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·Review·

Signaling mechanisms regulating myelination in the central nervous system

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The precise and coordinated production of myelin is essential for proper development and function of the nervous system. Diseases that disrupt myelin, including multiple sclerosis, cause significant functional disability. Current treatment aims to reduce the inflammatory component of the disease, thereby preventing damage resulting from demyelination. However, therapies are not yet available to improve natural repair processes after damage has already occurred. A thorough understanding of the signaling mechanisms that regulate myelin generation will improve our ability to enhance repair. In this review, we summarize the positive and negative regulators of myelination, focusing primarily on central nervous system myelination. Axon-derived signals, extracellular signals from both diffusible factors and the extracellular matrix, and intracellular signaling pathways within myelinating oligodendrocytes are discussed. Much is known about the positive regulators that drive myelination, while less is known about the negative regulators that shift active myelination to myelin maintenance at the appropriate time. Therefore, we also provide new data on potential negative regulators of CNS myelination.

Keywords: myelination; signaling; oligodendrocyte; Akt kinase

Introduction

Myelin is the specialized, lipid-rich membrane that forms an insulating sheath around axons. Traditionally considered an evolutionary adaptation resulting in rapid and efficient transduction of action potentials *via* 'saltatory' impulse propagation[1], it is also essential for the proper development of the vertebrate nervous system. While optimizing the electrical activity of axons, myelin also clearly provides trophic and metabolic support to ensheathed axons[2,3]. Myelin is produced by oligodendrocytes in the central nervous system (CNS) and Schwann cells in the peripheral nervous system (PNS). The process of myelination involves enormous energy expenditure for massive membrane biogenesis to generate concentric, spiral wraps of myelin around axons. In mammals, this process occurs in large part during postnatal development[4,5] and is modulated by electrical activity[6,7] as well as axon-derived molecular signals[8].

It is well-established that myelin thickness is directly related to axon diameter[9,10]. Extensive bidirectional signaling between axons and myelinating glia regulates this relationship. The maturation of axons and their long-term survival both depend on the presence of myelin[11]. In turn, the proliferation, migration, survival, and differentiation of myelinating glia require axon-derived signals[12], and the long-term maintenance of the myelin sheath also depends on axonal signals[13].

Disruption of this axon-myelin relationship is seen in many congenital and acquired neurological diseases, including the leukodystrophies and multiple sclerosis (MS). MS is the most common cause of neurological disability in young adults and is characterized by CNS demyelination induced by inflammation and immune responses. Acute demyelinating episodes result in neurological impairment that is generally followed by functional recovery as the inflammation resolves. However, permanent disability is

eventually seen in MS, resulting primarily from axonal transection after chronic demyelination or other pathologies[14]; however axonal damage can occur at the same time as demyelination[15]. Clearly, investigating the mechanisms regulating axon-myelin interactions is pivotal in order to improve treatment for myelin disorders.

Currently, the only FDA-approved medications for treating MS are immunomodulating agents, which help to prevent immune and inflammatory attacks during the relapsing-remitting stage of MS. However, none of these agents is effective in treating the progressive phase of the disease that results from accumulated axon damage. An additional approach to treating this disease would be to enhance the endogenous repair processes that occur naturally after acute demyelination. Remyelination occurs during early stages of MS and, while rarely complete, allows for some functional recovery[16,17]. However, after multiple episodes of demyelination, repair fails, resulting in progressive neurodegeneration[18]. The process of remyelination shares many features with developmental myelination[19]. Therefore, a thorough understanding of the mechanisms regulating developmental myelination may help target remyelination therapeutically, promoting functional recovery and preventing MS progression.

In this review, we summarize the current state of knowledge of the signaling mechanisms regulating myelination, focusing primarily on CNS myelination, although studies elucidating important mechanisms in the PNS are also described. CNS myelination is discussed in terms of (1) axon-derived signals; (2) extracellular matrix and soluble signals; and (3) intracellular signaling cascades within myelinating oligodendrocytes. Both positive and negative influences on myelination are discussed. The precise coordination of positive and negative regulators of myelination is crucial in producing and maintaining the correct amount of myelin in order to optimize neural function. Many signaling pathways are known to be positive regulators, but much less is currently known about the negative regulators of myelination. We therefore also provide new data on potential negative regulators of CNS myelination.

Control of Myelination at the Axolemma: Neuregulin/ErbB Signaling and the Secretases

The neuregulins belong to the superfamily of epidermal growth factor (EGF)-like ligands. Four genes encode the neuregulins, of which neuregulin I (NRG1) has been studied most extensively[20,21]. The NRG1 gene is large and complex, contributing to at least 15 different NRG1 isoforms by alternative promoter usage and RNA splicing[22].

NRG1 signals through ErbB receptors, a family of receptor tyrosine kinases that modulate numerous intracellular signaling pathways[23,24]. Both ErbB3, which has no kinase domain, and ErbB4 bind NRG1 directly[24,25]. ErbB2, which does not bind NRG1, also participates in signal transduction by heterodimerizing with ErbB3[26].

NRG1 and ErbB receptors are expressed widely in the CNS and PNS and play major roles in neuronal development[23,27,28]. NRG1 type-III is a transmembrane protein with a cytosolic N-terminus that influences the amount of neuregulin that is targeted to the membrane[29]. Its expression is restricted mainly to neurons[30,31]. In the PNS, axonal NRG1 type-III expression can influence whether an axon is myelinated[32], and the amount of axonal NRG1 type-III regulates Schwann cell myelin sheath thickness[33]. Axonal NRG1 signaling acts through ErbB receptors on Schwann cells to regulate PNS myelination[34], and the peripheral hypermyelination disorder Charcot-Marie-tooth disease type 1A results from mutations leading to overexpression of ErbB2 and ErbB3 receptors[35].

