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The Initial Myelination in the Central Nervous System

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Abstract

Myelination contributes not only to the rapid nerve conduction but also to axonal insulation and protection. In the central nervous system (CNS), the initial myelination features a multistep process where oligodendrocyte precursor cells undergo proliferation and migration before differentiating into mature oligodendrocytes. Mature oligodendrocytes then extend processes and wrap around axons to form the multilayered myelin sheath. These steps are tightly regulated by various cellular and molecular mechanisms, such as transcription factors (Olig family, Sox family), growth factors (PDGF, BDNF, FGF-2, IGF), chemokines/cytokines (TGF-β, IL-1β, TNFα, IL-6, IFN-γ), hormones (T3), axonal signals (PSA-NCAM, L1-CAM, LINGO-1, neural activity), and intracellular signaling pathways (Wnt/β-catenin, PI3 K/AKT/mTOR, ERK/MAPK). However, the fundamental mechanisms for initial myelination are yet to be fully elucidated. Identifying pivotal mechanisms for myelination onset, development, and repair will become the focus of future studies. This review focuses on the current understanding of how CNS myelination is initiated and also the regulatory mechanisms underlying the process.

Introduction

Myelination is a well-coordinated program that generates myelin sheaths to wrap around axons. The ensheathment of axons results in an increased membrane resistance, a decreased membrane capacitance, and a specific molecular organization at the nodes of Ranvier (nodes, paranodes, and juxtaparanodes), thereby significantly facilitating a rapid saltatory impulse propagation along with the axons (Coman et al., 2006; Nave & Werner, 2014). As a result, action potentials can conduct along with myelinated axons up to 100-fold faster than unmyelinated ones with similar diameters (Monje, 2018). Apart from its role in speeding up nerve conduction, myelin also provides trophic axonal support by transferring pyruvate/lactate through monocarboxylate transporters (Philips & Rothstein, 2017), especially for longer axons whose segments are far (many centimeters or even meters in humans) away from the cell body but adjacent to local glia cells. Moreover, myelin also regulates axonal transport, the process whereby substances (such as organelles) are transferred between the cell body and the axon tip (Edgar & Garbern, 2004). Hence, central nervous system (CNS) myelination significantly benefits motor, sensory, and cognitive functions of the brain due to its essential roles in increasing the speed of action potential conduction and neuronal homeostasis.

In the CNS, the myelin sheath is formed as a multilamellar membrane structure by oligodendrocytes (OLs) (Nave & Werner, 2014; Simons & Nave, 2015), which occurs as a multistep process during development. These steps include oligodendrocyte precursor cell (OPC) proliferation, OPC migration, OPC differentiation, subsequent wrapping, and myelin compaction (Barateiro et al., 2016). Each step is efficiently orchestrated by both cellular and extracellular factors. However, the fundamental mechanism regulating initial myelination is not fully understood. Failure of CNS myelination would eventually lead to neurologic and neurodegenerative diseases, such as leukodystrophies (Kolodny, 1993). Hence, a comprehensive understanding of physiological behaviors

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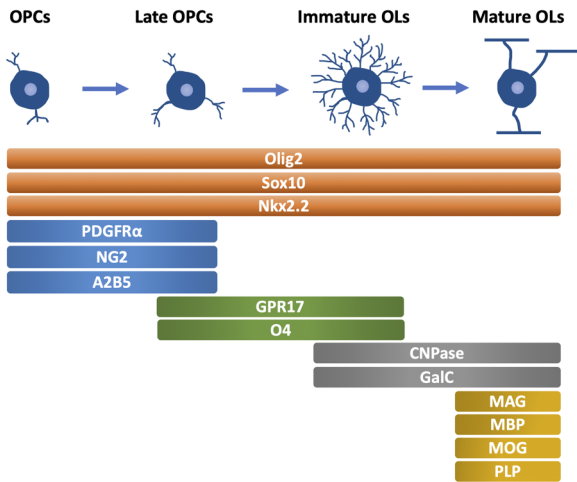Email: jiming.kong@umanitoba.ca

Figure 1. Oligodendrocyte Lineage Development and Specific Markers in Each Stage (mammals). OPCs, oligodendrocyte precursor cells. OLs, oligodendrocyte. PDGFRα, platelet-derived growth factor receptor α. CNPase, 2′,3′-cyclic nucleotide 3′-phosphodiesterase. GalC, galactocerebroside C. MAG, myelin associated glycoprotein. MBP, myelin basic protein. MOG, myelin oligodendrocyte glycoprotein. PLP, proteolipid protein.

Figure 2. Timeline of CNS Myelination Development in Humans, Rodents, and Zebrafish. The green box indicates the time of OPCs appearance. The orange box indicates the stage where OPCs and pre-myelinating OLs exist. The blue box indicates the time of myelination onset. g.w.= gestational weeks. E = embryonic day. OPCs, oligodendrocyte precursor cells. OLs, oligodendrocyte. hpf, hours post fertilization. dpf, days post fertilization. CNS, central nervous system.

in CNS myelination is required to identify potential therapeutic targets in pathological conditions.

In this review, we first summarize the key processes of initial myelination. Next, we highlight current progress in our understanding of mechanisms of initial CNS myelination from the aspects of transcription factors, extracellular factors, axonal regulation, and signaling pathways. Finally, we compare initial myelination with remyelination before concluding the review with open questions in this field.

