DEVELOPMENT

Chronic NoGo with or without receptor

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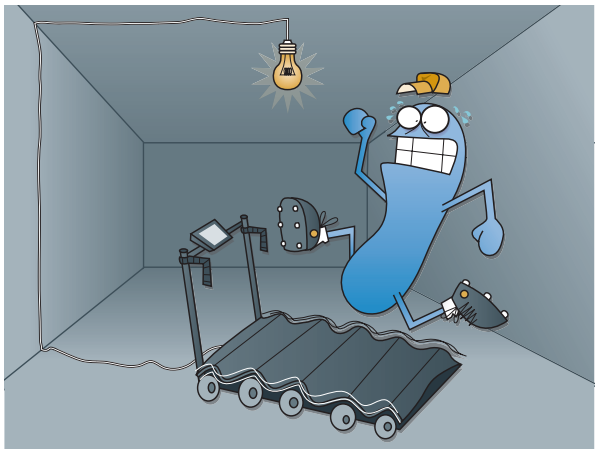
The inability of injured CNS neurons to repair and restore lost connections is partially due to the axonal-growth inhibiting properties of myelin. The neuronal Nogo-66 receptor 1 (NgR1) receptor has been identified as a mediator of myelin-associated inhibition. Giger and colleagues now show that NgR1 plays a part in growth-cone collapse, but not in substrate-mediated neurite outgrowth inhibition.

Neuronal NgR1 has been proposed to be the converging point for several endogenous myelin-associated growth inhibitors that signal growth arrest. To examine the role of NgR1 in more detail, the authors used *NgR1*-knockout mice and transient NgR1 depletion by short hairpin RNA interference (shRNAi) in primary cultured neurons, and studied three different myelin-associated inhibitors that bind to NgR1 with high affinity: Nogo-A, myelin associated glycoprotein (MAG) and oligodendrocyte myelin glycoprotein (OMgp). They investigated the effects of chronic and acute presentation of these inhibitors on neurite outgrowth and growth-cone collapse in primary cultured neurons.



In the first set of experiments, primary neurons isolated from wild-type or NgR1-null mice were chronically exposed to myelin-associated inhibitors. Neurons of both genotypes showed robust and comparable neurite outgrowth when cultured on Chinese hamster ovary (CHO) feeder cells but, independent of their genotype, outgrowth was strongly inhibited in the presence of MAG-expressing CHO cells. Substrate-bound OMgp and Nogo-66 were also able to inhibit neurite outgrowth independently of NgR1. Similar results were obtained when transient NgR1 knock-down was introduced by shRNAi in neurons that were cultured in the presence of control or MAG-presenting CHO cells. Together, these findings suggest that the underlying mechanism for outgrowth inhibition is independent of the Nogo receptor.

Interestingly, when soluble MAG or OMgp were applied acutely to adult wild-type or *NgR*1-null dorsal root ganglion (DRG) neurons in culture, a statistically significant increase in growth-cone collapse occurred in wild-type but not NgR1-null neurons, indicating that NgR1 mediates growth-cone collapse.

These findings support the notion that NgR1 is a convergence point for different growth inhibitors; however, they also demonstrate that different molecular mechanisms, which diverge at the receptor level, underlie growth-cone collapse and substrate-mediated neurite outgrowth inhibition. In light of these findings, current projects exploiting NgR1 as a therapeutic target to promote long-distance axonal regeneration following spinal cord injury may have to be carefully reassessed. Further studies are required in order to identify the receptors that mediate axonal growth inhibition in the presence of adult mammalian CNS myelin.

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ORIGINAL RESEARCH PAPER Chivatakarn, O. *et al.* The Nogo-66 receptor NgR1 is required only for the acute growth cone-collapsing but not the chronic growth-inhibitory actions of myelin inhibitors. *J. Neurosci.* **27**, 7117–7124 (2007)