The role of NRG/ErbB signaling in the CNS is still under debate. Neuregulins mediate survival and differentiation of cultured oligodendrocyte progenitor cells (OPCs)[36,37], and spinal cord explant studies demonstrate the requirement for NRG signaling in oligodendrocyte development[38]. Other studies suggest that, while axonal NRG1 does not direct initial oligodendrocyte differentiation, it promotes myelination in some CNS areas[39]. ErbB2 signaling has also been shown to positively regulate terminal oligodendrocyte differentiation and myelination *in vivo*[40,41]. ErbB4 signaling in oligodendrocytes is quite complex. The complete loss of ErbB4 signaling in neural tube explants increases the number of differentiated oligodendrocytes[42], whereas expression of a dominant negative ErbB4 that binds NRG1, but cannot signal in oligodendrocytes *in vivo*, results in fewer oligodendrocytes and reduced myelin thickness of CNS axons[43]. While these studies suggest at least regional CNS regulation of oligodendrocyte development or myelination by NRG1, mice with complete NRG1 knockout or elimination of both ErbB3 and ErbB4 receptors in oligodendrocytes

have normal CNS myelination, indicating that these factors are not required for normal CNS myelination[44]. On the other hand, that same study demonstrated that overexpression of either NRG1 type-I or type-III could induce CNS hypermyelination. Thus, it clearly can impact some elements of CNS myelination.

Alterations in CNS white matter and NRG1/ErbB signaling have been implicated in several psychiatric disorders, including schizophrenia[45,46], obsessive-compulsive disorder[47,48] and bipolar disorder[49]. NRG1 in particular is a schizophrenia susceptibility gene[50]. Social isolation of juvenile mice alters the expression level of NRG1 in the prefrontal cortex, and causes hypomyelination that resembles ErbB3 knockout[51]. Furthermore, social isolation of adult mice also influences myelin thickness in the prefrontal cortex and is reversed by social reintegration[52]. A direct connection between altered myelin structure or function and psychiatric disease remains to be identified, but these observations are suggestive of a potential impact of subtle myelin changes.

Regulation of the NRG/ErbB system is achieved by proteolytic cleavage of membrane-bound neuregulins by secretase enzymes. β-secretase (BACE1) is able to cleave NRG1 type-III[53], a process regulated by the metalloendopeptidase nardilysin[54]. Both BACE1- and nardilysin-deficient mice are hypomyelinated in both the PNS and CNS[54,55]. However, the effects of BACE1 may be region-specific, since while optic nerve and hippocampus are hypomyelinated[55], myelin in the corpus callosum of BACE1-null mice is indistinguishable from that of wild-type mice[56]. Other secretases, including 'a disintegrin and metalloprotease' (ADAM) and γ-secretase, are also involved in regulating NRG1 signaling and myelination. For example, knockdown of ADAM17 inhibits PNS myelination[57]. In primary culture, γ-secretase, which cleaves both NRG1[58] and the intracellular domain of the ErbB4 receptor[59] induces oligodendrocyte maturation[59]. By contrast, in myelinating co-cultures, it likely blocks myelination, since its inhibition accelerates and enhances myelination [60].

These studies suggest that distinct mechanisms may regulate myelination in the PNS and CNS. Whereas Schwann cells maintain a one-to-one relationship with axons, oligodendrocytes can myelinate as many as 40 axons[61,62], and it may be that more diverse environmental input is needed to regulate CNS myelination. Thus, multiple axolemmal/extracellular cues directing parallel signaling pathways likely regulate the somewhat more complex CNS myelination.

Control of Myelination by the Extracellular Matrix and Soluble Factors

In addition to membrane-derived juxtacrine signals from axons, elements in the extracellular matrix (ECM) and other soluble factors also modulate myelination. Numerous components in both the PNS and CNS have important effects on the development and function of myelinating glia[63]. Of particular interest with respect to CNS myelination is the effect of laminin. Laminin receptors on oligodendrocyte lineage cells, including integrin and dystroglycan, mediate a variety of effects including oligodendrocyte survival, differentiation, and spatio-temporal targeting during development[64]. Laminin binding to dystroglycan is necessary for oligodendrocyte process dynamics, including process outgrowth and branching, and it could regulate the myelinating capacity of individual cells[65]. The cellular origin of laminin in the developing brain is unknown, and laminin is virtually absent from fully myelinated white matter tracts[64,66]; although it is re-expressed during remyelination[67]. Laminin-deficient mice have dysmyelinated axons and reduced myelin sheath thickness[68]. In addition to signaling through integrins and dystroglycan, laminin also signals through oligodendrocyte-expressed integrin-linked kinase (ILK), and the expression of a dominant negative form of ILK inhibits laminin-induced myelin-like membrane formation[68]. Thus, extracellular laminin creates an environment that facilitates myelin production and could provide instructional cues through several signaling pathways to myelinating oligodendrocytes.