Initial Events of CNS Myelination

OL Lineage Development

The maturation of OLs is a prerequisite for myelin sheath formation, highlighting the importance of OL lineage development for myelination. Generally, the OL lineage development can be divided into four stages, OPCs, late OPCs, immature (or premyelinating) OLs, and mature (or myelinating) OLs, which are characterized by the morphological changes and different expression patterns of specific markers (Figure 1) (Barateiro & Fernandes, 2014).

In the mouse brain, OPCs are first observed in the ventricular germinal layer of the lateral basal plate of the diencephalon at around embryonic day (E) 9 (Timsit et al., 1995). Interestingly, in the forebrain, a study describes three distinct waves of OPCs in a ventral-to-dorsal progression (Kessaris et al., 2006). Specifically, the first wave of OPCs originates in the ventral forebrain at E12.5, followed by a second wave of OPCs from the lateral and/or caudal ganglionic eminences at around E14.5. Finally, a third wave of OPCs occurs within the postnatal cortex. OPCs are proliferative cells with highly
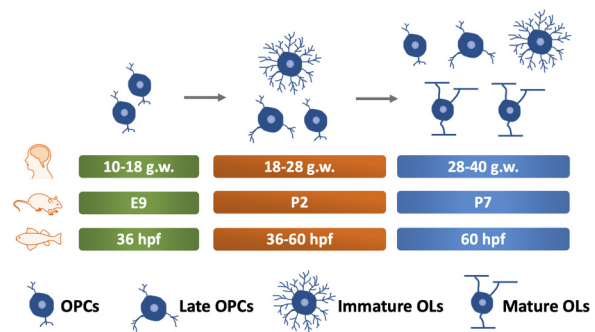
migratory capabilities, allowing them to migrate along with vasculature (Tsai et al., 2016) to the whole CNS before maturation and myelination. Unlike neurons that proliferate and migrate in the embryonic stage, these two processes in OPCs occur mainly in postnatal phases in rodents (Snaidero & Simons, 2014). At about postnatal day (P) 2, late OPCs account for the majority of OL lineage cells, with a small amount of immature OLs existing. Mature OLs appear at P7 to initiate the CNS myelination (Figure 2), which is almost completed in most brain regions by P60 (Snaidero & Simons, 2014). In adults, OPCs and intermediately differentiated OLs are present across the entire CNS (Dawson et al., 2003). Of note, CNS myelination follows a specific time course and sequence rather than occurring simultaneously. Generally, in mammals, CNS myelination starts in the brainstem and then continues rostrally to the forebrain and caudally to the spinal cord. This pattern correlates very closely with developmental milestones (Dietrich et al., 1988). For instance, myelination occurs early from motor-sensory roots, special senses, and the brainstem (Kinney et al., 1988), which are the necessary structures for reflex behaviors and survival.

Compared with rodents, only a few studies have addressed the OLs lineage in humans. OPCs in humans are first observed in the forebrain at 10 gestational weeks (g.w.). Immature OLs are observed between 18 and 28 g.w., although OPCs and late OPCs are still the major cell types during this stage (Barateiro et al., 2016). Thus, OLs lineage development during 18–28 g.w. of humans is similar to that of rodents at P2. Myelin basic protein (MBP) positive OLs are initially observed at around 28 g.w. during human development (Back et al., 2001; Barateiro et al., 2016; Hüppi et al., 1998), resembling the time point of P7 in rodents (Figure 2).

In zebrafish, another broadly used model for myelination study, OPCs are initially observed as early as 36 h post fertilization (hpf) (Kirby et al., 2006) and MBP, a marker of mature
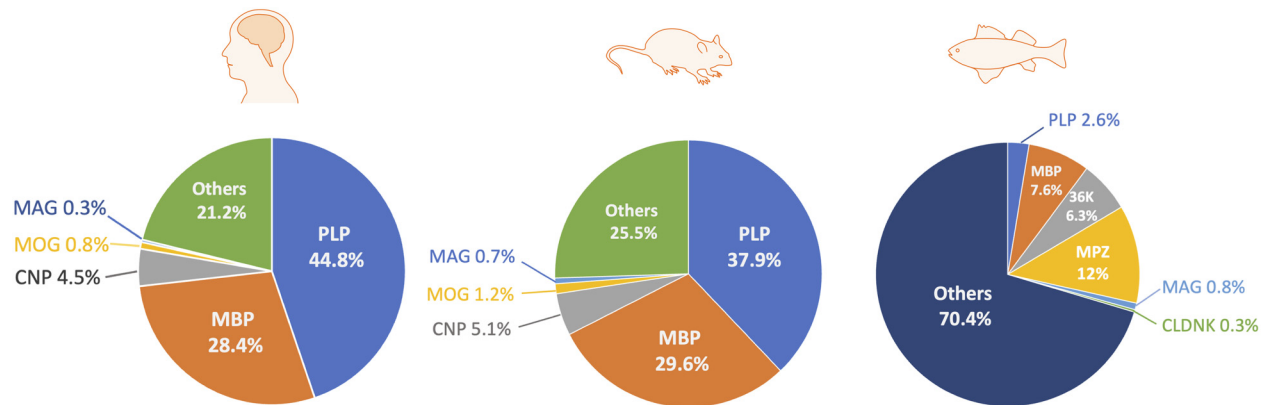
Figure 3. Relative Abundance of CNS Myelin Proteins in Humans (Jahn et al., 2020), Rodents (Gargareta et al., 2022), and Zebrafish (Siems et al., 2021). OPCs, oligodendrocyte precursor cells. OLs, oligodendrocyte. CNP, CNPase, 2′,3′-cyclic nucleotide 3′-phosphodiesterase. MAG, myelin-associated glycoprotein. MBP, myelin basic protein. MOG, myelin oligodendrocyte glycoprotein. PLP, proteolipid protein. MPZ, myelin protein zero. CLDNK, claudin K. CNS, central nervous system.

