This Week in The Journal

● Cellular/Molecular

Gephyrin Oligomerization Is Required for GlyR Clustering

Martino Calamai, Christian G. Specht, Janosch Heller, Damien Alcor, Patricia Machado, Christian Vannier, and Antoine Triller

(see pages 7639–7648)

Untethered transmembrane proteins diffuse rapidly in the plasma membrane. To ensure reliable synaptic transmission, neurotransmitter receptors are held at postsynaptic sites adjacent to presynaptic terminals by interactions with scaffolding proteins that link the receptors to the cytoskeleton. Modification of these interactions can alter the number of receptors at postsynaptic sites and thus modulate synaptic strength. Postsynaptic clustering of glycine receptors (GlyRs) is thought to be mediated by the scaffolding protein gephyrin. Interaction with gephyrin is not sufficient for clustering, however, because GlyRs also associate with gephyrin at nonsynaptic sites. Previous studies have suggested that oligomerization of gephyrin proteins is required for GlyR clustering. Calamai et al. support this hypothesis by showing that interfering with gephyrin oligomerization by expressing isolated interaction domains reduced the number and size of gephyrin–GlyR clusters in cultured spinal cord neurons and increased lateral mobility of extrasynaptic GlyRs. The mobility of synaptic GlyRs was not affected, however.

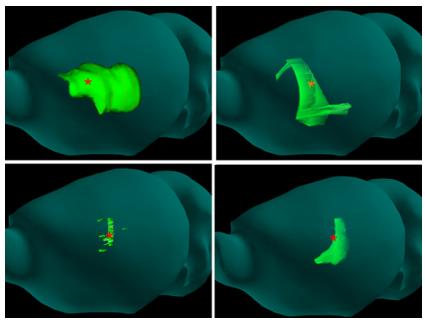
▲ Development/Plasticity/Repair

Newly Discovered Primitive Cells Produce Widespread Remyelination

Chuanshen Wu, Ansi Chang, Maria C. Smith, Roy Won, Xinghua Yin, Susan M. Staugaitis, Dimitri Agamanolis, Grahame J. Kidd, Robert H. Miller, and Bruce D. Trapp

(see pages 7649–7657)

The prospect of replenishing damaged cells in the brain using transplanted stem cells is perhaps most hopeful in the case of replacing oligodendrocytes in demyelinating diseases such as multiple sclerosis (MS). Wu et al. report what might be a landmark step in this direction: the discovery of a previously unrecognized population of cells in the adult subventricular zone (SVZ) that can differentiate into neurons, astrocytes, and oligodendrocytes, depending on culturing conditions. These cells, distinguishable from other SVZ cells by their expression of β4 tubulin (βT4), were scattered throughout the SVZ in humans, and their numbers were significantly elevated near lesions in MS patients. βT4-expressing cells exhibited several features of stem cells in addition to multipotency: low basal proliferation rate, contact inhibition via homophilic adhesion, and resistance to dissociation. Most importantly, when injected into the brain of myelin-deficient rats, βT4 cells produced mature oligodendrocytes that migrated far from the injection site and produced widespread remyelination.



Serial reconstructions of myelin-deficient rat brains show that remyelination (green) was more widespread after injection of βT4 cells (top panels) than after injection of other oligodendrocyte precursor cells (bottom panels). See the article by Wu et al. for details.

■ Behavioral/Systems/Cognitive

Role of VNO in Sex-Specific Behaviors Is Questioned

Kristine L. Martel and Michael J. Baum

(see pages 7658–7666)

Sex-specific behaviors were long thought to require circulating gonadal hormones both during development and for activation in adulthood. Two years ago, this paradigm was challenged by experiments in which the vomeronasal organ (VNO) was inactivated or removed in adult female mice. This caused the females to exhibit male sexual behaviors—mounting and pelvic thrusting—toward both males and females. The authors concluded that neural circuits underlying these male-specific behaviors are functional in females, and do not require activation by testosterone, but instead are tonically inhibited by the VNO. Martel and Baum challenge these conclusions. Using a different strain of mice and experimentally controlling gonadal hormone levels, the authors found no difference between VNO-ablated and control females in the frequency of male-typical behaviors. Similarly, lesion of the accessory olfactory bulb, which receives inputs from the VNO, produced no change in the frequency of these behaviors. In contrast, testosterone injections in ovariectomized females increased male-typical behaviors, independent of VNO status.

♦ Neurobiology of Disease

Oligonucleotides That Block SMN2 Splicing Improve Motor Function

Jason H. Williams, Rebecca C. Schray, Carlyn A. Patterson, Semira O. Ayitey, Melanie K. Tallent, and Gordon J. Lutz

(see pages 7633–7638)

Spinal muscular atrophy, the most common genetic cause of death in infants, is characterized by motor neuron degeneration and subsequent muscular atrophy resulting from functional loss of a protein called survival motor neuron (SMN). Although the disease is caused by mutations in the gene *SMN1*, a second human gene, *SMN2*, is a promising target for treatment. The coding sequences of *SMN1* and *SMN2* are nearly identical, but a single point mutation in *SMN2* promotes alternative splicing that results in excision of a crucial exon. Inhibition of this alternative splicing is expected to increase production of functional SMN, compensating for loss of *SMN1*. Williams et al. demonstrate the potential of this strategy by injecting steric-block oligonucleotides, which prevent splisosomes from acting at the alternative splice site, into the cerebral ventricles of transgenic mice. This increased expression of SMN in brain and spinal cord, improved weight gain, and improved righting response, a measure of motor function.