In addition to ECM molecules, which provide a substrate structure for the developing cell, a variety of diffusible factors influence CNS myelination, including insulin growth factor 1 (IGF-I)[69,70], and fibroblast growth factor (FGF)[71]. Other soluble factors have been implicated in regulating CNS myelination, including ciliary neurotrophic factor[72], brain-derived neurotrophic factor[73,74], and neurotrophin-3[75]; however, these factors seem to affect oligodendrocyte differentiation more than myelination.

IGF-I exerts effects on all major cell types in the CNS and acts primarily through the type 1 IGF receptor (IGF1R)[70]. Overexpression of IGF-I in mice results in increased brain

growth and myelination[76], and induces both increased myelin protein gene expression and increased oligodendrocyte number[77,78]. By contrast, IGF-I knockout mice have decreased amounts of myelin proteins and reduced numbers of oligodendrocytes and their precursors, and IGF-II can only partially compensate[79]. The source of IGF-I in the CNS is unclear, since increased myelination can be driven by either oligodendrocyte- or astrocyte-produced IGF-I[80,81]. IGF-I likely acts directly through IGF1R on the surface of oligodendrocyte lineage cells, since IGF1R conditional knockout from this lineage decreases OPC proliferation, increases apoptosis, and results in reduced numbers of oligodendrocytes[82]. IGF-I signaling is transduced *via* insulin receptor substrate (IRS)[83]. However, the hypermyelination effects of IGF-I overexpression are not eliminated by IRS-1 deficiency[84]. In IRS-2 knockout mice, however, myelin protein expression is delayed, suggesting that IRS-2 may be the major mediator of IGF-I responses to control the proper timing of myelination[85]. IGF-I is capable of protecting oligodendrocytes and myelin from hypoxia-ischemia[86], TNF-α-induced damage[87], and glutamate toxicity[88], and these and other data have led to the suggestion that IGF-I treatment may be an effective therapy to enhance myelination or remyelination in humans[89]. On the other hand, IGF-I impacts many cells, not only protecting oligodendrocytes during injury, but also enhancing astrogliosis, which would limit remyelination[90].

FGFs are a family of growth factors that, like IGF and neuregulin, serve diverse functions. FGF-1 and FGF-2 are produced by neurons and astrocytes[91,92], and are upregulated during active myelination[93]. FGF is even found in purified axolemma from adult myelinated axons[94]. Although FGF-2 increases the formation of myelin-like sheets *in vitro*[95], FGF-2 treatment of myelinating mixed brain cultures actually reduces myelin formation[96]. Moreover, intracerebral injection of FGF-2 increases the number of promyelinating oligodendrocytes in rats, but reduces, rather than promotes, myelination[78,97].

FGF receptor 1 (FGFR1), FGFR2 and FGFR3 are expressed by oligodendrocyte lineage cells[98,99] and influence oligodendrocyte specification and differentiation[100]. Their differential expression at multiple stages of oligodendrocyte development suggests that they may have different roles. For example, FGFR2 is specifically expressed in differentiated oligodendrocytes, is enriched in lipid-raft microdomains, and is localized within paranodal myelin[101], suggesting a potentially positive role in myelination. On the other hand, expression of a dominant-negative FGFR1 under control of the MBP promoter shows a slight but significant increase in myelin thickness of optic nerve axons, suggesting a potentially negative role for FGFR1 signaling in myelin production[102]. Unfortunately, FGF signaling was not completely blocked in these mice, and compensation by FGFR2 may have occurred. In more recent work, Furusho and colleagues demonstrated the impact of FGF/FGFR signaling during myelination in mice lacking both FGFR1 and FGFR2 in oligodendrocyte lineage cells. In these animals, OPC proliferation and differentiation were unaffected and the initiation of myelination was normal. However, the overall degree of CNS myelination was severely reduced, suggesting a role for FGFR1/2 in regulating CNS myelin thickness[71]. These results parallel studies in the PNS, but further work is needed to establish whether FGF signaling is both necessary and sufficient to regulate myelin sheath thickness in the CNS. These results also highlight that a given molecule (e.g. FGF) can have quite dissimilar effects during different stages of oligodendrocyte differentiation.

Control of Myelination by Intracellular Signaling Cascades

Pathways Impacting the Cytoskeleton

Oligodendrocytes must integrate the vast array of extracellular signals not only to properly differentiate into mature, myelin-producing cells, but also to determine when active myelination should cease and the cell should transit into a state of myelin maintenance. Signaling molecules within oligodendrocytes that have gained attention for their role in regulating myelination include Fyn, FAK, MAPK/ERK, and PI3K/Akt/mTOR[8,12,63,103,104].

Fyn kinase belongs to the Src family of non-receptor tyrosine kinases. It is expressed throughout the brain and is highly expressed in oligodendrocytes[105]. Fyn likely integrates signals from ECM molecules[63] and axonal ligands[106] in order to induce widespread changes in cytoskeletal dynamics leading to differentiation and myelination[103,107,108]. Fyn-deficient mice display severe hypomyelination in patterns consistent with a role in the initial stages of myelination process[109,110], in stimulating MBP gene

transcription[111], and in regulating local translation of MBP mRNA[112-114]. Activation of Fyn depends on both phosphorylation and dephosphorylation events at different sites on the molecule, and the necessary signals are provided at least in part by integrin-contactin complexes[115]. Loss of either of the protein tyrosine phosphatases CD45 or PTPα, both positive regulators of Fyn activity, causes dysmyelination[116,117].