myelin, appears at about 60 hpf (Figure 2) (Almeida et al., 2011). Generally, CNS myelination is structurally and functionally conserved between zebrafish and mammals, although differences regarding the composition of myelin proteins are noticed (Figure 3) (Gargareta et al., 2022; Jahn et al., 2020; Siems et al., 2021). For example, myelin protein zero, a protein only found in the peripheral nervous system (PNS) of mammals, is present in the CNS of zebrafish (Brösamle & Halpern, 2002). Besides, zebrafish myelin also expresses some proteins that are absent in mammals, such as claudin K (Münzel et al., 2012), 36 K (Morris et al., 2004), and Zwilling-A/B (Schaefer & Brösamle, 2009). Moreover, a recent study shows that CD59 is the fourth most abundant (4.6%) myelin protein in zebrafish (Siems et al., 2021), while its abundance in mammals is comparatively low (0.01%) (Gargareta et al., 2022). Hence, more studies are required to explain the differences and determine the precise role of different myelin proteins in both zebrafish and mammals.

Axon Targeting, Contact, and Process Polarization

After ceasing migration, OPCs undergo continual process extension until making stable contact with the axonal membrane, subsequently forming an axon–glial interaction domain for further communication, namely, branching (Figure 4).

How OLs precisely target axons during initial myelination remain largely unknown. A recent study suggests that axon caliber alone, in the absence of axonal signals, allows myelination to initiate (Mayoral et al., 2018). Moreover, a study shows that OLs can sense the diameter of microfibers *in vitro*, thereby increasing sheath length with larger fibers (Bechler et al., 2015). These results are in line with the fact that nearly all axons with a diameter greater than 0.2 μm are myelinated (Goebbels et al., 2017), indicating an important role of axonal biophysical properties in axon selection during

myelination. Presumably, this may involve a curvature-dependent mechanism, such as regulations of certain membrane-anchored proteins (Chang-Ileto et al., 2011; McMahon & Boucrot, 2015). Interestingly, similar to the "growth cone" model in axon outgrowth and pathfinding, a growing body of evidence also suggests that OLs processes extend or retract following permissive or repulsive cues on axons, respectively. In rodents, such permissive cues include laminin-2/merosin, EphA4/B1, L1-CAM, N-cadherin, and Netrin-1 (Figure 4) (Thomason et al., 2020). The negative/repulsive cues include axonal ephrin-A1/B2, PSA-NCAM, LINGO-1, Jam2, and Galectin-4 (Sherman & Brophy, 2005; Thomason et al., 2020). However, none of these cues are sufficient to instruct OLs to target axons in the CNS, which requires further research for a better understanding of this.

Interestingly, recent studies also support the role of neural activity in regulating axon targeting during initial myelination. For example, blocking action potentials in the zebrafish spinal cord results in axonal mistargeting and hypomyelination (Hines et al., 2015). However, some *in vitro* studies show that OLs can also myelinate paraformaldehyde (PFA)-fixed axons (Rosenberg et al., 2008) and nanofibers (Lee et al., 2013) in the absence of neural activity. Likely, correct axonal targeting depends on multiple cues, including both neural activity and OL-intrinsic signals.

After an initial axon–glia contact, a series of changes in OLs occur, including the downregulation of RhoA activity (Baer et al., 2009) and the local enrichment of phospholipid in OL membranes, such as PIP2 and PIP3 (Goebbels et al., 2010; Snaidero et al., 2014), eventually leading to a polarization of myelinating cells toward axons.

