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REPAIR

Novel mechanisms to stimulate regrowth

The inability of adult CNS neurons to regrow their axons following injury results in loss of sensation and paralysis. Strategies to overcome this problem are eagerly sought after. Two papers in *Science* report how manipulations of the receptors that mediate the inhibitory effects of the extracellular environment on axon regrowth, or of the signalling molecules that stimulate intrinsic neurite growth pathways, could aid axon regeneration and functional recovery after injury.

Myelin-derived proteins, such as Nogo, MAG and OMGP, have been implicated in inhibiting axon regeneration. Their effect is partially mediated by the glycosylphosphatidylinositol-anchored Nogo receptor (NgR). Genetic removal of NgR prevents growth cone collapse when these factors are applied in solution, but does not block the inhibition of axon growth when they are presented as a substrate, suggesting that other inhibitory receptors are involved. Tessier-Lavigne and colleagues have now identified PirB, a mouse protein related to immunoglobulins, as another key inhibitory receptor and promising target for axon regeneration therapies.

They found that preventing the interaction between PirB and Nogo66 or MAG blocked the effect of the myelin-derived inhibitors on axon outgrowth in cerebellar granule neurons. Similar effects were observed with neurons from mice carrying a loss-of-function PirB allele, indicating that PirB is a functional receptor for myelin-mediated inhibition of neurite outgrowth. Interestingly, blocking both PirB and NgR restored neurite outgrowth on myelin to nearly control levels, suggesting that it might be necessary to block both receptors to achieve maximal regrowth *in vivo*.

In a separate study, He and colleagues focused on the mammalian target of rapamycin (mTOR) signalling pathway in retinal ganglion cells, which has been shown to facilitate axon regeneration after injury to the optic nerve. They showed that when the negative regulators of the mTOR pathway, phosphatase and tensin homologue (PTEN) and tuberous sclerosis complex (TSC), were conditionally deleted in the retinas of adult mice, the axons of retinal ganglion cells could regrow as far as the optic chiasm after optic nerve crush. Furthermore, the decline in phosphorylated ribosomal protein S6 (p-S6) levels that occurs in wild-type mice after injury was prevented, suggesting that activation of the mTOR pathway stimulates regrowth by boosting protein translation in injured axons. Conversely, pharmacological inhibition of mTOR markedly reduced the levels of p-S6 and abolished the effects of PTEN deletion on axon regrowth.

These studies suggest that both blocking the effects of extracellular inhibitory molecules and stimulating the intrinsic growth pathways of neurons could prove beneficial for promoting axon regeneration after CNS injury. Although the details on the mechanisms involved remain to be determined, a two-pronged approach might be the most efficient way of stimulating regrowth.

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ORIGINAL RESEARCH PAPERS Park, K. K. *et al.* Promoting axon regeneration in the adult CNS by modulation of the PTEN/mTOR pathway. *Science* **322**, 963–966 (2008) | Atwal, J. K. *et al.* PirB is a functional receptor for myelin inhibitors of axonal regeneration. *Science* **322**, 967–970 (2008)