Fyn is negatively regulated by several signaling systems. In laminin-deficient brains, increased repression of Fyn is accompanied by elevated levels of Csk, another Src-family kinase that negatively regulates Fyn[118]. Likewise, tenascin C blocks Fyn activation, thereby inhibiting MBP expression and myelination[119]. In addition, protein tyrosine phosphatase receptor type Z (PTPRZ) was recently identified as the counterpart phosphatase to Fyn kinase, and loss of PTPRZ from oligodendrocytes was shown to enhance myelination during development[120]. Given the variety of positive and negative regulators of Fyn function, further studies are required in order to fully assess its role in CNS myelination.

Focal adhesion kinase (FAK) is a non-receptor protein tyrosine kinase that is also expressed ubiquitously in the CNS. FAK is present in cells of the oligodendrocyte lineage[121] and in myelin[122]. FAK is activated in post-migratory, differentiating OPCs[123] and like Fyn, FAK also seems to integrate signals from the ECM in order to induce cytoskeletal changes within oligodendrocytes necessary for myelination[63]. In mature oligodendrocytes, FAK co-localizes with dystroglycan-enriched structures, potentially involved in remodeling oligodendrocyte process extensions based on ECM input[65]. In Schwann cells, FAK is found in complex with ErbB2/ErbB3 heterodimers[38,124]. Both FAK and Fyn are necessary mediators of laminin-induced oligodendrocyte process formation along with downstream mediators Rac1 and Cdc42[123]. FAK promotes morphological maturation of oligodendrocytes in response to laminin-2, and restricts process extension in the presence of fibronectin[125]. Conditional knockout of FAK in oligodendrocytes reduces process outgrowth, suggesting a positive role for FAK in the initial stages of myelination[126]. FAK signaling often feeds into other signaling networks, such as the Akt/mTOR pathway (see below).

Pathways Integrating Multiple Signaling Systems

The mitogen-activated protein kinase (MAPK)/extracellular-related kinase (ERK) pathway is a point of convergence of many external signals in oligodendrocytes, including NRG1[53], BDNF[127], IGF-I[128], and FGF[129,130]. Conditional ablation of B-Raf, an upstream activator of MAPK/ERK signaling, results in dysmyelination, defective differentiation, and reduced ERK activation[131]. Double mutants lacking both FGFR1 and FGFR2 have reduced ERK activation, which results in normal oligodendrocyte differentiation and initial myelin wrapping, but significant myelination deficits[71]. ERK1 and ERK2 signaling promotes oligodendrocyte myelination in an *in vitro* myelination assay[132] and *in vivo* double knockout of ERK1 and ERK2 from oligodendrocytes results in dysmyelination[133]. p38MAPK has been shown to positively regulate oligodendrocyte differentiation and the expression of myelin genes[134,136]. p38MAPK activity in oligodendrocytes involves cross-talk with the ERK and c-Jun N-terminal kinase (JNK) pathways that blocks c-Jun-mediated inhibition of myelin gene expression[137]. Collectively, these studies suggest that FGF signaling through FGFR1/2 in oligodendrocytes activates the MAPK/ERK signaling pathway and may regulate CNS myelination, and that cross-talk between the ERK, p38MAPK, and JNK pathways is important for this process. The MAPK/ERK pathway needs to be explored further, using pharmacological inhibitors and gain-of-function experiments, in order to fully elucidate its role in regulating the timing and extent of myelination.

Akt is a serine/threonine protein kinase that is activated upstream by lipid second messengers generated by PI3-kinase. Loss of the p85α regulator subunit of PI3-kinase results in decreased numbers of myelinated axons in several CNS regions[138]. Akt activates a variety of downstream targets, including the mammalian target of rapamycin (mTOR). Like the MAPK/ERK pathway, the PI3K/Akt/mTOR pathway is a powerful integrator of multiple extracellular signals that influence oligodendrocyte development. Akt signaling in oligodendrocytes is activated by neuregulins[37,53,55], integrins[139,140], IGF-I[141,142], NT-3[143,144], and leukemia inhibitory factor[145,146]. Akt is also activated downstream of both Fyn and FAK[63]. Furthermore, signaling through FGFR2 activates Akt in oligodendrocytes[101], suggesting a cross-talk between the Akt and ERK signaling pathways. Our lab, among others, has shown that Akt/mTOR signaling could be a master regulator of myelination in the CNS. The expression of constitutively active Akt in

oligodendrocytes (Akt-DD) causes CNS hypermyelination, without affecting oligodendrocyte differentiation, proliferation, or survival[147]. Hypermyelination in these animals is driven by Akt signaling through mTOR, and is reversible upon treatment with the mTOR inhibitor rapamycin[148]. In other studies, conditional expression of the mTOR activator Rheb (a downstream effector of Akt) in neural progenitors has been shown to promote myelination in the brain, while conditional Rheb knockout from the same cells inhibits myelination[149]. mTOR in oligodendrocytes is required for the developmentally regulated expression of several myelin proteins and lipid biogenesis enzymes such as those driving cholesterol and fatty acid synthesis[150]. Together, these results provide strong evidence that Akt signaling through mTOR is both necessary and sufficient to regulate myelination in the CNS.

Regulation of Akt signaling is complex and multifaceted (Fig. 1). The classic regulator of Akt signaling, phosphatase and tensin homolog (PTEN), reduces the production of upstream lipid second messengers that activate Akt[151,152]. In the PNS, PTEN is stabilized by the scaffolding protein Dlg1 in order to downregulate Akt and thereby prevent peripheral nerve hypermyelination[153]. These results suggest that, at least in the PNS, PTEN serves to terminate the myelination process and allows for long-term protection against abnormal membrane outgrowth[154].