Myelin Wrapping

Once contact is formed and the polarization is finished, the wrapping process initiates. In the CNS, individual OL can
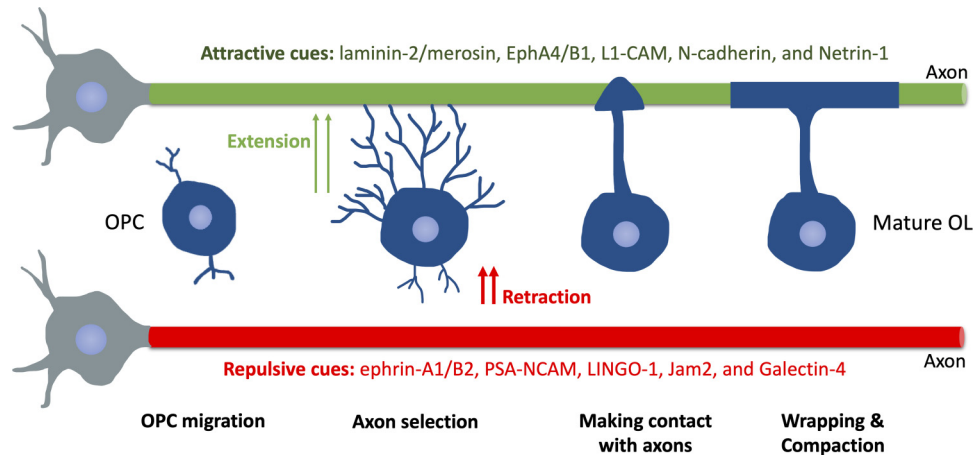
Figure 4. Schematic of Myelination Progression in Mammals. After migrating to the final spot, OPCs extend or retract processes following attractive or repulsive cues on axons. OPC, oligodendrocyte precursor cell. OL, oligodendrocyte.
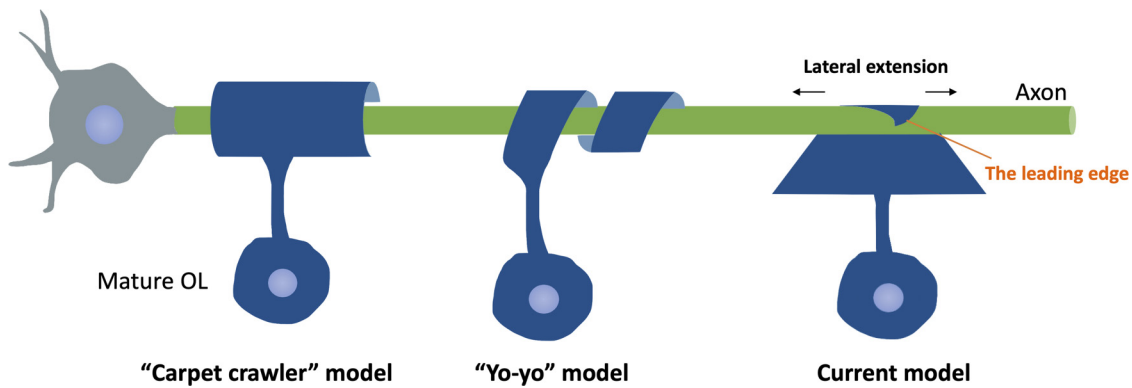

Figure 5. Schematic of Different Wrapping Models Proposed. The "carpet crawler" model proposes that the process flattens into a broad sheet before wrapping. The "yo-yo" model suggests that the OL processes wrap around the axons until an appropriate number of layers are formed, then extend laterally into overlapping sheets. The current model suggests that the triangle-shaped leading edge moves underneath previously deposited layers, followed by lateral extension of each layer of myelin.

myelinate up to 50 axons (Baumann & Pham-Dinh, 2001), with the number of membrane layers in one axon reaching up to 160 (Hildebrand et al., 1993). Nevertheless, the exact geometry of myelin wrapping is challenging to document due to the limitation of imaging technologies. Previously, two wrapping models are proposed, namely the "carpet crawler" model and the "yo-yo" model (Figure 5). The "carpet crawler" model suggests that, after axon–glia contact formation, the leading edge of the OLs membrane spreads and flattens into a broadsheet and then moves underneath itself to form the mature myelin sheath (Bunge et al., 1961). Alternatively, the "yo-yo" model proposes that the OL processes wrap around the axons until an appropriate number of layers are formed, then extend laterally into overlapping sheets (Pedraza et al., 2009). However, neither of these models provides the mechanisms of how synthesized molecules go through the compact myelin and reach the innermost layer, which cannot be easy as the inner layers become more and more distant to neural somas as the wrapping

proceeds. With the advancement of imaging technologies, better visualization and understanding regarding the wrapping model are gained. By taking advantage of three-dimensional electron microscopy (3D EM), a newer model is proposed: the triangle-shaped leading edge moves underneath previously deposited layers, followed by lateral extension of each layer of myelin (Snaidero et al., 2014). This wrapping model allows close contact between each myelin layer and its underlying axon, thereby contributing to axon–glia communication. Notably, the authors also suggest that cytoplasmic channels appear transiently within compact myelin to provide a short connection between the outer and inner tongue, allowing the transportation of newly synthesized membrane components from the soma to the inner tongue. As myelination completes, these cytoplasmic channels resolve (Snaidero et al., 2014).

The molecular mechanisms of the wrapping process have also become a focus of many studies. Of note, OLs show a periodic actin pattern that is not seen in astrocytes or microglia,

indicating tight cytoskeletal regulation during myelination (Brown & Macklin, 2019). In addition, one study indicates that actin polymerization in the leading edge is the main force driving the wrapping process, while actin depolymerization promotes membrane spreading by reducing surface tension (Nawaz et al., 2015). This is in line with another model proposing that actin polymerization powers OLs process extension in an Arp2/3-dependent manner, while actin depolymerization drives myelin wrapping (Zuchero et al., 2015). In this model, MBP prevents the actin disassembly factors cofilin and gelsolin from binding to PIP2, resulting in a release of cofilin/gelsolin to disassemble actin, thereby driving myelin wrapping.

Myelin Compaction

Myelin compaction coincides with wrapping. Initially, myelin membranes are negatively charged due to the abundance of phospholipids (PIP2, PIP3). Therefore, a mechanism of neutralizing these negative charges and pulling adjacent layers together is needed for compaction, which is now recognized as the key role of MBP. MBP shows a high affinity to negatively charged phospholipids, such as PIP2, thereby functioning as a "zipper" by pulling together two bilayers. Mice with *MBP* gene mutation (shiverer mice) fail to form compact myelin, resulting in severe dysmyelination with a characteristic "shivering" symptom (Readhead & Hood, 1990).

