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Advances in myelinating glial cell development

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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.

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Intrinsic factors guiding oligodendrocyte and SC development

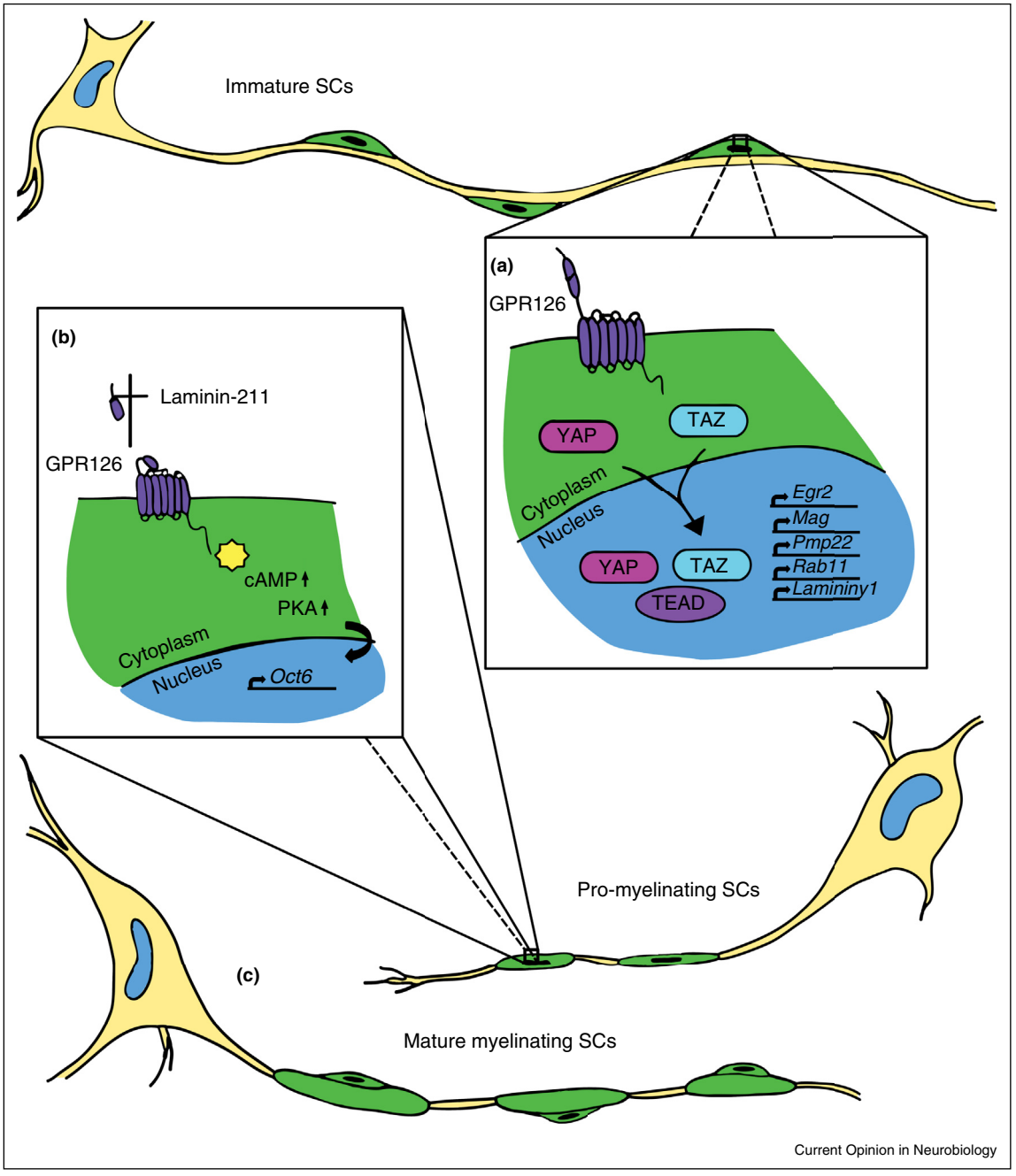
Although both cells produce myelin to insulate and support axons, oligodendrocytes and SCs differ early in their genesis. Oligodendrocytes originate from neuroepithelial precursors, whereas SCs are derived from the neural crest. Furthermore, one oligodendrocyte can myelinate multiple axon segments, but one SC myelinates only a single axon segment (Figures 1 and 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, *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 [5–8] and GPR44 and the zinc finger Zeb2 in the PNS [9–11]. 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 (Figure 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,

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)**.

plating on Laminin-211, and experimentally applied stretching (Figure 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*γ*1*. The polarity protein Crb3 inhibits YAP nuclear translocation and