MYELINATION

Switching modes of myelination

> application of the NMDA receptor blocker MK-801 in the presence of NRG1 led to a dramatic reduction in myelination

Neuronal activity, the neurotransmitter glutamate and the growth factor neuregulin have all been implicated in the regulation of myelination, although their involvement in this process continues to be debated. In a new study, Káradóttir and colleagues show that myelination may proceed in activity-dependent and -independent manners and that activity-dependent myelination is 'switched on' by neuregulin-induced signalling in oligodendrocytes, which makes these cells more sensitive to glutamate release.

To examine the regulation of myelination, the authors used a co-culture system in which rat dorsal root ganglion (DRG) neurons are myelinated by forebrain oligodendrocytes. They assessed the overlap in the expression patterns of myelin basic protein, which labels the processes of myelinating oligodendrocytes, and neurofilaments, which are expressed in axons, to reveal myelination levels.

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Several studies have indicated that neuregulin promotes myelination, although it has also been reported that knockout of neuregulin has no effect on this process. The authors found that, in their co-cultures, application of the extracellular domain of neuregulin 1 (NRG1) — which activates the receptor tyrosine protein kinase ERBB expressed on oligodendrocytes — markedly increased the rate and steady-state level of myelination. However, they also found that brain-derived neurotrophic factor (BDNF) could elicit similar effects to NRG1 on myelination, suggesting that BDNF might compensate for neuregulin in its absence.

Interestingly, tetrodotoxin, which blocked action potentials, inhibited the effects of NRG1 on myelination but had no effect on myelination in co-cultures that were not treated with NRG1. These findings indicate that myelination can occur in the absence of neuronal activity but that myelination in the presence of NRG1 is, at least partly, dependent on action potentials.

Strikingly, application of the NMDA receptor blocker MK-801 in the presence of NRG1 led to a dramatic reduction in myelination (to a level below that seen under control conditions). The authors suggest that NRG1 therefore acts as a switch that increases the dependence of DRG axon myelination on neuronal activity.

How does it do this? NRG1 did not elicit increased activity in DRG neurons or have an effect on membrane resistance in oligodendrocytes. However, it did potentiate NMDA receptor-mediated currents in oligodendrocytes by 6-fold and thus made such cells more sensitive to glutamate.

These findings may help to resolve apparently contradictory data from previous studies on the involvement of neuronal activity, glutamate and neuregulin in myelination. The importance of the neuregulin-induced switching mechanism remains unclear, but the authors argue that it may enable myelination, at a certain point in development, to be targeted to the most active axons, limiting metabolic costs.

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