Of note, Snaidero et al. (2014) demonstrate that there is a delay of two or three wraps behind the growing tip during compaction, which makes room for newly formed layers. In this study, knockout of 2′,3′-Cyclic nucleotide 3′-phosphodiesterase (CNP), the third most abundant protein in CNS myelin in humans and rodents (Figure 3), results in a reduction of uncompacted wraps within the myelin sheath, indicating a potential role of CNP in preventing the myelin compaction in the innermost regions. It is likely that the leading edge grows together with the accumulation of CNP, while MBP appears two or three wraps behind to initiate myelin compaction. Therefore, proper myelin compaction may require equilibrium between MBP and CNP.

Regulation of the Initial CNS Myelination

Transcription Factors

OL lineage development and myelination are under tight transcriptional control (Figure 6). The Olig family is one of the most studied transcriptional regulators for CNS myelination. Olig2 is required during OPCs specification and maintenance, as exemplified by the loss of OPCs in Olig2 null mice (Ligon et al., 2006; Lu et al., 2002). In addition, Olig2 also plays a prominent role in promoting OPCs migration and OLs differentiation (Maire et al., 2010; Wegener et al., 2015; Zhu et al., 2012). Therefore, Olig2 is considered a master transcriptional regulator for most stages of OL lineage development, from OPCs specification to myelin protein production
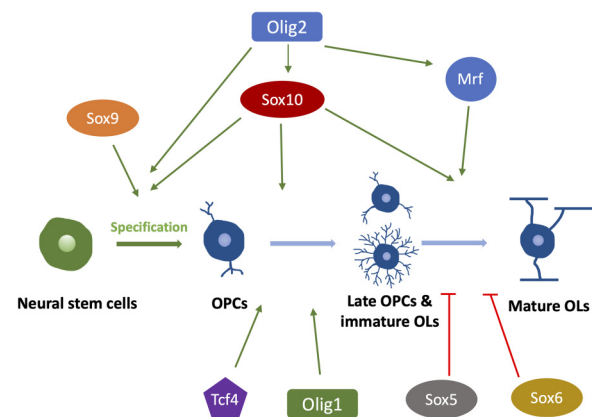

Figure 6. Schematic of Transcriptional Regulations in Different Stages of the OL Lineage Development. Arrows (→) indicate positive regulations, and the symbol (T) represents negative regulations. OPCs, oligodendrocyte precursor cells. OLs, oligodendrocyte. TFEB, transcription factor EB.

(Zhang et al., 2022). In contrast, Olig1 seems to be more involved in OLs maturation. For example, *Olig1* null mice exhibit severer dysmyelination due to the loss of mature/myelinating OLs, eventually leading to death within the third postnatal day (Xin et al., 2005). However, a subsequent study using new Olig1 knockout mice models shows that Olig1 null mice only exhibit a delay of OL differentiation but do not develop long-term myelin deficits (Paes de Faria et al., 2014), indicating a nonessential role of Olig1 in OL development. The possible reasons for the conflicting results may lie in how the mice lines were generated in these two studies. Paes de Faria et al. generated two independent Olig1 null mice models by different methods—one by homologous recombination in mouse embryonic stem cells, and the other one by transgenic rescue of an Olig1/Olig2 double-null mice line. Both lines showed consistent results. In contrast, Xin et al. crossed Olig1 null mice (with a Cre-Pgk-Neo cassette at the Olig1 locus) with FLP-expressing mice to remove the Pgk-Neo, which could potentially affect Olig2 expression considering that Olig1 and Olig2 locate close to each other. In zebrafish, both Olig1 and Olig2 are reported to control OL differentiation (Li et al., 2007; Park et al., 2002), indicating the similar role of the Olig family in regulating OL development.

The Sox family is another major group of transcriptional regulators involved in myelination (Figure 6). Sox10 is required for terminal OLs differentiation, as exemplified by the complete loss of MBP + and PLP + OLs in Sox 10 null mice (Stolt et al., 2002). In zebrafish, the *in vivo* time-lapse imaging shows that the myelinating OLs in Sox 10 mutants can initiate axon ensheathment without expressing myelin proteins but soon die after the onset of myelination (Takada et al., 2010). This may suggest a more important role of Sox10 in myelin maintenance than during the onset of myelination. Like Olig2, some Sox factors, such as Sox8 and Sox9, are also required for OL specification and differentiation

(Stolt et al., 2003, 2004). In contrast, other Sox members are found to inhibit OL differentiation by competing with Sox10, such as Sox5 and Sox6 (Emery & Lu, 2015).

In addition to the two major families of transcriptional regulators mentioned above, some new factors have been recently identified. For example, Tcf4 positively regulates OL differentiation in both myelination and remyelination without engaging its downstream Wnt/ β-catenin pathway (Hammond et al., 2015). Tcf4 null mice develop myelin deficits due to a lack of mature OLs (Phan et al., 2020). More recently, an elegant study shows that transcription factor EB induces selective OLs elimination in normally unmyelinated brain regions, thereby controlling when and where the initial myelination occurs (Sun et al., 2018). In addition, the myelin gene regulatory factor (Mrf) is also proven to crucially regulate CNS myelination by cooperating with Sox10. Mrf physically and functionally interacts with Sox10, synergistically promoting myelin gene expression (Hornig et al., 2013). Indeed, most transcriptional factors regulate myelination by directly binding to the promoter regions of myelin genes, thereby influencing myelin protein (MBP, PLP, and MAG) production (Tiane et al., 2019).

