This Week in The Journal

● Cellular/Molecular

Total Darkness Allows Rod Regeneration

Damian C. Lee, Felix R. Vazquez-Chona, W. Drew Ferrell, Beatrice M. Tam, Bryan W. Jones, et al.

(see pages 2121–2128)

Progressive degeneration of rods defines retinitis pigmentosa (RP), but its genetic causes are diverse. Mutations in >30 genes have been linked to RP, and nearly 100 disease-causing mutations occur in rhodopsin alone. These mutations appear to affect different cellular processes, complicating efforts to develop treatments. For example, no significant effect of light restriction on RP progression has been found in humans, but genotype was not controlled for in these studies, and some evidence suggests that degeneration resulting from a common RP-causing mutation—a proline-to-histidine substitution (P23H) in rhodopsin—is accelerated by light. Moreover, rearing P23H-expressing animals in complete darkness attenuates rod degeneration. Lee et al. found that in P23H-expressing *Xenopus* tadpoles, many rods remain viable despite losing outer segments, and keeping tadpoles in total darkness after outer segments degenerated allowed regeneration of outer segments. If human P23H rods behave similarly, limiting light exposure may slow degeneration in this subset of RP patients.

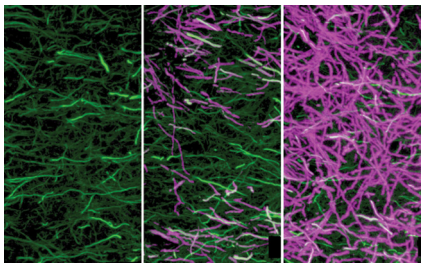
▲ Development/Plasticity/Repair

LIF Promotes Remyelination

Benjamin E. Deverman and Paul H. Patterson

(see pages 2100 –2109)

In traumatic brain injury and multiple sclerosis (MS), chronic demyelination leads to axonal damage. Although oligodendrocyte precursors proliferate, differentiate, mature, and remyelinate axons in adult brains, this happens too slowly to compensate for the loss in MS. Stimulating endogenous processes might be an effective means to treat



Axons (green) in mouse hippocampus lose all myelin (purple) after 12 weeks of cuprizone treatment (left). Although some spontaneous remyelination occurs (center), remyelination is greatly increased by LIF (right). See the article by Deverman and Patterson for details.

the disease, however. Leukemia inhibitory factor (LIF) stimulates oligodendrocyte precursor cell (OPC) proliferation, oligodendrocyte maturation, and myelination in cultures, and Deverman and Patterson show that it produces similar effects *in vivo*. Intracerebroventricular injection of adenovirus expressing LIF (Ad-LIF) increased OPC proliferation in mice. Furthermore, after cuprizone-induced demyelination, Ad-LIF greatly increased the number of mature oligodendrocytes and the extent of myelination in the hippocampus. Interestingly, some remyelination does not depend on LIF: enhanced proliferation and maturation were not detected in white matter tracts that underwent extensive spontaneous remyelination after cuprizone treatment, and inactivating the LIF receptor blocked the effects of Ad-LIF without affecting spontaneous recovery.

■ Behavioral/Systems/Cognitive

Trial-to-Trial Variability Does Not Follow Firing Rate in FEF

Mindy H. Chang, Katherine M. Armstrong, and Tirin Moore

(see pages 2204 –2216)

In the absence of overt stimulation, cortical neuronal firing patterns are highly variable. Trial-to-trial variability decreases when a sensory stimulus is presented and, in some cortical areas, during anticipatory periods in which a stimulus or motor response is imminent. In monkey frontal eye field (FEF), which is involved in directed saccadic eye movements, some neurons fire during delays after a cue indicates that a stimulus will appear within the neurons' receptive field. Furthermore, these neurons fire more when a receptive-field stimulus was cued than when the same stimulus appears unexpectedly. Chang et al. asked whether the trial-to-trial variability of FEF neurons is similarly affected by cues and found that it is not. Decreases in variability occurred whenever a stimulus was presented in a neuron's receptive field and returned to baseline between stimuli, no matter where the cue appeared. Thus, trial-to-trial variability in the FEF does not appear to reflect anticipation or attention.

♦ Neurobiology of Disease

γ-Secretase Modulator Improves Memory Performance

Yasuyuki Mitani, Junko Yarimizu, Kyoko Saita, Hiroshi Uchino, Hiroki Akashiba, et al.

(see pages 2037–2050)

β-Amyloid (Aβ) is formed by cleavage of amyloid precursor protein (APP), first by β-secretase, which produces a soluble ectodomain and a membrane-bound C-terminal fragment (β-CTF), then by γ-secretase, which cleaves β-CTF to produce an intracellular domain and Aβ. Because Aβ likely contributes to Alzheimer's disease (AD), γ-secretase inhibitors have been tested as therapeutics. Unfortunately, these inhibitors worsened cognitive performance in clinical trials, possibly because other γ-secretase functions were also affected. But γ-secretase can cleave β-CTF at various positions, creating Aβ peptides of different lengths. AD-linked mutations in γ-secretase increase production of $A\beta_{42}$, suggesting this peptide is particularly neurotoxic. Therefore, biasing γ-secretase cleavage to reduce $A\beta_{42}$ production may be beneficial. Indeed, Mitani et al. report that treating mice expressing AD-linked APP with a γ-secretase modulator improved performance in a spatial memory task, whereas γ-secretase inhibitors had no effect, and worsened performance in wild-type mice. Additional evidence suggested that accumulation of β-CTFs underlies inhibitor-induced cognitive impairment.