The conditional knockout of PTEN from oligodendrocytes causes dramatic hypermyelination in the CNS, but is insufficient to enhance remyelination after injury in the adult CNS[155]. This suggests that there may be additional negative regulators of myelination in the adult, although the induced knockout of PTEN from adult glia, after normal myelination has ceased, can reactivate active myelin accumulation in both the CNS and PNS[154,156]. Based on these data, we began to investigate whether additional signaling molecules might be involved in cessation of active myelination in the CNS. We examined the expression profiles of mRNA and protein levels of PTEN and other putative negative regulators of Akt signaling during postnatal development in isolated corpus callosum from wild-type (WT) and hypermyelinating Akt-DD mice. We hypothesized that expression of a potential 'myelination brake', i.e., the signaling system that shifts the oligodendrocyte from active myelination to myelin maintenance, would peak in WT mice as active myelination comes to an end and would likely

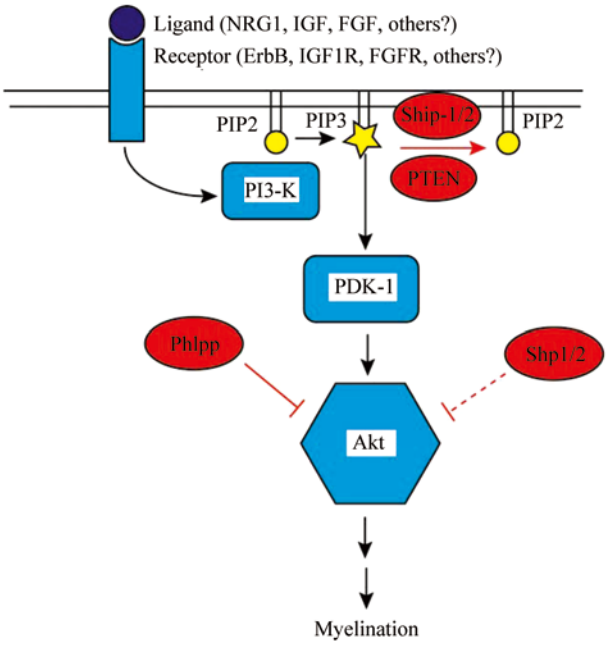

Fig. 1. Schematic of Akt signaling and regulation. Extracellular ligand (purple) binding a transmembrane receptor and activating the PI3K/Akt pathway (blue icons). Lipid second messengers PIP2 and PIP3 indicated in yellow. Negative regulators indicated in red. Blunted arrows indicate inhibition. Dashed line indicates indirect regulation.

decrease to steady-state levels during adulthood, when myelin maintenance is the predominant oligodendrocyte phenotype. In Akt-DD mice, in which active myelination continues throughout the animal's lifetime[147,148], the myelin brake seems to have been overridden. Therefore, in Akt-DD mice, we expected a continual increase in expression of proteins that might act as a myelin brake throughout development, in an effort to curb the continuous myelin production in these mice. However, the expression profile of PTEN did not fit either of these expectations (Fig. 2). PTEN mRNA expression in white matter samples from WT and Akt-DD mice remained relatively unchanged throughout development and into adulthood, and did not differ between WT and Akt-DD mice (Fig. 2A). At the protein level, PTEN expression was highest on postnatal day 7 (P7) and gradually decreased throughout development, again with no difference between WT and Akt-DD mice (Fig. 2B). PTEN activity and stability are also regulated by post-translational modifications of its C-terminal tail, where phosphorylation increases PTEN stability but renders the protein less