Extracellular Factors

Many studies have highlighted the importance of some growth factors in CNS myelination. Notably, many of them are released by astrocytes and microglia, the other two major glial cell types in the CNS (Figure 7). As an example of astrocyte-derived factors, the platelet-derived growth factor-alpha significantly promotes OPC proliferation while inhibiting its maturation (Traiffort et al., 2020). This is considered an important mechanism for maintaining the OPC pool and preventing OPCs from premature differentiation (Noble et al., 1988; Raff et al., 1988). The brain-derived neurotrophic factor (BDNF), derived from astrocytes and neurons (Miranda et al., 2019), is required for myelin development, as exemplified by the delayed CNS myelination in BDNF null mice (Cellerino et al., 1997). Moreover, the fibroblast growth factor 2 (FGF-2), highly expressed in astrocytes (Newman et al., 2000), is suggested to promote OPCs proliferation and inhibit their differentiation into mature OLs (Bansal & Pfeiffer, 1994; McKinnon et al., 1990). In addition, astrocytes also secrete ciliary neurotrophic factor (CNTF) to benefit OL maturation through the Janus kinase (JAK) pathway (Stankoff et al., 2002). Some microglia-derived growth factors are also reported to regulate myelin development, such as insulin-like growth factor 1 (IGF-1, also produced by neurons) and insulin-like growth factor 2 (IGF-2). IGF-1 null mice exhibit reduced OL survival and maturation, suggesting an important role of IGF-1 in regulating OL lineage development (Ye et al., 2002). Interestingly, IGF-1 is expressed in the activated (ameboid-like) microglia within the corpus callosum until P7, the time point of myelination onset. After P7, IGF-1 expression levels decrease along with the morphological changes of microglia from
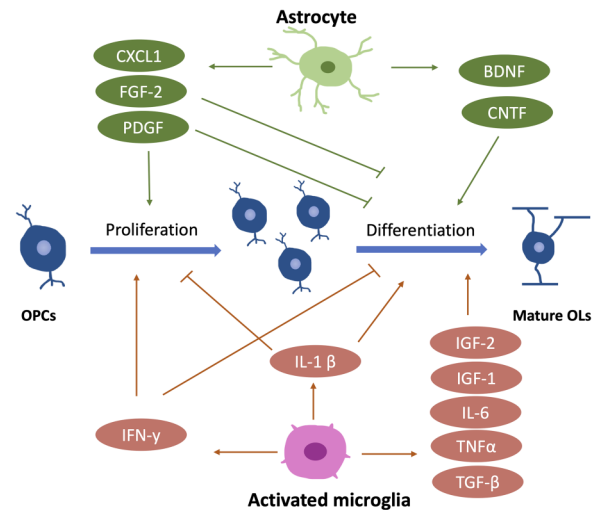

Figure 7. Major Growth Factors, Chemokines and Cytokines Released from Astrocytes and Microglia During Oligodendrocyte Lineage Development and Myelination. Arrows (→) indicate positive regulations, and the symbol (T) represents negative regulations. OPCs, oligodendrocyte precursor cells. OLs, oligodendrocyte. PDGF, platelet-derived growth factor. BDNF, brain-derived neurotrophic factor. CNTF, ciliary neurotrophic factor. IGF, insulin-like growth factor. FGF-2, fibroblast growth factor 2.

ameboid to ramified shape (Traiffort et al., 2020). Therefore, IGF-1 may play a unique role during the initiation of myelination rather than after the myelination onset. Besides IGF-1, IGF-2 also promotes OL survival *in vitro* (Nicholas et al., 2002), although its role in myelination is less extensively studied.

Interestingly, compared to astrocyte-derived factors, microglia-derived factors appear to play a more significant role in OL differentiation and myelination. A study shows that microglia-conditioned medium, but not astrocyte-conditioned medium, significantly enhances myelin protein expression and myelin sheath formation in the neuron-OL myelination coculture (Pang et al., 2013). However, the fundamental mechanism of how microglia regulate myelination through their secretome remains unclear.

Cytokines and chemokines are also important players in the regulation of CNS myelination, and most of them are microglia-derived (Figure 7). Activated microglia secrete TGF-β, IL-1β, TNF-α, IL-6, and IFN-γ to regulate OL development during development, and a blockade of these factors leads to impaired oligodendrogenesis (Shigemoto-Mogami et al., 2014). Specifically, IL-1β enhances OL maturation but negatively regulates OPC proliferation (Vela et al., 2002). In contrast, IFN-γ promotes OPC proliferation while inhibiting its differentiation (Baerwald & Popko, 1998; Chew et al., 2005), indicating that different microglia-derived cytokines may have opposite influences on OL development, and they work synergistically to determine OL fates. Besides microglia, astrocytes also produce chemokines to regulate OL development, such as CXCL-1. CXCL-1 may inhibit OPC migration while promoting its proliferation (Tsai et al., 2002).

Hormones, such as thyroid hormone (T3), are also closely involved in myelination. During early development, brain T3 is of maternal origin via placenta (Morreale de Escobar et al., 1987). T3 controls OL development in mammals by inhibiting OPC proliferation before promoting OL differentiation *in vitro* and *in vivo* (Almazan et al., 1985; Calza et al., 2002). Consistently, a lack of T3 in zebrafish results in hypomyelination, which is restored after T3 supplementation (Farías-Serratos et al., 2021). This sheds light on a well-conserved regulation mechanism of CNS myelination between mammals and zebrafish.

