Neural Prosthesis Seminar

“Inhibitors of Neuronal Growth and Synaptic Plasticity”

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E501 School of Medicine, Robbins Building
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Abstract:
In higher vertebrates, including humans, the regenerative capacity of severed axons following CNS injury is extremely limited. Inhibitory molecules in CNS myelin (including MAG, Nogo, and OMgp) and chondroitin sulfate proteoglycans (CSPGs) associated with glial scar tissue contribute to a growth hostile environment for regenerating axons. Several neuronal cell surface receptors for myelin inhibitors and CSPGs have been identified. Paired-immunoglobulin receptor B (PirB) and members of the Nogo receptor (NgR) family support binding of MAG, Nogo-66, and OMgp, and the receptor protein tyrosine phosphatases LAR and RPTPα have been identified as high-affinity receptors for CSPGs. We found a novel interaction between select members of the NgR family and CSPGs. NgR1 and NgR3 bind with high affinity to the glycosaminoglycan moiety of neural proteoglycans and participate in CSPG inhibition in cultured neurons. /Nogo receptor/ triple mutant mice (/NgR123ΔΔΔ/), but not single mutants, show enhanced retinal ganglion cell (RGC) axon regeneration following retro–orbital optic nerve crush injury. The combined loss of /NgR1/ and /NgR3/ (/NgR13ΔΔΔ/ is sufficient to mimic the /NgR123ΔΔΔ/ regeneration phenotype, suggesting that NgR1 and NgR3 are functionally redundant CSPG receptors. Optic nerve regeneration in /NgR13ΔΔΔ/ mice is further enhanced by simultaneous ablation of /RPTPα/, suggesting a genetic interaction among these three CSPG receptors. When combined with activation of RGC intrinsic growth programs, genetic manipulations result in a further increase in optic nerve regeneration. Collectively, our findings provide evidence for shared receptor mechanisms for myelin inhibitors and CSPGs, two major classes of CNS growth inhibitory molecules.

For more information, please contact Cathy Naples at (216) 707-6490.

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