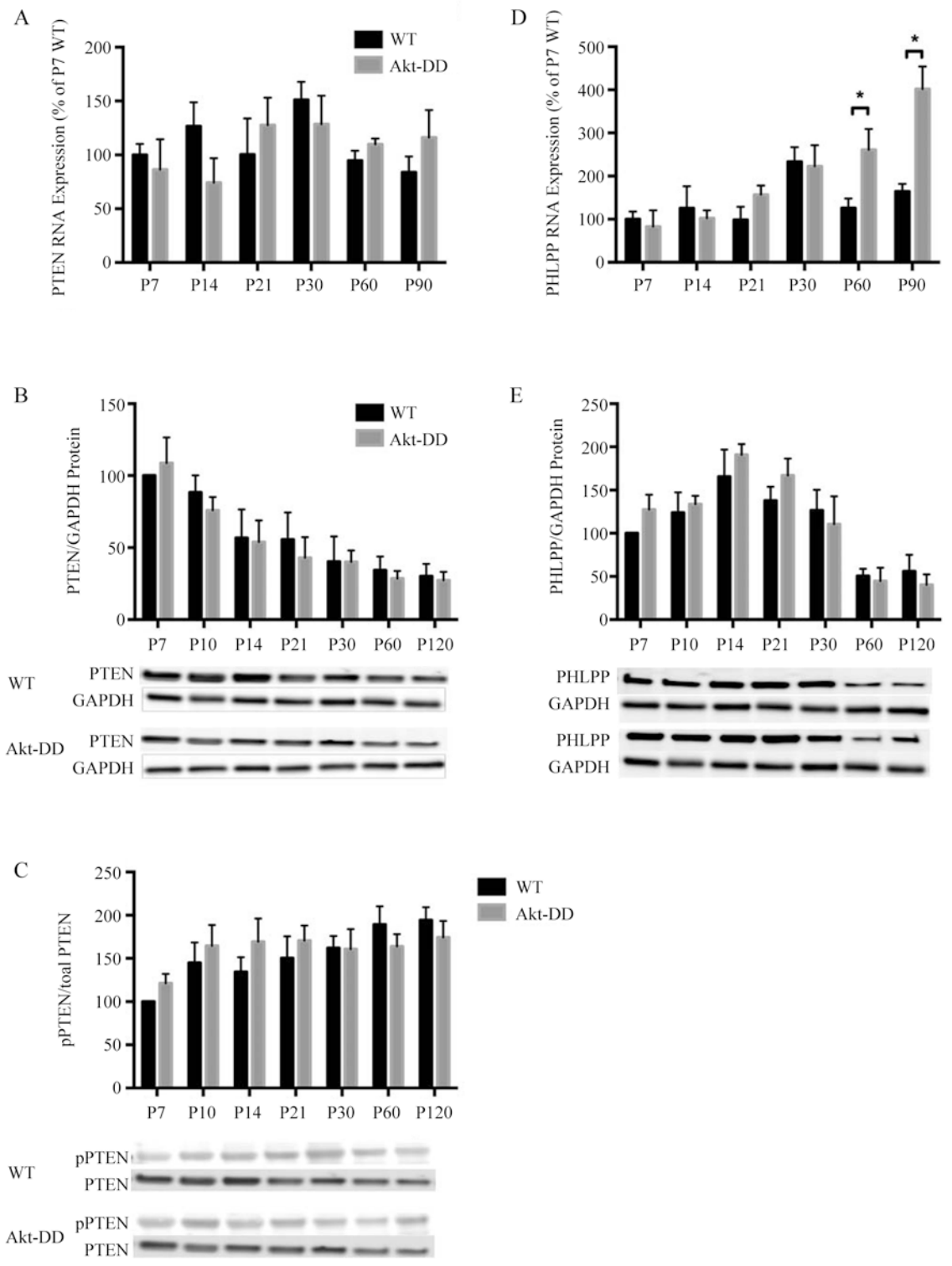

Fig. 2. Developmental expression profiles of PTEN and PHLPP phosphatases. Expression of PTEN and PHLPP mRNA (A and D, respectively) and protein (B and E, respectively), relative to P7 wide-type (WT) is presented. The ratio of phospho-PTEN to total PTEN relative to the ratio in P7 WT samples is presented (C). Representative Western blots shown below the respective quantification. Mean ± SEM for three animals per group. ****P* **<0.05 (unpaired Student's *t*-test).

active[157]. When we examined the levels of phospho-PTEN in these samples, we observed a relatively constant ratio of phospho-PTEN to total PTEN from P10 through P120, and that ratio did not differ between WT and Akt-DD mice (Fig. 2C). Collectively, there are no differences between WT and Akt-DD mice in PTEN mRNA or protein expression or in the ratio of phospho-PTEN/PTEN, and the expression profiles did not meet our expectations of a *bona-fide* "myelin brake" in the CNS. Although the conditional knockout studies presented above suggest that PTEN may play a role in curbing active myelination[154,156], the developmental studies presented here suggested that some other molecule(s) may also have an important role in curbing active myelin production in the CNS.

We therefore extended our developmental expression profiling studies to other putative regulators of Akt signaling (Fig. 1). PHLPP (Plekstrin Homology domain Leucine-rich repeat Protein Phosphatase) is a protein phosphatase that dephosphorylates and inactivates Akt directly[158], and forms a tumor-suppressor network with PTEN and the scaffolding protein Nherf that is disabled in glioblastoma[159]. The role of PHLPP has not been previously studied in myelinating glia; however, PHLPP has been shown to regulate Akt signaling in a feedback mechanism mediated by mTOR[160]. The expression profile of PHLPP mRNA in WT mice peaked at the end of active myelination (P30), while protein levels peaked earlier, at P14. PHLPP mRNA and protein then decreased to steady-state levels during later development (Fig. 2D, E). The expression of PHLPP mRNA increased throughout the time points examined in Akt-DD mice, and it was more than 2-fold increased relative to WT at P90 (Fig. 2D); however, the protein expression was not different between WT and Akt-DD mice (Fig. 2E). These results suggested differential regulation of PHLPP mRNA and protein during the development of the corpus callosum, where levels of PHLPP mRNA were increased by constitutively active Akt signaling but protein levels were not. Although PHLPP mRNA met our criteria for a putative myelin brake, PHLPP protein did not. These results suggested a differential regulation of PHLPP at the transcriptional and translational levels and/or differential stability of PHLPP mRNA compared to PHLPP protein. Since PHLPP protein inhibits Akt activity, differences in protein levels are more relevant for our studies than mRNA levels, and we have focused less on PHLPP as a likely myelin brake candidate.

Ship-1 and Ship-2 are upstream lipid phosphatases that inhibit the formation of lipid second messengers that activate Akt signaling[161,162]. In WT mice, Ship-1 mRNA levels remained constant throughout development. mRNA levels in Akt-DD mice matched WT levels at early time points, and then increased dramatically at later time points (P60 and P90) (Fig. 3A). Ship-1 protein could not be detected *via* Western blot analysis, most likely because of very low expression levels in the tissue. Ship-2 mRNA in WT mice slowly increased during early development and peaked at P30, corresponding to the end of active myelination; mRNA levels then dropped back down to baseline levels at later time points. In Akt-DD mice, Ship-2 mRNA peaked sooner at P21, remained elevated at P30, and then similarly dropped back down to baseline levels at later time points (Fig. 3B). As with Ship-1, Ship-2 protein expression was too low to be detected. Given the interesting differences in their RNA levels, these phosphatases have potential to regulate aspects of Akt signaling in oligodendrocytes. However, because of the difficulty in detecting these proteins, pursuing Ship-1/2 as myelin brake candidates may be difficult.

