formed a “1:1” relationship with axons in the pro-myelinating stage, maturation of the basal lamina and subsequent polymerization of Laminin-211 is thought to activate GPR126, which initiates a

transcriptional cascade activating *Oct6* and promoting myelination (b). Eventually, SCs wrap myelin around axon segments to form internodes (c).

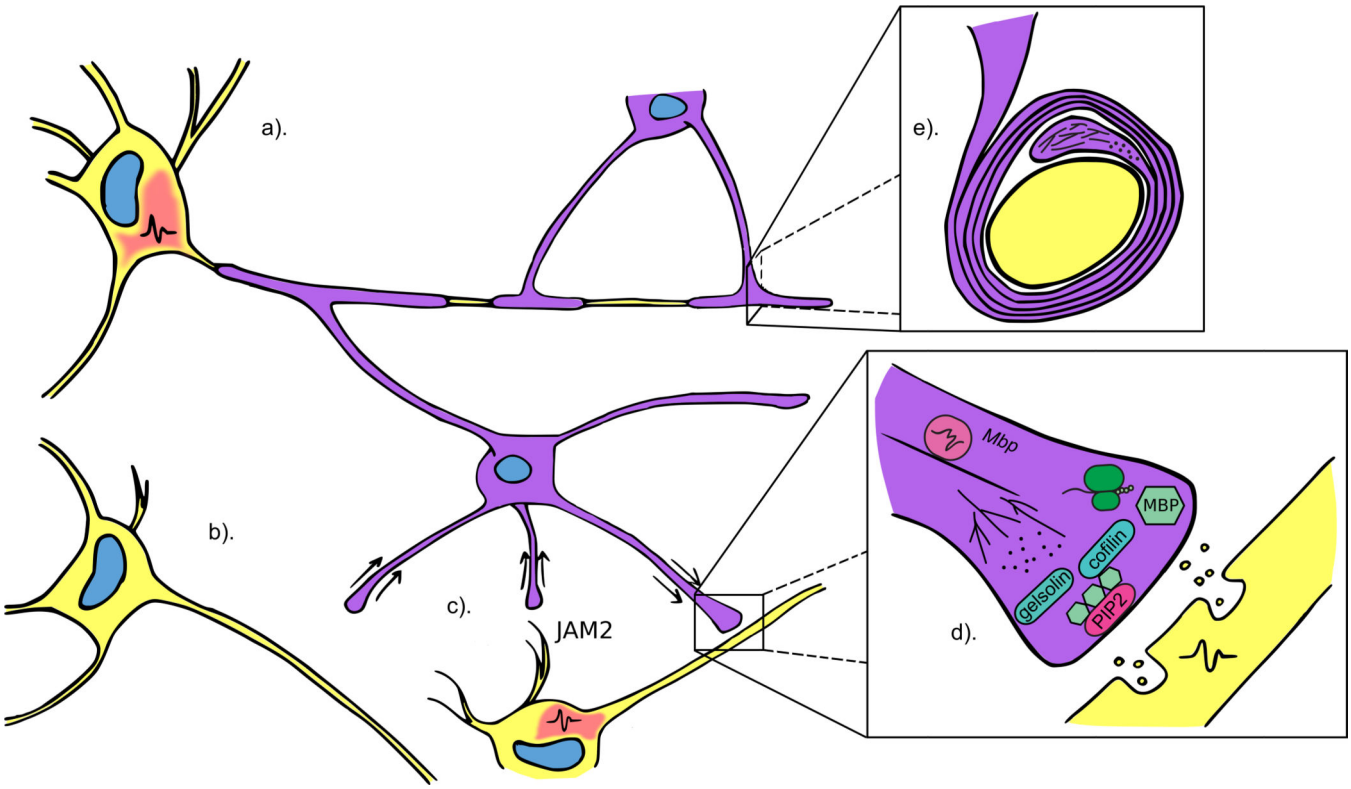


Figure 2.

Multiple factors fine tune the myelination potential of oligodendrocytes. Oligodendrocytes preferentially myelinate electrically active axons (a) and retract processes from inactive axons (b). Furthermore, the intrinsic myelination program is moderated by negative regulators, such as JAM2, which are expressed on dendrites (c). Vesicular release from active axons initiates a cascade of events, one of which is the translation of locally transported *Mbp* mRNA. MBP then competes with the factors gelsolin and cofilin for binding to PIP2 on the inner oligodendrocyte membrane, resulting in release of the two proteins and subsequent actin disassembly (d). During wrapping, filamentous actin is located at the leading edge of the inner tongue and is proposed to propel the membrane forward by actin disassembly (e) (image adapted from Nawaz et al. 2015).

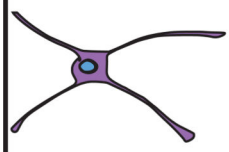
	Intrinsic factors	Mechanical regulation	Myelin sheath production	Activity dependent myelination	Myelin and metabolism
Schwann cells 	GPR126 GPR44 Zeb2 Oct6/Pou3f1 Krox-20/Egr2 Sox10 Yy1	Laminin-211 polymerization YAP/TAZ TEAD TFs	Actin polymerization during differentiation No intrinsic myelinating capacity	Early work showed ATP from active axons inhibits SC proliferation and differentiation	Metabolic support for axons
Oligodendrocytes 	Sox10 Yy1 Olig1 Olig2 Nkx2.2 Myrf GPR17 GPR56 GPR37	Density dependent differentiation SYNE1	Actin dissasembly promotes myelination Intrinsic myelinating capacity	Activity promotes oligodendrogenesis Action potentials stimulate *Mbp* translation Electrically active axons are preferentially myelinated	Metabolic support for axons

Figure 3.

Comparing and contrasting SC and oligodendrocyte development and differentiation. Although both SCs and oligodendrocytes produce the myelin critical for nervous system function, there are important differences in the mechanisms by which they generate myelin. The similarities and differences between SCs and oligodendrocytes discussed in this review are summarized in the table above.