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Review

Axonal activity-dependent myelination in development: Insights for myelin repair

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ABSTRACT

Recent advances in transgenic tools have allowed us to peek into the earliest stages of vertebrate development to study axon-glial communication in the control of peri-natal myelination. The emerging role of neuronal activity in regulating oligodendrocyte progenitor cell behavior during developmental myelination has opened up an exciting possibility—a role for neuronal activity in the early stages of remyelination. Recent work from our laboratory and others has also shown that contrary to previously established dogma in the field, complete remyelination up to pre-demyelination levels can be achieved in mouse models of MS by oligodendrogenic neural precursor cells that derive from the adult subventricular zone. These cells are electrically active and can be depolarized, suggesting that neuronal activity may have a modulatory role in their development and remyelination potential. In this review, we summarize recent advances in our understanding of the development of axon-glia communication and apply those same concepts to remyelination, with an emphasis on the particular roles of different sources of oligodendrocyte progenitor cells.

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1. Introduction

Axonal pathology is a hallmark of virtually all major neurodegenerative diseases including multiple sclerosis (MS), an autoimmune disorder where the host immune system attacks the myelin sheath and its structural components. Although the precise etiology of immune-mediated myelin destruction remains a matter of serious debate, the downstream effects and pathophysiology of MS are considerably better understood. For instance, in relapsing-remitting MS, the most common presentation of the disease, successive bouts of demyelination are interspersed with phases of intense and active myelin repair that are critical for preventing axonal degeneration (Hagemeier et al., 2012; Irvine and

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Blakemore, 2008). However, as the pathological processes underlying the disease continue unabated and outpace spontaneous repair mechanisms, the disease enters a secondary progressive stage during which axonal pathology and degeneration become the driving force behind significant cognitive and functional decline (Lassmann et al., 2012). Remyelination not only restores saltatory conduction, but is also neuroprotective as demonstrated by the increased susceptibility of demyelinated axons to secondary degeneration compared to remyelinated axons (Irvine and Blakemore, 2008; Trapp et al., 1998). Nevertheless, remyelination is often incomplete, becomes less efficient with both disease chronicity and age and the myelin produced during remyelination is generally of poorer quality than normal healthy myelin (Blakemore and Murray, 1981). For this reason a major focus of current research efforts is to understand the environmental cues that drive remyelination and the reasons underlying the reduction in remyelination efficiency in chronic disease. While much attention has focused on understanding various inflammatory and inhibitory cues that can curtail remyelination, less well understood is the extent to which pro-myelinating signals might be disrupted with ongoing disease. Recent research has provided critical new insights into the role of electrical activity in driving myelination during postnatal development. In this review, we will examine recent advances in our understanding of activity dependent axon-glial communication during developmental myelination and discuss their potential roles in myelin repair following demyelination.

2. Developmental myelination: a role for neuronal activity

Myelination is a very finely orchestrated process that involves a myriad of extracellular signaling molecules converging on several well-characterized intracellular signaling pathways to drive the timely activation of key transcriptional programs that regulate all aspects of oligodendrocyte behavior (Bercury and Macklin, 2015; Emery and Lu, 2015). Following initial glial lineage specification, oligodendrocyte progenitor cells (OPCs) undergo a massive proliferation and migration phase during which they populate the entire central nervous system (CNS) (Dawson et al., 2003; de Castro et al., 2013). During this time they come in contact with various extracellular chemotactic cues as well as axonally expressed factors such as PSA-NCAM, Neuregulin-1 and laminin-α2 which direct their growth and process extension towards pre-myelinated axons (Mitew et al., 2014). Axonal caliber also has a direct influence on myelination such that axons larger than 0.4 μm in diameter are competent for myelination (Sturrock, 1980). Interestingly, this relationship is preserved *in vitro* and appears to be independent of axonal signaling since cultured oligodendrocytes will myelinate inert microfibres provided they are the right diameter (Bechler et al., 2015; Bullock and Rome, 1990; Lee et al., 2012). Finally, once OPCs have identified their appropriate axonal targets they undergo terminal differentiation and transition into mature oligodendrocytes. At this point they begin synthesizing prodigious amounts of lipids and myelin proteins that constitute the myelin internodes of up to 50 individual axons (Chong et al., 2012; Dumas et al., 2015).

Although certain white matter tracts are completely myelinated, more than 50% of axons in the corpus callosum, the largest white matter tract in the mammalian brain, remain unmyelinated in the adult mouse brain despite meeting the minimum diameter to be competent for myelination (Sturrock, 1980). This begs the obvious question, what additional factors confer selection for myelination? One attractive possibility is that groups of axons that are more active would have a higher chance of becoming myelinated. This simple yet elegant mechanism would ensure that precious resources are not squandered on blanket myelination and constitutes an adaptive response to environmental cues enabling axonal conduction velocity to be fine-tuned according to demand. Indeed such myelin plasticity has recently been suggested to play an integral role in learning and cognition (Wang and Young, 2013; Zatorre et al., 2012). The possibility that neuronal activity directly influences myelination is supported by early studies which demonstrated that blocking action potential firing using tetrodotoxin (TTX), an inhibitor of voltage-sensitive sodium channels,

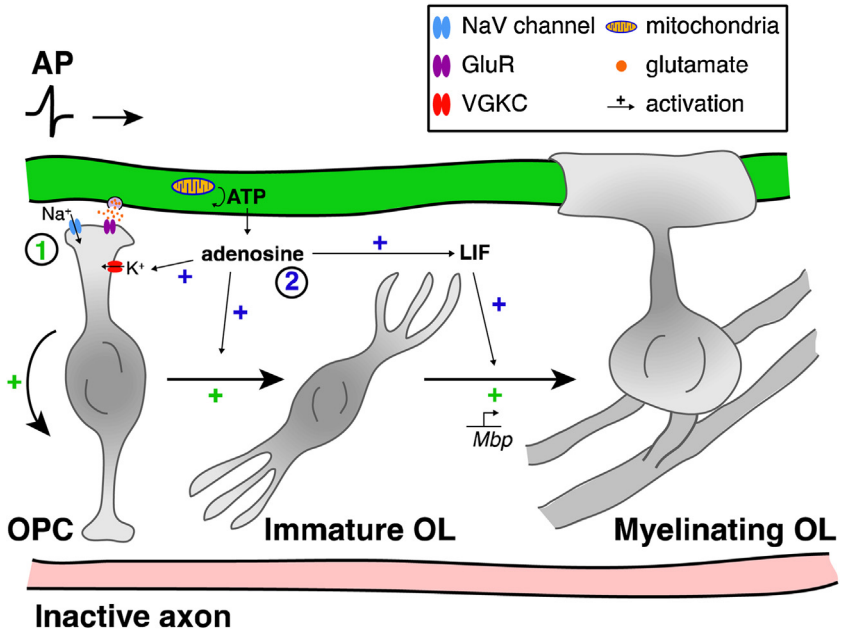

Fig. 1. Action potential firing by electrically active axons results in the release of neurotransmitters at both synaptic and extrasynaptic sites. Release of glutamate (1) at putative axon-OPC synapses has been postulated to activate AMPA receptors and depolarize OPCs, leading to increases in intracellular Ca^{2+} which in turn promotes (+) proliferation, differentiation and translation of myelin-regulatory genes. Active axons can also signal OPCs via non-synaptic release of ATP/adenosine (2) which signals via purinergic receptors either directly on OPCs or via astrocyte-mediated release of LIF.