Axonal Regulations

Regarding axonal signaling during initial myelination, one interesting fact is that OLs can myelinate PFA-fixed axons and even nanofibers *in vitro*. This is agreed by a more recent study showing OLs derived from different areas (cortex and spinal cord) can myelinate microfibers *in vitro* with the same internode length as seen in corresponding regions *in vivo* (Bechler et al., 2015). However, there may be other explanations. Alternatively, it is very likely that some inhibitory molecules expressed on the surface of axons prevent myelination from happening until neutralized *in vivo*. Indeed, many studies have identified various axonal adhesion molecules that negatively regulate OLs development and myelination. PSA-NCAM and L1, the best-studied adhesion molecules, are expressed on non-myelinated axons and are significantly downregulated during the onset of myelination (Charles et al., 2000; Jakovcevski et al., 2007). Presumably, these inhibitory adhesion molecules need to be neutralized before the wrapping process initiates, although a more direct correlation between these two events awaits testing. LINGO-1 is another inhibitor of myelination. In rats, downregulation of LINGO-1 promotes myelination, and conversely, overexpression of LINGO-1 inhibits myelin formation by activating RhoA signaling (Mi et al., 2005). Consistently, LINGO-1 knockdown in zebrafish enhances OL differentiation and promotes subsequent myelination (Yin & Hu, 2014). Together, these inhibitory molecules are closely involved in regulating myelination development, potentially the onset of myelination. If these inhibitors are the key factors to control the timing of myelination onset, some mechanisms must exist to regulate the persistence of the inhibitory signals during initial myelination, such as the "inhibitor of the inhibitor."

In addition to adhesion molecules, neuronal activity is also suggested to profoundly regulate myelination *in vivo*. A study shows that pharmacogenetic stimulation of somatosensory axons in the mouse brain increases OPCs differentiation, resulting in thicker myelin in simulated axons compared to neighboring nonsimulated ones (Mitew et al., 2018). Moreover, using zebrafish, a recent study (Mensch et al., 2015) shows that a reduction in synaptic vesicle release results in a decrease in the axon numbers myelinated by one single OL. Furthermore, when increasing neural activity, 40% more axons are myelinated by a single OL, indicating an activity-dependent regulation during myelination. However, even without neural activity, an individual OL still myelinates around 60% axons of its full capacity. Therefore, it is reasonable to believe that neuronal activity is an essential modulator for myelin sheath development and refinement, although it may not be required for the ensheathment itself. Indeed, an emerging consensus nowadays is that the activity-driven myelination plasticity is essentially important for the myelination maintenance stage, during which learning and exercising occur frequently. Socially isolated mice develop hypomyelination in the prefrontal cortex (Liu et al., 2012; Makinodan et al., 2012). Consistently, an enriched environment increases myelination in rat corpus callosum (Zhao et al., 2012). Together, these studies highlight the important role of environmental input in myelin sheath formation. One can assume that the results are led by the changes in neuronal activity, although more straightforward evidence is needed in future studies.

The molecular mechanisms of this activity-dependent myelination remain unclear. Some studies propose that the glutamate released from axons may interact with myelinating OLs since both OPCs and OLs express the AMPA and NMDA receptors for glutamate (Bakiri et al., 2009; Butt, 2006; Káradóttir & Attwell, 2007). Alternatively, another study suggests that neuronal activity may control the release of neuregulin 1 from neural axons, thereby switching OLs between activity-dependent mode and activity-independent mode (Lundgaard et al., 2013).

Signaling Pathways

Many highly conserved intracellular signaling pathways, such as Wnt/β-catenin, PI3 K/AKT/mTOR, and ERK/MAPK signaling pathways, are suggested to tightly regulate CNS myelination. Initially, Wnt signaling is identified as a negative regulator of OL differentiation and myelination. Activation of Wnt signaling in mice leads to a delayed appearance of mature OLs and myelin proteins, while the number of OPCs remains unchanged (Feigenson et al., 2009), suggesting that the Wnt pathway is potentially involved in the OL differentiation stage. Similarly, upregulation of Wnt/β-catenin by deleting its antagonist in mice, such as APC and Axin2, results in impaired OL maturation, subsequently leading to hypomyelination (Fancy et al., 2011; Lang et al., 2013). However, conflicting results are obtained when inhibiting endogenous β-catenin in the conditional knockout mice. One study demonstrates that the Cre activity-induced β-catenin knockout does not influence OL differentiation (Lang et al., 2013), whereas another study shows that the conditional knockout of β-catenin causes a significant reduction in the numbers of mature OLs in mice brains from E18 to P15 (Dai et al., 2014). Of note, the latter study applies tamoxifen to delete the β-catenin gene much earlier than the former (E10.5 versus P6), potentially leading to conflicting results. Early loss of β-catenin may have more meaningful influences on

OL development. However, in a zebrafish study, siRNA-induced knockdown of β-catenin inhibits OL differentiation and myelination in zebrafish larvae (Tawk et al., 2011), suggesting that the Wnt signaling pathway may also have promoting effects on myelination. Further studies are needed to clarify these seemingly conflicting conclusions.

PI3K/AKT/mTOR is another classic intracellular signaling pathway involved in many basic processes, such as cell proliferation and survival (Dudek et al., 1997; Franke et al., 1997). OL development is no exception. Overactivation of PI3 K/AKT/mTOR results in increased myelin thickness in mice (Flores et al., 2008; Harrington et al., 2010). Conversely, the downregulation of mTOR by its inhibitor rapamycin significantly impairs myelination in transgenic mice (Narayanan et al., 2009). Interestingly, in studies using knockout mice, the spinal cord seems more vulnerable to the deletion of mTOR than the brain. Mice with mTOR conditional ablation exhibit nearly unaffected myelination in the corpus callosum, while the spinal cord, in contrast, shows severe hypomyelination (Bercury et al., 2014; Wahl et al., 2014). Many studies show that mTOR deletion causes a reduction in MBP mRNA and MBP proteins in the spinal cord (Bercury et al., 2014; Wahl et al., 2014), highlighting the role of mTOR signaling in regulating MBP production at both transcription and translation levels.

