This Week in The Journal

Cellular/Molecular

Autophagy Promotes Myelin Formation

Chelsey M. Smith, Joshua A. Mayer, and Ian D. Duncan

(see pages 8088 – 8100)

The Long Evans shaker (*les*) rat has a mutation that hinders translation of myelin basic protein (MBP), a structural protein involved in assembly, compaction, and maintaining integrity of the myelin sheath. In *les* mutants, oligodendrocytes form thin, uncompacted myelin early in development, but myelination peaks at 2 weeks and is lost by 8 weeks. During this time, vesicles, lysosomes, and membrane-bound organelles accumulate in the cytoplasm of *les* oligodendrocytes. Among these cytoplasmic inclusions, Smith et al. identified double-membraned autophagosomes that contained degenerating organelles. High levels of autophagy in *les* oligodendrocytes was suggested by elevated levels of an autophagosomal protein and of ubiquitinated protein aggregates targeted for degradation by autophagy. Although increased autophagy often indicates degeneration, no significant increase in oligodendrocyte death or decrease in mature oligodendrocyte number was found in *les* rats. Indeed, increased autophagy appeared protective, and intermittent fasting over 2 months increased both autophagy and myelination in spinal cords of control and *les* rats.

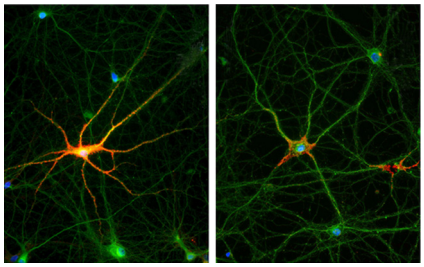
Development/Plasticity/Repair

Neuron-Derived Matrix Proteins Help Form Perineuronal Nets

Maren Geissler, Christine Gottschling, Ainhara Aguado, Uwe Rauch, Christian H. Wetzel, et al.

(see pages 7742–7755)

The extracellular matrix (ECM) that surrounds cells in the CNS is composed of aggregates of glycosaminoglycans, proteoglycans, and glycoproteins such as tenascins. These molecules interact with transmembrane receptors and affect neurite growth, synaptic plasticity, and synapse stabilization. Long-term potentiation (LTP) is impaired in mice lacking tenascins-C or -R or the chondroitin sulfate proteoglycan (CSPG) brevican. Although mice lacking these three ECM components along with the CSPG neurocan are viable and fertile, Geissler et al. report that synapse formation and maintenance are reduced in cultured hippocampal neurons from these mice. Growing mutant neurons with wild-type cortical astrocytes or vice versa revealed that wild-type neurons secrete all four ECM components, whereas astrocytes secrete only tenascin-C and brevican. Furthermore, neuron-derived ECM components were required for normal formation of perineuronal nets and for maintaining synaptic input: the frequency of miniature EPSCs and IPSCs was reduced in mutant neurons, even when grown with wild-type astrocytes. Both neuron- and astrocyte-derived ECM proteins were required for synapse formation and stabilization, however.



Unlike control neurons (left, green), neurons deficient in ECM components do not form normal perineuronal nets (red), even when grown with wild-type astrocytes (right). See the article by Geissler et al. for details.

Systems/Circuits

The Parabrachial Nucleus Participates in Hypercapnic Arousal

Satvinder Kaur, Nigel P. Pedersen, Shigefumi Yokota, Elizabeth E. Hur, Patrick M. Fuller, et al.

(see pages 7627–7640)

Obstruction of respiration during sleep causes CO_2 levels to increase, which triggers arousal. The neural circuit responsible for this hypercapnia-induced arousal likely includes the pontine parabrachial (PB) nucleus, which receives CO_2 chemosensory afferents, is active during hypercapnia and hypoxia, has roles in respiratory control, and projects to forebrain areas involved in arousal. Kaur et al. provide strong evidence that the PB nucleus is, in fact, involved in hypercapnia-induced arousal by knocking out the vesicular glutamate transporter vGlut2 to disrupt glutamatergic output from this nucleus. Knocking out vGlut2 in the external lateral PB greatly delayed arousal after exposure to hypercapnic air. Arousal was not universally disrupted in these mice, however: their latency to arousal by an acoustic stimulus was similar to that of controls. In contrast, knocking out VGlut2 in medial PB did not affect hypercapnia-induced arousal, but increased NREM sleep duration, frequency, and EEG delta power compared to controls, suggesting this area is involved in normal arousal from NREM sleep.

Behavioral/Cognitive

Effects of Maternal Infection Vary with Mouse Disc1 *Genotype*

Tatiana V. Lipina, Clement Zai, Daniela Hlousek, John C. Roder, and Albert H. C. Wong

(see pages 7654 –7666)

Schizophrenia likely stems from interactions between multiple genetic and environmental factors. Epidemiological studies have suggested that maternal infection during pregnancy increases risk of schizophrenia in offspring, particularly if there is a family history of the disease. In mice, maternal immune activation (MIA) and mutation of schizophrenia-linked genes such as *Disc1* produce similar phenotypes, including enlarged ventricles, deficits in both latent inhibition (LI) and prepulse inhibition of startle reflexes (PPI), and decreased social interaction, all of which characterize schizophrenia. Lipina et al. demonstrate that the effects of MIA differ by genotype. MIA impaired LI in wild-type mice, but did not affect PPI or time spent investigating another mouse. In mice with an LI-impairing point mutation in *Disc1*, however, MIA impaired PPI and reduced investigation of another mouse. In mice with a *Disc1* mutation that impaired PPI but not LI, MIA impaired the latter but not the former. Muting the immune response with antibodies against interleukin-6 prevented the effects of MIA in all mice.