Shp1 (PTPN6) and Shp2 (PTPN11) are non-receptor type protein tyrosine phosphatases originally described in terms of their ability to regulate MAPK/ERK signaling, but they have since been shown to regulate multiple intracellular signaling networks[163]. Shp1 is expressed predominantly in hematopoietic cells[164]; however, mice homozygous for the motheaten loss-of-function mutation in Shp1 display a variety of defects, including hypomyelination, dysmyelination, and decreased numbers of differentiated oligodendrocytes in the brain[165,166]. WT oligodendrocytes have been shown to express functional Shp1, regulating oligodendrocyte differentiation in response to cytokine signaling[167]. In our analysis, Shp1 mRNA levels peaked at P14 in WT mice, and then slowly decreased during later development. In Akt-DD mice, a gradual increase in Shp1 mRNA was observed, with very high levels at P90 that differed significantly from WT (Fig. 4A). In both WT and Akt-DD, Shp1 protein expression increased slowly, peaked at P30, and remained high during adulthood (Fig. 4B). The expression profile for Shp1 protein suggested it could be involved as a myelin brake, as expression peaked at P30 and remained elevated during later developmental stages. Furthermore, Shp1 transcripts were markedly elevated in Akt-DD mice. The role of Shp1 has not been studied during later stages

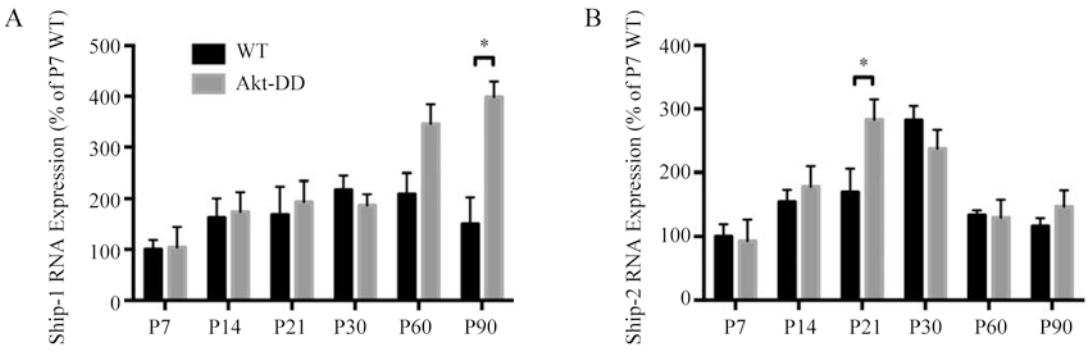

Fig. 3. Developmental expression profiles of Ship-1 and Ship-2 phosphatases. Expression of Ship-1 and Ship-2 mRNA (A and B, respectively), relative to P7 wide-type (WT). Mean ± SEM for three animals per group. *P <0.05 (unpaired Student's t-test).

