This Week in The Journal

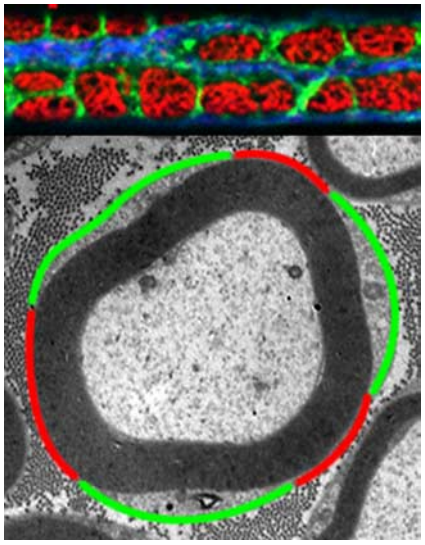
● Cellular/Molecular

Schwann Cell Compartmentalization Determines Internode Length

Felipe Court, Jane E. Hewitt, Kay Davies, Bruce L. Patton, Antonino Uncini, Lawrence Wrabetz, and M. Laura Feltri

(see pages 3908–3919)

During peripheral nerve development, Schwann cells extend a process that wraps around an axon and compacts to form a myelinated internode between two nodes of Ranvier. When myelin compaction is complete, the Schwann cell cytoplasm is restricted to the outer ring of the fiber, where it is compartmentalized into a meshwork of channels surrounding patches of close apposition between the outer plasma membrane and the underlying myelin. This compartmentalization is required for normal elongation of Schwann cells, which maintains the appropriate internode length as axons grow. Court et al. have developed a new measure of compartmentalization, the *f*-ratio, which compares the area of channels to that of appositions. This ratio is constant across axon diameters, and it is maintained in part by a protein assembly that connects the actin cytoskeleton to the extracellular matrix. Mutations that disrupt this protein complex decrease apposition size, increase *f*-ratio, and decrease internode length, demonstrating the importance of compartmentalization.



Top, Immunostaining of a portion of a nerve fiber shows Schwann cell compartments: appositions (red), longitudinal cytoplasmic channels (Cajal bands, blue) and transverse trabeculae (green). Bottom, Electron microscopic image of a cross section of a nerve fiber, showing Schwann cell appositions (red) and cytoplasmic channels (green).

▲ Development/Plasticity/Repair

Target-Derived BMP Maintains Neuronal Phenotype

Kevin E. Eade and Douglas W. Allan

(see pages 3852–3864)

In many neurons, retrograde signaling from targets induces gene expression that drives phenotypic specification. Although some specified neurons maintain their phenotype autonomously, others appear to require continued signaling from the target to maintain their phenotype. Eade and Allan demonstrate that this is the case in *Drosophila* Tv neurons, which are distinguished by their expression of the neuropeptide FMRFamide (FMRFa). Target-derived bone morphogenetic protein (BMP) activates a transcription factor, Mad, in Tv neurons, and Mad induces transcription of FMRFa. Conditional expression of dominant-negative Mad or BMP receptors in adult Tv neurons quickly decreased FMRFa levels. Conditional expression of a mutant protein that regulates retrograde axonal transport and is linked to ALS (amyotrophic lateral sclerosis) prevented nuclear accumulation of Mad, also decreasing FMRFa expression. Remarkably, when expression of these mutant proteins was switched off, expression of FMRFa returned to normal levels. The results suggest that neuropathologies caused by loss of target-derived signaling may be reversed by restoring the signal.

■ Behavioral/Systems/Cognitive

mGluR5 Is Essential for Inhibitory Learning

Jian Xu, Yongling Zhu, Anis Contractor, and Stephen F. Heinemann

(see pages 3676–3684)

An animal's survival requires not only learning associations between environmental stimuli and rewards or punishments, but also learning when those associations no longer persist. The latter process, often called inhibitory learning, includes extinction of conditioned fear responses and reversal learning, i.e., learning to perform a different task to receive a reward. This week, Xu et al. present evidence that metabotropic glutamate receptor 5 (mGluR5) is essential for inhibitory learning. Mice lacking mGluR5 were trained to associate a tone with a foot shock, or were trained to find a submerged platform in a water maze. Although mGluR5-null mice exhibited less freezing or took longer to find the platform than control mice, they did learn the association. In contrast, inhibitory learning was profoundly impaired in mutant mice. No decrease in freezing occurred when the tone was repeatedly presented without the shock; and when the platform was moved, mutant mice continued to search in the original location.

♦ Neurobiology of Disease

STAT1 Mediates Cisplatin-Induced Ototoxicity

Nicole C. Schmitt, Edwin W. Rubel, and Neil M. Nathanson

(see pages 3843–3851)

Cisplatin is used to treat a variety of cancers, but it has serious side effects, including loss of hair cells and subsequent permanent hearing loss. DNA damage, oxidative stress, and cytokines have all been proposed to mediate cisplatin-induced ototoxicity. Because these processes have also been linked to activation of the signal transducer and activator of transcription STAT1, a normally latent transcription factor whose activation by extracellular stimuli leads to apoptosis, Schmitt et al. have examined the role of STAT1 in cisplatin-induced ototoxicity. STAT1 was phosphorylated within 1 h of cisplatin treatment in cultured utricular hair cells. Epigallocatechin gallate (EGCG), a green-tea extract that inhibits STAT1, increased hair cell survival after cisplatin treatment. Similarly, cisplatin ototoxicity was reduced in hair cells from STAT1-knockout mice. Together with data suggesting that EGCG potentiates the effects of chemotherapy in some cancers, these results suggest that EGCG may be a useful treatment for limiting cisplatin-induced ototoxicity.