This Week in The Journal

● Cellular/Molecular

Fascin-2 Mutation Underlies Age-Related Hearing Loss in Mice

Jung-Bum Shin, Chantal M. Longo-Guess, Leona H. Gagnon, Katherine W. Saylor, Rachel A. Dumont, et al.

(see pages 9683–9694)

Sound perception begins with the deflection of stereocilia atop auditory hair cells. Extensive cross-linking of actin within stereocilia makes them rigid, so they pivot at their bases without bending along their lengths. This pivoting causes shearing between adjacent stereocilia, exerting tension on filamentous tip links, which causes transduction channels to open. Disrupting the structure of stereocilia or tip links causes hearing loss. DBA/2J mice, for example, have a mutation in cadherin 23, a component of tip links, which increases their susceptibility to age-related hearing loss. A second DBA/2J mutation in a heretofore unidentified gene accelerates hearing loss. Shin et al. report that this second defect is a point mutation in *Fscn2*, which encodes the actin-cross-linking protein fascin-2. Fascin-2 was highly expressed in stereocilia—especially in the tallest—in a gradient from base to tip. The position of the mutation suggests that it might disrupt an actin-binding domain, and thus abolish effective cross-linking.

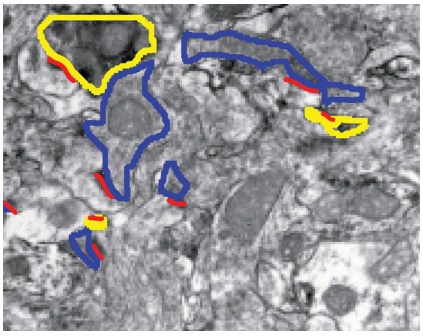
▲ Development/Plasticity/Repair

Changes in Synaptic Number and Size Reflect Ocular Dominance Shifts

Jason E. Coleman, Marc Nahmani, Jeffrey P. Gavornik, Robert Haslinger, Arnold J. Heynen, et al.

(see pages 9670–9682)

Occluding one eye during development reduces that eye's influence on cortical neurons, resulting in an overall decrease in thalamocortical drive to the contralateral V1 within 3 d (in mice). Subsequently, the influence of the spared eye increases, restoring thalamocortical drive. The cellular underpinnings of this shift are not fully understood: although thalamocortical axons representing the occluded eye eventually retract, this occurs well after electrophysiological changes are detected. Examining synapses expressing a thalamocortical-specific vesicular glutamate transporter, Coleman et al. found that 3 d after monocular deprivation, the prevalence and cross-sectional area of boutons and the length of postsynaptic densities in V1 contralateral to the deprived eye were decreased relative to ipsilateral V1. By 7 d of deprivation, the number and size of synapses returned to control levels, paralleling the increase in drive from the spared eye. Importantly, blocking activity in one eye, which does not produce an ocular dominance shift, did not alter synaptic number or size.



After 3 d of monocular occlusion, the number and size of thalamocortical synaptic terminals (outlined in yellow) and the length of postsynaptic densities (red) decrease. Intracortical boutons are outlined in blue. See the article by Coleman et al. for details.

■ Behavioral/Systems/Cognitive

Knock-out of Sirtuin1 Impairs Learning

Shaday Michán, Ying Li, Maggie Meng-Hsiu Chou, Edoardo Parrella, Huanying Ge, et al.

(see pages 9695–9707)

Sirtuins are NAD^+-dependent deacetylases that gained prominence when they were linked to extension of lifespan by caloric restriction in yeast. Although sirtuin knock-out abolishes the effect of caloric restriction on lifespan in mice, elevating sirtuin activity does not extend life. Nonetheless, mammalian sirtuins are important in many processes essential for cellular health, including DNA repair, stress resistance, and maintaining blood glucose levels. They are also involved in neuronal differentiation and, as now reported by Michán et al., in learning and memory. Sirtuin1 is expressed in neurons throughout the mouse hippocampus, and sirtuin1 knock-out reduced length and branching of dendritic arbors without noticeably affecting spine density or shape. Short-term spatial memory, fear conditioning, and long-term potentiation were impaired in sirtuin1 knock-outs, but sirtuin1 levels in wild-type hippocampus were unchanged by fear conditioning or spatial training. These data suggest that sirtuin1 is required for learning to take place, but it might not participate directly in the learning process.

♦ Neurobiology of Disease

Transfected Monocytes Hold Promise for Gene Therapy

Lori Lebson, Kevin Nash, Siddharth Kamath, Donna Herber, Nikisha Carty, et al.

(see pages 9651–9658)

A great hope for gene therapy to treat neuropathology is to deliver proteins to injured areas with minimal disruption of healthy brain. One vehicle for achieving this might be peripheral monocytes, which differentiate into microglia when they enter the brain. Lebson et al. injected GFP-labeled, bone marrow-derived, CD11b-expressing cells (likely to be primarily monocytes) into the bloodstream of transgenic mice that expressed two mutant proteins associated with Alzheimer's disease. Many labeled cells entered the brain, expressed a microglial marker, and congregated near amyloid plaques, suggesting they specifically targeted the pathology. CD11b-expressing cells were then transfected with a secreted form of neprilysin, an endogenous protease that degrades amyloid deposits, before injection. Whereas amyloid deposition greatly increased in untreated mice, transfected cells prevented any increase in deposition during the 2 month treatment period. This form of therapy could allow a patient's own monocytes to be transfected with an appropriate therapeutic agent and introduced into the brain without surgery.