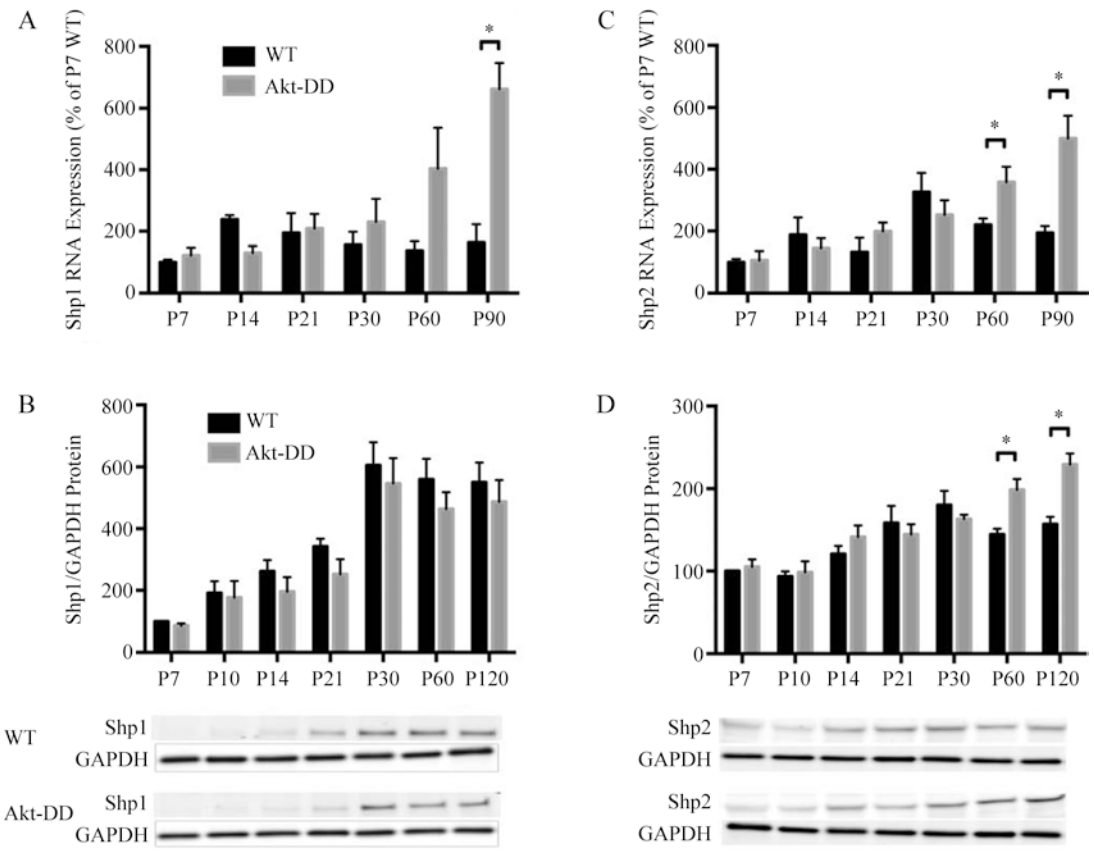

Fig. 4. Developmental expression profiles of Shp1 and Shp2 phosphatases. Expression of Shp1 and Shp2 mRNA (A and C, respectively) and protein (B and D, respectively), relative to P7 wide-type (WT). Representative Western blots shown below the respective quantification. Mean ± SEM for three animals per group. *P <0.05 (unpaired Student's t-test).

of myelination, myelin maintenance, or remyelination.

Shp2 was the first protein tyrosine phosphatase identified to function as an oncogene[168] but has since been shown to behave also as a tumor suppressor in certain tissue types[169]. Similarly, although it has been traditionally considered a positive regulator of many signaling pathways, including Akt and ERK[163], Shp2 is now known also to negatively regulate Akt/mTOR signaling[170,171]. Shp2 in-

fluences neuronal and glial development[172,173]. In particular, it is expressed by oligodendrocytes and influences the *in vitro* differentiation of oligodendrocytes *via* Akt and ERK1/2 signaling[174]. Shp2 activity maintains cultured OPCs in a state of proliferation and opposes the pro-differentiation effects of Shp1[175]. Likewise, Shp2 conditional knockout decreases OPC proliferation and generation *in vivo*, but its effects during later stages of oligodendrocyte differentiation and myelination could not be analyzed due to early postnatal lethality[176]. We examined the developmental expression profiles of Shp2 mRNA and protein in order to assess its function during development. In WT mice, Shp2 mRNA peaked at P30, corresponding to the end of active myelination, and then decreased to steady-state levels during later time points (Fig. 4C). The same expression pattern was observed with Shp2 protein (Fig. 4D). In Akt-DD mice, both Shp2 mRNA and protein increased gradually throughout the time points examined, with significant differences between WT and Akt-DD at the mRNA level at P90 and P60 and significant differences between WT and Akt-DD at the protein level at P60 and P120 (Fig. 4C, D). Like PTEN, Shp2 activity is also regulated by post-translational modifications, where phosphorylation of two carboxy-terminal tyrosine residues relieves basal inhibition of the phosphatase domain[177]; however, we were unable to detect phospho-Shp2 in our experimental conditions (data not shown). Nevertheless, the expression profiles of Shp2 transcript and protein in WT and Akt-DD mice strongly suggest that this protein may play a role in regulating Akt/mTOR signaling driving myelination as a potential myelin brake in the CNS.

Concluding Remarks

Collectively, the data presented here demonstrate that molecules other than PTEN deserve consideration as potential 'myelin brake' candidates in the CNS. PTEN seems to fulfill the role of the 'myelin brake' in the PNS; however, many fundamental differences between PNS and CNS myelination exist, only some of which have been highlighted here. In addition to PTEN, other mechanisms may exist to regulate the hypothesized master regulatory function of Akt/mTOR signaling in CNS myelination. It is likely that crosstalk between Akt/mTOR and other signaling pathways, notably MAPK/ERK, exists in order to provide intricate regulation over this highly advanced and delicate system.

Myelin overproduction is observed in the PNS in diseases such as Charcot-Marie-Tooth disease[178,179] and the hereditary neuropathy with liability to pressure palsies (HNLPP)[180]. Genetic analyses have helped to pinpoint specific genes responsible for the disruptions and further our understanding of myelination[153,154]. An obstacle impeding progress in understanding myelination in the CNS is the fact that hypermyelination is rarely observed in human disease, and the molecules involved in PNS myelination are not always conserved in CNS myelination[44]. The hypermyelinating phenotype observed in the CNS as a result of constitutively active Akt signaling in oligodendrocytes[147] represents a significant advance on this front and will serve as a useful tool in elucidating more precise mechanisms of regulatory control over CNS myelination.

A key to understanding CNS myelination is to identify cell-autonomous changes within myelinating oligodendrocytes as the cell progresses from initiation of myelination to active myelin accumulation and then to myelin maintenance. Differentiation of oligodendrocytes does not imply myelination *per se*, and the developmental program of oligodendrocytes appears to be more complex than traditionally viewed. Achieving a thorough understanding of the molecular mechanisms responsible for the regulation of CNS myelination will undoubtedly improve our knowledge about human myelin disorders and pathology. This heightened understanding will elucidate novel therapeutic approaches that will enable more effective treatments.

Supplemental Data: Supplemental Data include Materials and Methods for Figs. 2–4, and can be found online at http://www.Neurosci.cn/epData.asp?id=76.

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