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Previews

A New Player in CNS Myelination

The formation of the myelin sheath in the CNS is the endpoint of a defined developmental program along which oligodendrocytes progress. However, the molecular signals required for the initiation of myelination are largely unknown. Ishibashi et al. report in this issue of *Neuron* that ATP released by axons as a result of electrical stimulation serves as an important myelination signal. Surprisingly, they found that ATP does not act directly on oligodendrocytes but rather on astrocytes, causing the release of leukemia inhibitory factor (LIF), which in turns affects promyelinating oligodendrocytes. These findings uncover a novel role for astrocytes in mediating the intricate communication between axons and myelinating glial cells.

Oligodendrocytes (OLs) form multiple myelin segments by spirally wrapping their membrane around the axons, thereby allowing efficient and rapid propagation of action potentials. During development, oligodendrocytes progress along a very precise differentiation program: oligodendrocyte progenitor cells (OPCs) differentiate into preoligodendrocytes and subsequently into immature and promyelinated oligodendrocytes, which then can myelinate axons. Although many of the factors affecting oligodendrocyte development are known, little is known about the mechanisms governing the onset of myelination. One factor that was suggested to be required for myelination is electrical activity (Demerens et al., 1996). This notion is further supported by the observations that functional and cognitive activity, which are associated with increased neuronal activity, results in correlative changes in white matter tracks (reviewed in Fields, 2005). Previous experiments have shown that adenosine, released at extrasynaptic sites upon electrical stimulation of neurons, induces the differentiation of OPCs, eventually leading to an increase in myelination (Stevens et al., 2002). Although the exact molecular mechanism is not entirely clear, this effect was found to be mediated by activation of purinergic receptors in OPCs. In the present study, Ishibashi et al. went a step further and examined whether neuronal activity influences the ability of more mature oligodendrocytes to myelinate (Ishibashi et al., 2006 [this issue of *Neuron*]). The way they approached this question was to allow OPCs that were cocultured with DRG neurons to reach their mature promyelinating stage before the neurons were stimulated. The result was very clear: electrical activity of the neurons promoted myelination of mature oligodendrocytes through an activity-dependent release of ATP. Adenosine, which regulated the proliferation and differentiation of OPCs, had no affect on the ability of mature oligodendrocytes to myelinate. Conversely, ATP only affected mature oligodendrocytes, not their precursors, suggesting that different signaling mechanisms are involved. Experiments using various ATP-receptor agonists raised the possibility that ATP may induce myelination through a novel mechanism, which potentially involved cytokines. Likely candidates that came to mind were members of the leukimia inhibitory factor (LIF)/CNTF family, which were previously shown to stimulate myelination when added to mature cortical cocultures (Stankoff et al., 2002). It turned out that they were right: LIF was found in their cultures in a similar age- and activity-dependent manner as ATP, function-blocking anti-LIF antibodies abolished the promyelinating effect observed, and the addition of LIF mimicked the promotion of myelination by electrical activity and ATP. Interestingly, myelination was increased significantly by the addition of low concentrations of LIF, but was inhibited at high concentrations. This biphasic response may resolve early discrepancies reported in the literature on the effects of this cytokine on myelination (Park et al., 2001; Stankoff et al., 2002).

What is the source of LIF? Ishibashi et al. showed that, surprisingly, LIF was released by astrocytes that were present in their cocultures. In agreement with a previous study showing that activation of P2 receptors on astrocytes induces LIF mRNA (Yamakuni et al., 2002), the authors found that the expression of LIF mRNA was upregulated in response to the electrical activity of axons. This increase was eliminated by the addition of apyrase, an enzyme that degrades extracellular ATP, suggesting that ATP released from electrically active neurons stimulates the production and secretion of LIF from astrocytes, which in turn promotes oligodendrocyte myelination. LIF was also present in optic nerves during the early phase of myelination, further supporting a role for this cytokine in CNS myelination. Finally, by adding astrocytes isolated from wild-type or LIF-deficient mice to cocultures containing DRG neurons and mature oligodendrocytes, it was found that the presence of LIF-expressing astrocytes was imperative for the activity-dependent increase in myelination.

