This Week in The Journal

● Cellular/Molecular

Distribution of Kv Channels Depends on Subunit Composition

Paul M. Jenkins, Jeremy C. McIntyre, Lian Zhang, Arun Anantharam, et al.

(see pages 13224–13235)

In bimolecular fluorescence complementation (BiFC) assays, fragments of a fluorescent molecule are attached to different proteins; interaction between the two proteins facilitates the formation of a complex between the fragments, thus producing fluorescence. This enables visualization of protein interactions in living cells. Jenkins et al. have developed a BiFC assay using fragments of pHluorin, a molecule whose fluorescence is low at low pH. Because the pH inside vesicles is lower than outside the cell, the technique allows visualization of protein interactions occurring at the cell surface. The authors used this method to localize homomeric and heteromeric voltage-sensitive potassium (Kv) channels in cultured rat hippocampal neurons. Unexpectedly, they found that channel subunit composition had a large effect on localization. For example, whereas Kv1.4 homomers were distributed diffusely in axons, assembly with Kv1.1 caused Kv1.4 to be largely excluded from axons, and interaction with Kv1.2 caused Kv1.4 to be clustered into relatively stable axonal puncta.

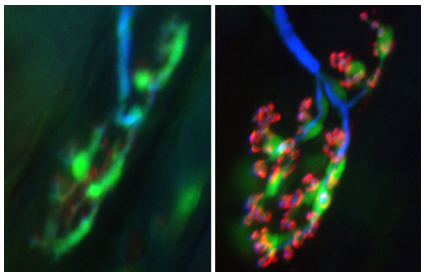
▲ Development/Plasticity/Repair

Nerves Do Not Retract When Muscle Degenerates

Yue Li and Wesley J. Thompson

(see pages 13191–13203)

Although neuromuscular junctions (NMJs) are usually stable, damage to the muscle fiber—which occurs frequently as a result of contraction during muscle lengthening—causes remodeling of the nerve terminal. In NMJs on uninjured muscle fibers, smooth nerve processes contact continuous gutters of acetylcholine receptors (AChRs); but after a muscle fiber



After the muscle fiber of an NMJ degenerates (left), the axon terminal (blue) and its associated Schwann cell (green) remain in place. Regrowth of the muscle (right) stimulates growth of varicose branches from the nerve terminal, which then induce clustering of AChRs (red). See the article by Li and Thompson for details.

regenerates, nerve terminals at NMJs become highly branched with numerous varicosities that contact patches of AChRs. This led to the hypothesis that maintenance of nerve terminals requires a target-derived factor: nerves retract when muscle degenerates and regrows with a new structure when muscle regenerates. Surprisingly, however, Li and Thompson found that after ablation of single muscle fibers in living mice, nerve terminals remained largely intact and unchanged until the muscle began to regenerate. Only then did nerves extend small, varicose processes through holes in the collapsed basal lamina that formerly surrounded the muscle, inducing clustering of AChRs at the new contact sites.

■ Behavioral/Systems/Cognitive

Hippocampus Aids Learning from Delayed Feedback

Karin Foerde and Daphna Shohamy

(see pages 13157–13167)

The striatum has been hypothesized to be involved in predicting the result of possible actions, thus enabling selection of the action associated with the best expected outcome; dopaminergic inputs report whether the outcome is different than expected, and future predictions are updated accordingly. This type of learning is important when outcomes are probabilistic, e.g., when a given choice is correct 80% of the time. People with Parkinson's disease (PD) are impaired on tasks requiring such learning. Surprisingly, however, Foerde and Shohamy found that PD patients were not impaired if the outcome was withheld for 6 s after a choice was made. Healthy subjects did equally well regardless of when feedback was given. Functional imaging in healthy subjects revealed that the striatum responded more to positive than negative outcomes when immediate feedback was given, whereas the hippocampus showed differential responses when feedback was delayed. This suggests that the hippocampus contributes to learning from delayed reward.

◆ Neurobiology of Disease

Tau Is Secreted from Healthy Neurons

Kaoru Yamada, John R. Cirrito, Floy R. Stewart, Hong Jiang, Mary Beth Finn, et al.

(see pages 13110–13117)

Intracellular aggregates of hyperphosphorylated tau characterize several neurodegenerative diseases. Although tau is a microtubule-associated protein that does not contain a signal sequence for secretion, tau aggregates can also be detected extracellularly, including in CSF. Evidence suggests that extracellular tau aggregates propagate tau pathology within the brain. The presence of extracellular tau is not limited to pathology, however. Using *in vivo* microdialysis probes, Yamada et al. detected monomeric tau in the interstitial fluid of hippocampus in wild-type mice. This suggests that tau is one of several molecules secreted by unconventional pathways under normal conditions. Mice that overexpressed a disease-associated form of human tau had higher levels of extracellular monomeric tau than wild-type mice, even before tau aggregates were detectable. Levels declined as aggregates appeared, and injection of aggregated tau into the hippocampus caused the levels of monomeric extracellular tau to decrease in presymptomatic mice, supporting the hypothesis that aggregates promote further aggregation of monomeric tau.