This Week in The Journal

● Cellular/Molecular

AMPA Receptor Cycling with and without hsp90

Nashaat Z. Gerges, Irwin C. Tran, Donald S. Backos, Jennifer M. Harrell, Michael Chinkers, William B. Pratt, and José A. Esteban
(see pages 4758 – 4766)

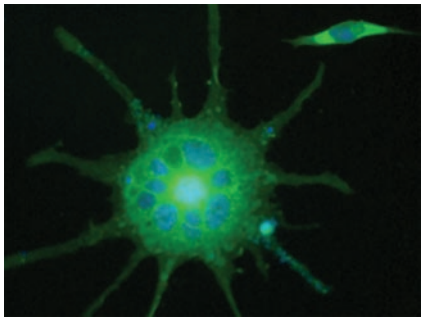
The molecular chaperone heat shock protein 90 (hsp90) works in conjunction with the cytoskeleton to deliver membrane-bound signaling molecules to their destinations. This week, Gerges et al. explore a role for hsp90 in both transmitter release and trafficking of AMPA-type glutamate receptors. Movement of AMPA receptors to and from synapses is thought to use constitutive pathways and regulated pathways. hsp90 inhibitors increased paired-pulse facilitation and also preferentially decreased AMPA receptor-mediated EPSCs, consistent with both presynaptic and postsynaptic actions. The authors present evidence that hsp90 participates in delivery of AMPA receptors to synaptic sites (but not to nonsynaptic membrane) and that hsp90 is active in the constitutive but not the regulated movement of the receptors. As predicted from other hsp interactions, hsp90 action involved a tetratricopeptide repeat (TPR) domain of an as yet unidentified effector molecule. Thus hsp90 joins *N*-ethylmaleimide-sensitive fusion protein (NSF) as a chaperone necessary for constitutive trafficking of AMPA receptors.

▲ Development/Plasticity/Repair

HHV-6 Infection and Human Glial Precursor Cells

Joerg Dietrich, Benjamin M. Blumberg, Mikhail Roshal, Jeffrey V. Baker, Sean D. Hurley, Margot Mayer-Pröschel, and David J. Mock
(see pages 4875– 4883)

Although the trigger for demyelination in diseases such as multiple sclerosis (MS) is still not clear, effective repair certainly depends on a healthy population of oligodendrocyte precursor cells (OPCs) as a source of remyelinating cells. Although OPCs are present in MS lesions, they often remain quiescent, seemingly unaware of the need to produce mature oligodendrocytes. In this week's *Journal*, Dietrich et al. examine a common viral resident of CNS, the human herpesvirus 6 (HHV-6), as a possible culprit in the faulty repair process. Using a recently derived population of A2B5$^+$ glial precursor cells from fetal human brain, they show that HHV-6 does indeed infect these cells *in vitro* via the CD46 receptor, thus affecting their ability to self-renew and differentiate. RT-PCR and immunocytochemistry documented the expression of viral structural proteins in infected cells. Infection did not cause cell death, but it did arrest the cell cycle and inhibit proliferation. These studies provide a plausible mechanism for impaired repair after CNS demyelination or inflammation.



Enlarged multinucleated syncytia seen in HHV-6-infected human glial progenitor cells. See the article by Dietrich et al. for details.

■ Behavioral/Systems/Cognitive

Probing Impulsivity in the Rat

Catharine A. Winstanley, David E. H. Theobald, Rudolf N. Cardinal, and Trevor W. Robbins
(see pages 4718 – 4722)

The orbitofrontal cortex (OFC) and the basolateral amygdala (BLA) share reciprocal connections, and both are important to goal-directed behavior. Winstanley et al. set out to dissociate the contribution of each region after excitotoxic lesions in rats. The OFC and BLA are thought to contribute to impulse control, a behavior that can be assessed in humans or rodents by delivering a reward after an increasing delay period. In this assay, increased impulsivity is manifest as a willingness to take a small immediate reward rather than wait for the grand prize, in this case four food pellets instead of one. BLA lesions caused the rats to choose the smaller, more rapid reward. Surprisingly, the opposite effect was seen in OFC-lesioned rats, which were happy to wait longer for those extra three pellets. The authors interpret their results as indicating that the BLA is necessary to maintain a representation of reward value, whereas the OFC acts to update the expectancy of a reward.

♦ Neurobiology of Disease

A Neuroligin Mutation and Autism

Davide Comoletti, Antonella De Jaco, Lori L. Jennings, Robyn E. Flynn, Guido Gaietta, Igor Tsigelny, Mark H. Ellisman, and Palmer Taylor
(see pages 4889 – 4893)

With its severe impairment of children's communication skills and social interactions, autism is a devastating and heartbreaking developmental disorder. The high concordance in monozygotic twins has suggested a genetic component. Recently, mutations in the X-linked genes neuroligin-3 (NL3) and NL4 have been identified in pairs of siblings with autism. The neuroligins are transmembrane proteins that bind to neurexins in another cell and thus are thought to be important in synapse formation. In this issue, Comoletti et al. examined the biochemical properties of the Arg451Cys mutation in NL3. Mutant NL3 expressed in HEK cells appeared to retain the correct secondary structure. However, trafficking of the mutant protein was impaired, with most of the protein retained in the endoplasmic reticulum. The small amount of protein that reached cell surface did not bind effectively to β-neurexin. Thus two separate molecular mechanisms are apparent in this loss-of-function mutation.