Strikingly, this study shows that the decision whether an axon should be myelinated does not only depend on the axon itself and the oligodendrocyte attached to it, but also on the presence of an astrocyte in the close vicinity. So, are astrocytes key players in the decision whether to myelinate at all, or do they play more of a modulating role, like the fine-tuning of the extent of myelination? Another possibility is that myelination is governed by different signals that together have to reach a certain threshold; in such a scenario, the influence of astrocytes would be only one of several cues that direct oligedondrocytes toward myelination. Analysis of LIF-deficient mice revealed that the brains of female animals exhibit reduced amounts of GFAP-positive astrocytes and lower levels of MBP (Bugga et al., 1998). Thus, although astrocytes and astrocyte-derived LIF appear to have an important function in CNS myelination, myelin could nonetheless still be formed in the absence of LIF, indicating that this cytokine has a modulatory role in this process. This notion is further supported by observations made using GFAP null mice, which exhibit various late-onset white matter aberrations, including ongoing myelination by oligodendrocytes in adult

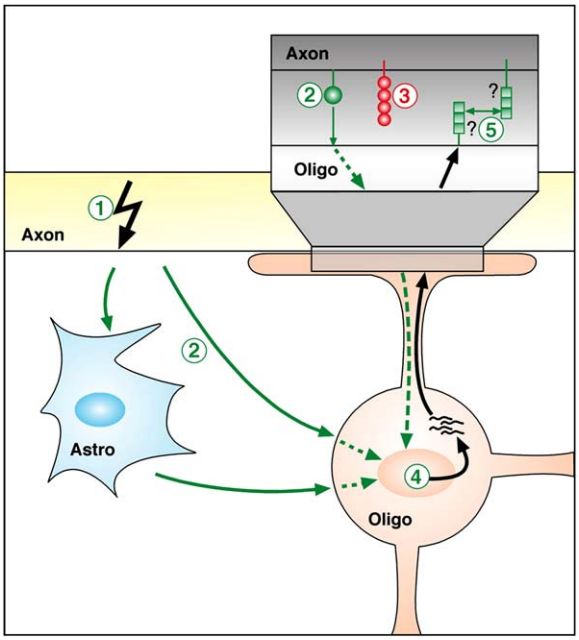

Figure 1. Regulatory Steps during the Initiation of Myelination

Increase in electrical activity in axons after target innervation (1) causes the release of promyelinating factors (2) that act directly or indirectly through astrocytes on oligodendrocytes. Concomitantly, axons downregulate the expression of inhibitory cell-adhesion molecules (3) and upregulate other membrane-bound molecules that are required for ensheathment (2). The multiple axonal-oligodendrocyte signals (4) result in the production of molecules that mediate axon-glia interaction (5) and myelination.

animals and demyelination (Liedtke et al., 1996). Interestingly, myelin abnormalities are also the hallmarks of Alexander disease (AXD), a disorder caused by dominant, usually sporadic mutations in the *gfap* gene. The results presented by Ishibashi et al. may suggest that the myelin defects seen in *gfap* deficiency are secondary effects caused by impaired astrocyte physiology leading to deregulation of astrocyte-derived myelination signals.

A question arising from the current study is whether the regulation of myelination by electrical activity occurs only at the onset of myelination or whether it also plays a role in mature myelinated nerves. The later possibility is tempting, as it could explain whether and how the insulating properties of the myelin sheath (e.g., the number of myelin wraps) are adapted to the electrical activity of the underlying axon; such activity-dependent plasticity of myelin formation was suggested in the past but was not proven experimentally. Mechanisms where electrical activity is represented in cellular cytoarchitecture are well described in CNS synapses. Interestingly, astrocytes also have important functions in synapse physiology, including synapse formation, the control of their number, and in fine-tuning of synaptic strength (Volterra and Meldolesi, 2005).

A general scheme is beginning to emerge of how myelination is initiated (Figure 1). Target innervation by the axons leads to increased electrical activity and axon-glia communication, effecting a change in the expression of various molecules on both the axonal membrane and oligodendrocyte processes. An important consequence of this communication is a dramatic change in the expression of cell-adhesion molecules, which may drive myelination and establish specialized functional domains at and around the node of Ranvier that are necessary for proper saltatory conduction (Poliak and Peles, 2003). For example, electrical activity was shown to regulate the expression of two axonal members of the immunoglobulin superfamily of cell-adhesion molecules (IgSF-CAMs) that were implicated in myelination: polysialated NCAM (PSA-NCAM), whose disappearance was found to be a prerequisite for myelination to commence, and axonal L1, which is required for the alignment of glial processes with the underlying axon (Coman et al., 2005). Given the large number of cell surface molecules that are expressed by myelinating glia (Spiegel et al., 2006), the effect of electrical activity and the surprising involvement of astrocytes in regulating myelination (Ishibashi et al., 2006), it seems that the molecular mechanisms controlling this process are only starting to come into light.

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