This Week in The Journal

● Cellular/Molecular

Cytoskeleton and Cholesterol Limit Lipid Diffusion in Synapses

Marianne Renner, Daniel Choquet, and Antoine Triller

(see pages 2926–2937)

Unconstrained molecules diffuse rapidly and randomly in cell membranes. Protein diffusion is slowed in some regions, such as synaptic sites, by scaffolding proteins and tethers to the cytoskeleton. Dense clustering of proteins at these sites can impede the diffusion of other molecules not directly linked to them. Molecular diffusion can also be limited by cholesterol-rich microdomains called lipid rafts. To determine which of these structures is more important for constraining lipid mobility within and outside of synapses, Renner et al. tracked individual lipid molecules labeled with fluorescent markers. Diffusion rates were lower at synaptic than at extrasynaptic sites, and were lower in inhibitory than in excitatory synapses. Moreover, single lipid molecules were temporarily confined when they entered synaptic sites. Both actin depolymerization and cholesterol depletion increased mobility of lipid molecules within synapses, but only actin depolymerization reduced synaptic confinement. These results suggest that both protein barriers and raft-like properties reduce diffusion of lipid molecules in synapses.

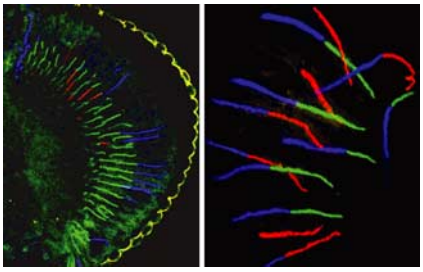
▲ Development/Plasticity/Repair

rhomboid *Helps Coordinate Rhodopsin Expression in* Drosophila

Denise A. Birkholz, Wen-Hai Chou, Meridee M. Phistry, and Steven G. Britt

(see pages 2666–2675)

Color discrimination in *Drosophila* depends on the coordinated expression of different rhodopsins in the two inner photoreceptors—R7 and R8—of each omatidium. Photoreceptor subtype specification occurs gradually, through iterative signaling between cells. To coordinate rhodopsin (rh) expression, R7 cells that express rh3 induce the expression of rh5 in the adjacent R8; without this signal (e.g., when R7 expresses rh4), R8 expresses rh6. Birkholz et al. now show that induction of rh5 in R8 also requires the expression of *rhomboid* in R8. Loss of *rhomboid* caused mispairing of rh6-expressing R8 cells with rh3-expressing R7 cells, whereas ectopic expression of *rhomboid* induced inappropriate rh5 expression in R8 cells paired with rh4-expressing R7 cells. *rhomboid* encodes a protease that activates an epidermal growth factor receptor (EGFR) ligand, which is expressed in R7. It appears that R8 must release an EGFR ligand that activates EGFRs in R7 to make R7 competent to induce rh5 expression in R8.



Loss of *rhomboid* (left) causes loss of rh5 (red) expression in R8 cells of *Drosophila* retina, and causes mispairing of Rh3 (blue) and Rh6 (green) in adjacent photoreceptors. Ectopic expression of *rhomboid* (right) causes mispairing of rh4 (blue) with rh5 (red), in addition to normal pairing with rh6 (green). See the article by Birkholz et al. for details.

■ Behavioral/Systems/Cognitive

Sound Detection Appears Late in Auditory Development

Masashi Tanimoto, Yukiko Ota, Kazuki Horikawa, and Yoichi Oda

(see pages 2762–2767)

Connections between auditory hair cells and brainstem nuclei are established before brainstem nuclei become responsive to sounds. The reason for this delay is unknown. To identify the missing components, Tanimoto et al. used zebrafish embryos to track the anatomical and electrophysiological development of this pathway. The VIIIth nerve established its first direct synaptic contacts with reticulospinal Mauthner cells at 23 h postfertilization (hpf). Synapses began forming between the peripheral processes of the VIIIth nerve and hair cells at 27 hpf. Some mechanotransduction channels were present in hair cells at this stage, and electrical or mechanical stimulation of hair cells led to postsynaptic currents in Mauthner cells. Microphonic potentials did not appear in hair cells until 40 hpf, however, indicating that the ability of hair cells to respond to sound is the last step in auditory system development. Closer examination of cellular and molecular changes during this period may help to elucidate the mechanisms of sound transduction.

♦ Neurobiology of Disease

Truncated $GABA_A$ Receptor $\gamma 2$ Subunit Reduces $\alpha 1$ Expression

Jing-Qiong Kang, Wangzhen Shen, and Robert L. Macdonald

(see pages 2845–2856)

Generalized epilepsy with febrile seizure plus (GEFS+) is a dominantly inherited disease caused by mutations in the $GABA_A$ receptor $\gamma 2$ subunit. One of these mutations results in the production of a truncated $\gamma 2$ subunit that is retained in the endoplasmic reticulum (ER) and subsequently degraded. One might predict that in heterozygotes, the unmutated $\gamma 2$ allele should continue to form normal $GABA_A$ receptors, and that the dominant epileptic phenotype must therefore result from reduced GABA receptor expression caused by haploinsufficiency. This does not appear to be the case, however: hemizygous mice with a single wild-type $\gamma 2$ allele do not have seizures. This week, Kang et al. present evidence that mutant $\gamma 2$ subunits act as dominant-negative suppressors of GABA receptor expression by oligomerizing with wild-type $\alpha 1$ and $\gamma 2$ subunits, causing their retention in the ER. This reduces trafficking of functional receptors to the cell surface, and reduces GABA-evoked currents to levels lower than those in hemizygotes.