

This Week in The Journal

● Cellular/Molecular

Glutamate Regulates Schwann Cell Proliferation and Myelination

Fuminori Saitoh and Toshiyuki Araki
(see pages 1204–1212)

After peripheral nerve injury, myelinating Schwann cells dedifferentiate and begin to proliferate. One protein upregulated after nerve injury is ZNRF1, an E3 ubiquitin ligase that tags proteins for proteasomal degradation. To investigate the role of ZNRF1 in proliferation, Saitoh and Araki looked for ZNRF1 targets and thus identified glutamine synthetase, an enzyme that synthesizes glutamine from glutamate. Knockdown of ZNRF1 increased glutamine synthetase levels in cultured Schwann cells and increased myelination of sensory neurons cocultured with Schwann cells. Likewise, overexpression of glutamine synthetase increased myelination in cultures. Because glutamine synthetase is expected to reduce levels of its substrate, glutamate, the results suggest that the switch from proliferation to myelination might be regulated by glutamate. Indeed, glutamate inhibited myelination and increased Schwann cell proliferation, and these effects appeared to be mediated by metabotropic glutamate receptors. In contrast, glutamine had no effect on Schwann cell proliferation or myelination.

▲ Development/Plasticity/Repair

Retinal Ganglion Cell Subtypes Mature via Different Processes

In-Jung Kim, Yifeng Zhang, Markus Meister, and Joshua R. Sanes
(see pages 1452–1462)

Retinal ganglion cells (RGCs) comprise many subtypes that respond differentially to visual features such as color, changes in light intensity, and direction of movement. The various functions are associated with differences in synaptic inputs, morphology, and projections. Different classes of RGCs appear to acquire their mature morphology and connection pattern through different developmental processes. To facilitate study of specific RGC types, Kim et al. have taken advantage of differences in protein expres-

sion to selectively express green fluorescent protein in single RGC types. They now describe four types of RGCs, and they show that these develop in different ways. Some developed their mature pattern at an early stage, suggesting that molecular cues are used to precisely guide process growth and termination. Others overgrew their targets and were later pruned to their mature pattern, suggesting activity-dependent plasticity might be involved. The availability of specifically labeled RGC types will allow future research to further elaborate differences in development and function.

■ Behavioral/Systems/Cognitive

Interneuron Subtypes Express Different Forms of Plasticity

Wiebke Nissen, Andras Szabo, Jozsef Somogyi, Peter Somogyi, and Karri P. Lamsa

(see pages 1337–1347)

The hippocampus contains several types of GABAergic interneurons, which differ in the proteins they express, where on pyramidal cells they form synapses, and whether they are principally driven by local or distant neurons. Some interneurons exhibit long-term potentiation and depression (LTP and LTD), but whether all do is not clear. To answer this question, Nissen et al. recorded

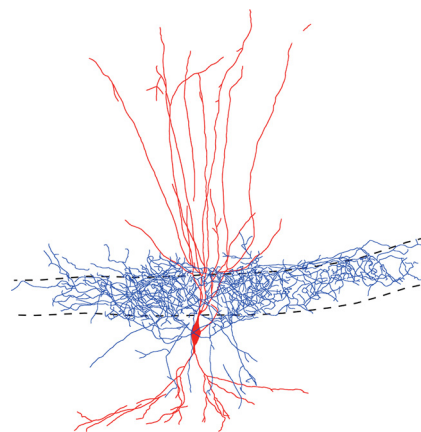
from unidentified interneurons that targeted different subcellular domains of pyramidal neurons and expressed either cannabinoid receptors or the calcium-binding protein parvalbumin. High-frequency stimulation of pyramidal cell axons produced LTP in parvalbumin-expressing axo-axonic interneurons and basket cells, which innervate pyramidal cells perisomatically. But, the same stimulation produced LTD in bistratified cells, which innervate pyramidal cell dendrites. Thus, high-frequency stimulation strengthens the inhibitory input to pyramidal cell somata relative to that to dendrites and might thereby enhance temporal integration. In contrast, neither high-frequency nor theta-burst stimulation induced LTP or LTD in interneurons that expressed cannabinoid receptors.

◆ Neurobiology of Disease

Early Effects of β -Amyloid on Mitochondria

Xiao-Liang Zhao, Wen-An Wang, Jiang-Xiu Tan, Jian-Kang Huang, Xiao Zhang, Bao-Zhu Zhang, Yu-Hang Wang, Han-Yu Yang, Cheng, Hong-Lian Zhu, Xiao-Jiang Sun, and Fu-De Huang
(see pages 1512–1522)

Excessive production of β -amyloid protein $A\beta_{1-42}$ is strongly tied to Alzheimer's disease (AD), but the critical cellular events leading to loss of synapses and neurodegeneration remain uncertain. To understand how AD pathology develops in a model system, Zhao et al. overexpressed $A\beta$ isoforms in flight-related motor and interneurons in *Drosophila* and examined the effects at different ages. $A\beta$ accumulated in neuronal somata and axons, and this correlated with accelerated age-related decline of flight behavior and shortened lifespan. The first cellular defect to appear was a reduction in the number of mitochondria in presynaptic terminals. Later, abnormal mitochondria appeared and their transport rate declined. Around the same time, the number of presynaptic vesicles decreased and their size increased, and synaptic fatigue during high-frequency stimulation increased. These data support the hypothesis that mitochondrial dysfunction is an early event in $A\beta$ -mediated toxicity and that this dysfunction contributes to synaptic decline in AD.



A parvalbumin-expressing basket cell. Dendrites and soma are red and axon is blue. Note that the axonal arbor is primarily restricted to the pyramidal cell layer, demarcated here by dashed lines. See the article by Nissen et al. for details.