ERK/MAPK is also considered a positive regulator of CNS myelination. Reduced myelin thickness is observed in Erk1/2 conditional knockout mice (Ishii et al., 2019). Furthermore, one study identifies the FGF-Receptor-type-2 (FGFR2) as a key upstream signal of ERK by showing that the myelin thickness reduction induced by conditional ablation of FGFR2 can be rescued by upregulating ERK signaling in transgenic mice (Furusho et al., 2017). ERK signaling also regulates adulthood myelination, as exemplified by the reinitiation of myelin growth in adult mice following ERK upregulation (Ishii et al., 2016; Jeffries et al., 2016). More recently, a study points out that the ERK/MAPK and the PI3 K/AKT/mTOR signaling pathways need to work both independently and cooperatively for a finely tuned myelination (Ishii et al., 2019), suggesting the presence of crosstalk among these key signaling pathways during myelination.

Some other signaling pathways also contribute to myelin development. For example, the bone morphogenetic protein (BMP) pathway is a potent inhibitor of OL differentiation and myelin protein expression (Grinspan, 2015). When treating rodent OPCs with BMP4 *in vitro*, their differentiation is significantly inhibited in a dose-dependent manner (Grinspan et al., 2000). Similarly, Notch signaling pathways are also suggested to inhibit OPCs differentiation during development (Genoud et al., 2002; Wang et al., 1998).

Remyelination Versus Initial Myelination

Remyelination refers to the adaptive responses to dys- and demyelination whereby the myelin sheath is structurally and functionally restored. Many similarities are shared between initial myelination and remyelination regarding the major steps and the regulating mechanisms. By analogy with initial myelination, remyelination starts with the recruitment of adult OPCs to the lesion sites, followed by morphological changes of OPCs, OPCs differentiation, wrapping, and myelin compaction. Both OPCs and adult OPCs proliferate and migrate to the spot where myelination is needed, although adult OPCs have a longer basal cell cycle time and slower migration speed (Wolswijk & Noble, 1989). As seen in initial myelination, an upregulation of several transcription factors (Olig2, Sox2) is also observed when remyelination initiates (Fancy et al., 2004; Shen et al., 2008; Watanabe et al., 2004). In addition, the inhibitory roles of LINGO-1 and Wnt signaling can also serve as important regulating mechanisms for remyelination (Fancy et al., 2009; Mi et al., 2007).

However, the differences between initial myelination and remyelination are documented. First, the relationship between the caliber of axons and the thickness of myelin sheath, namely g-ratio, is altered. The optimal g-ratio in initial myelination is 0.6, while remyelination only generates a thinner and shorter myelin sheath, resulting in a greater g-ratio than expected (Blakemore, 1974). Second, some molecular mechanisms vary between initial myelination and remyelination. On the one hand, some molecules are more involved in initial myelination than in remyelination. For example, a recent study shows that fatty acid–binding protein 7 (FABP7) is important in OPCs differentiation during development but not in remyelination (Foerster et al., 2020). On the other hand, some mechanisms are, at least for now, remyelination-specific. For example, CD47, a well-documented "don't eat me signal," may serve as a key mechanism of remyelination failure. CD47 tags myelin debris after demyelination and functions as a marker of "self," thereby preventing their clearance by microglia (Gitik et al., 2011). However, the role of CD47 in initial myelination has not been addressed yet. Indeed, since initial myelination and remyelination have similarities but are not identical, it is reasonable that they share some signaling pathways but also own their unique way of orchestrating the processes.

Concluding Remarks

Research regarding initial CNS myelination has gained great progression due to researchers' passion for this field. It is well recognized that myelination involves many steps regulated in time and space, during which various molecules and signaling pathways are responsible for the orchestration.

In this review, we have covered some mechanisms in initial CNS myelination. However, the picture is incomplete, with many challenging questions remaining to be answered. For example, the key signal that triggers the initiation of CNS myelination remains largely unknown. In contrast, a large body of evidence has suggested a key mechanism for PNS myelination. Specifically, the level of neuregulin 1

type III expressed on the PNS axons is a pivotal instructive cue for myelination. Myelinated axons express significantly higher levels of neuregulin 1 type III than unmyelinated ones, resulting in different ensheathment fates of PNS axons (Taveggia et al., 2005). This explains the fact that Schwann cells, the myelinating glia cells in the PNS, do not myelinate the neuregulin 1 type III-deficient nanofibers *in vitro* (Bechler et al., 2015). However, such key factors or mechanisms have yet to be identified in the CNS, which will become a focus in future studies. Fortunately, a diversity of animal models (zebrafish) and imaging techniques (3D EM) offer preeminent tools for *in vivo* myelination studies. Hopefully, researchers can take advantage of them to get a deeper insight into not only initial myelination but also myelin repair after injuries or demyelinating diseases, thereby helping identify the potential treatment targets for them.

Author contributions

J.K. selected the topic. Q.Y. wrote the paper; T.G. and Y.G. reviewed and edited the paper; J.K. critically revised the paper.

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