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Opinion Open Access

Dual Role of Oligodendrocyte-Derived Myelin in Visual System Plasticity and Regeneration

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Opinion

Oligodendrocytes are the cell type responsible to produce central nervous system (CNS) myelin sheaths. These sheaths consist of internodes of thin bilayers of oligodendrocyte plasma membrane concentrically wrapped around the axon, producing high-resistance/low-capacitance regions, flanked by low-resistance/high-capacitance unwrapped segments, called nodes of Ranvier. This organization greatly increases action potential conduction velocity, being crucial for normal nervous system physiology [1].

CNS myelination is a developmentally regulated event, usually completed during the third or fourth postnatal weeks, but presenting regional time-courses [2]. Within the rodent subcortical visual pathway, optic nerve myelination starts at post-natal day (P) 13 and reaches maturation at P21 in the optic nerve, and at P24 in the optic tract [2,3]. During this non-myelinated period, retinofugal axons undergo extensive reorganization, from initially expanded ipsilateral axon terminals within the whole superior colliculus, culminating in adult-like refined clusters of terminals in the antero-ventral border of the *stratum griseum superficiale* (SGS) at P8 [4]. These data could lead to the misinterpretation that retinofugal maturation is complete by P8, however transmission electron microscopy revealed that in this early stage, synapses are immature, consisting of axon- and dendrite-derived growth cones contact. Synapses undergo maturation and increase in number until P21-P30 [5]. Thus, transitory projections are eliminated before, while synapse maturation occurs after myelination is complete, suggesting that myelination might be important to synapse development. Interestingly, CNS myelin seems to contribute to maintenance of refined axonal pattern, since dysmyelinated rats, due to myelin basic protein genetic deletion, display sprouted optic nerve axons in a mature period, when the axonal arbor would have already been refined [6,7].

During the early non-myelinated period, before P14, SGS fibers present high levels of GAP-43 [8], suggesting a great ability to undergo plasticity. Indeed, temporal retinal lesions performed until P10 leads to complete reorganization of retinocollicular terminal fields by 48 hours, while rearrangements after P21 lesion takes longer to occur, not reaching maximal reorganization within 3 weeks [9]. Therefore, myelination inversely correlates with plasticity. One possible explanation of this phenomenon is that lesion within the myelinated stages results in myelin debris accumulation within the target, inhibiting axon growth. Indeed, CNS myelin presents diverse molecules, such as myelin-associated glycoprotein, oligodendrocyte-myelin glycoprotein, NOGO A and sulfatide, which inhibit mammalian axon growth, through Rho/ROCK-induced growth cone collapse [10,11]. Consistently, knockout mice for Nogo A or myelin inhibitory proteins receptors, as NgR1, PirB and S1PR2, maintain ocular dominance plasticity in adult visual cortex, which is a mechanism dependent on axonal remodeling and synapse formation. Indeed, NgR or S1PR2 dependent Nogo signaling has been demonstrated, in vitro, to inhibit excitatory synaptogenesis in motor cortex and hippocampal [12,13], while NgR loss or PirB blockade, in vivo, favor functional synapse formation in hippocampal and visual cortex, respectively [12]. Interestingly, synaptic potentiation is facilitated after Nogo-A or Nogo-A pathway neutralization [14], suggesting its restrictive role in synaptic plasticity. Therefore, myelination inversely correlates with plasticity.

A distinct mechanism from that described above which may also allow myelin to impact neuroplasticity is through neuronal activity modulation. It is well-known the crucial role of myelin in increase of action potential conduction velocity, allowing a temporally accurate information transmission. Corroborating this notion, Kim and collaborators recently reported [15] that dysmyelinated mature rats showed a non-reliable central neurotransmission due to delay between the pre- and postsynaptic transmission of action potential (AP) and frequent failure of postsynaptic excitatory potential. Accordingly, optic nerve partial demyelination using a cuprizone toxic model increases axonal potassium channels, raising the threshold for AP and, thereby, impairing neurotransmission [16]. Indeed, reduction of visual activity induced by tetrodotoxin induces axonal sprouting after critical period, indicating that neuronal activity regulates axonal plasticity [17]. Thereby, myelin might strengthen neurotransmission and inhibit neurite remodeling, maintaining synaptic contacts through lifespan and avoiding changes in adult central connectivity. On the other hand, demyelination, that represents a common process in many neuropathologies leads to plastic rearrangements [18,19]. Interestingly, multiple sclerosis patients show more widespread sensorymotor activation of brain areas, indicating connection remodeling [19]. Additionally, optic neuritis patients, initially displaying weak cortical activation in response to affected eye stimuli, recover within the next six weeks [20]. These phenomena might be due to sprouting of demyelinated visual axons [6].

Similar inhibitory role of CNS myelin occurs in mammalian CNS axon regeneration [21]. CNS neurons cannot regrow injured axons into a myelin-rich environment. Strategies such as MAG inactivation promote regeneration of the chick optic nerve [22]. Similarly, blockade of sulfatide formation or Ngr knockdown promotes optic nerve

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regeneration, while Ngr overexpression completely blocks regeneration after stimulation of the intrinsic growth program of retinal ganglion cells [11,23]. Alternatively, mammalian peripheral nervous system and fish/amphibians' CNS fully regenerate after lesion. Positive features shared by these last models are less inhibitory myelin, efficient clearance of myelin debris and trophic factors secretion [24,25]. Hence, CNS mammalian regeneration research has to avoid these important obstacles in order to reach satisfactory outcomes.

Besides axon-growth repressors production, oligodendrocytes also myelinate axons, optimizing their conduction and transmission properties. These features might be crucial to adequate synapse formation and functional recovery after regeneration. In-vivo studies of regeneration showed that goldfish restores visually-guided behavior after optic nerve crush [26]. Besides axon regeneration, CNS – remyelination occurs and might have a central role in providing adequate conduction properties to central visual targets [27]. Within mammalian peripheral nervous system, functional recovery after lesion is correlated to the Schwann cell-derived myelin thickness related to the regenerating axon diameter within each nerve fiber [28,29]. Until recently, full-length CNS regeneration has not been achieved. However, de Lima and co-workers [30] have shown that conditional deletion of Phosphatase and tensin homolog gene in retinal ganglion cells, combined to intravitreal injection of zymosan and cyclic-AMP analog, produce target re-innervation and axonal myelination, partially restoring simple visual behaviors.

Taken together, oligodendrocyte-derived myelin seems to have a dual role in CNS neuroplasticity and regeneration. In one side, myelin sheaths or debris restricts axonal rearrangements and regeneration. On the other side, myelination allows proper action potential conduction and accurate neurotransmission, leading to synapse maturation and maintenance. Therefore, early therapeutic interventions that blocks myelin inhibitors are required for axon reorganizations and rewiring to occur after CNS lesions. In a later stage of repair, proper myelination might be stimulated to achieve synapse maturation, which ultimately leads to functional recovery.

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