This Week in The Journal

● Cellular/Molecular

Retromer Influences APP Processing via sorLA

Anja W. Fjorback, Matthew Seaman, Camilla Gustafsen, Arnela Mehmedbasic, Suzanne Gokool, et al.

(see pages 1467–1480)

After synthesis or endocytosis, transmembrane proteins are shuttled to various intracellular compartments where different processing events occur. Disrupting protein trafficking can alter processing and impair function. For example, amyloid precursor protein (APP) is cleaved differently in endosomes than at the cell surface; because endosomal processing leads to production of β-amyloid, increasing endosomal delivery of APP increases the amyloidogenic processing associated with Alzheimer's disease (AD). Interaction with the sorting receptor sorLA slows APP exit from the Golgi network, thus preventing amyloidogenic processing. Mutations in sorLA are linked to AD. Similarly, levels of retromer, a protein complex involved in transporting sorting receptors from endosomes to the trans-Golgi network, are reduced in AD, and retromer deficiency increases β-amyloid production. Fjorback et al. provide evidence that retromer affects APP trafficking indirectly, via interactions with sorLA. Disrupting this interaction caused sorLA to leave the Golgi and accumulate in the tubular endosome network, taking APP with it.

▲ Development/Plasticity/Repair

Mirror Therapy Alters M1 and Improves Motor Performance

Ippei Nojima, Tatsuya Mima, Satoko Koganemaru, Mohamed Nasreldin Thabit, Hidenao Fukuyama, et al.

(see pages 1293–1300)

Mirror visual feedback (MVF) has been used to reduce phantom pain in amputees and it can improve hemiparesis after stroke. Few studies have used rigorous statistical measures to assess the effectiveness of mirror therapy, however, and the underlying mechanisms remain unknown. Nojima et al. advance the study of MVF by analyzing its effects in neurologically healthy people. Subjects practiced rotating two balls in their right hands, after which their ability to perform the task with their left hands was evaluated. Left hand performance improved only in subjects who viewed a mirror image of the practicing right hand superimposed over the position of the left hand. The improvement was correlated with increased excitability of right M1, as reflected by both the minimal intensity of transcranial magnetic stimulation (TMS) required to produce left-arm muscle evoked potentials (MEPs) and the amplitude of MEPs produced by TMS. Interfering with M1 activity via continuous theta burst stimulation blocked MVF-associated improvement.

■ Behavioral/Systems/Cognitive

Hair Cell Density Varies Seasonally in Singing Fish

Allison B. Coffin, Robert A. Mohr, and Joseph A. Sisneros

(see pages 1366–1376)

In seasonally breeding songbirds, males sing to attract females during the spring and sing more variable songs or none at all during nonbreeding seasons. The seasonal change in song production is paralleled by dramatic changes in the size of forebrain song nuclei, as well as by changes in auditory brainstem responses. Males in some fish species, including midshipman fish, also sing to attract females during the breeding season. Like songbirds, these fish show seasonal variation in auditory processing: the sensitivity of the auditory end organ—the saccule—of females peaks during the breeding season. Coffin et al. report that this change in sensitivity is paralleled by an increase in the density of saccular hair cells, partly resulting from reduced apoptosis. Fish add hair cells throughout life, but whether hair cell proliferation increases in the spring remains to be determined, as does the evolutionary advantage conferred by seasonal variation in hair cell density.

In spring, male midshipman fish contract muscles surrounding the swim bladder to produce a hum that attracts females. In females (pictured), sensitivity to these sounds increases, possibly because of an increase in saccular hair cell density. Photograph by Peter Alderks. See the article by Coffin et al. for details.

♦ Neurobiology of Disease

NP1 Facilitates BAX Accumulation in Mitochondria

Kevin B. Clayton, Petar Podlesniy, Joana Figueiro-Silva, Guillermo López-Doménech, Lluis Benitez, et al.

(see pages 1453–1466)

Programmed cell death is an essential feature of development and tissue homeostasis, but if improperly regulated, it can contribute to cancer or degenerative diseases. Death programs are regulated by anti- and pro-apoptotic proteins, including BAX. Apoptotic signals cause BAX to translocate from the cytosol to the mitochondrial outer membrane, where it forms homo-oligomers that permeabilize the membrane. Cytochrome *c* residing in the mitochondrial intermembrane space then escapes and activates a caspase cascade culminating in DNA fragmentation and cell death. This apoptotic pathway is activated in silenced neurons, but how activity blockade induces BAX translocation is unclear. Clayton et al. found that neuronal pentraxin 1 (NP1) is a link in the chain. Reducing activity of cultured rodent cerebellar neurons stimulated synthesis of NP1, which colocalized with BAX in mitochondria. NP1 overexpression increased BAX activation, cytochrome *c* release, caspase 3 activation, and apoptosis. In contrast, knockdown of NP1 reduced BAX activation and apoptosis when activity was blocked.