This Week in The Journal

● Cellular/Molecular

Intracellular Trafficking Defect May Underlie Schizophrenia

Avanti Gokhale, Jennifer Larimore, Erica Werner, Lomon So, Andres Moreno-De-Luca, et al.

(see pages 3697–3711)

Schizophrenia has a strong genetic basis, although no single mutation causes the disease. Variations in the noncoding regions of *DTNBP1*, which encodes dysbindin, are associated with an increased risk of schizophrenia, and dysbindin expression is reduced in prefrontal cortex and hippocampus of schizophrenics. Dysbindin is part of a large endosomal protein complex called the "biogenesis of lysosome-related organelles complex 1" (BLOC-1), which is involved in trafficking protein-containing vesicles between intracellular compartments. To better understand dysbindin function, Gokhale et al. used mass spectrometry to identify proteins that interact with dysbindin in neuroblastoma cells. In addition to proteins previously shown to interact with dysbindin—including other BLOC-1 proteins—they identified 11 new interacting proteins. These included peroxiredoxins, proteins involved in vesicle trafficking to and within the Golgi apparatus, and several synapse-associated proteins. Interestingly, genes encoding eight of the interacting proteins are located in chromosomal regions in which allelic variations are associated with increased schizophrenia risk.

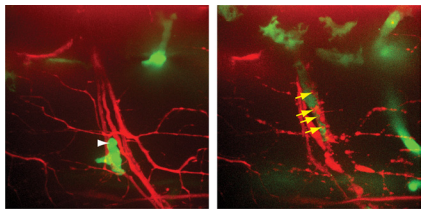
▲ Development/Plasticity/Repair

Macrophages Do Not Need Debris to Find PNS Injury

Allison F. Rosenberg, Marc A. Wolman, Clara Franzini-Armstrong, and Michael Granato

(see pages 3898–3903)

Various axonal insults cause Wallerian degeneration, a process involving axon fragmentation, myelin breakdown, and clearance of debris by macrophages. In the PNS, this process rapidly creates an environment favorable for regeneration; it occurs more slowly in the CNS, where lingering debris inhibits axonal regeneration. To better understand the mechanisms of Wallerian degeneration in the PNS, Rosenberg et al. imaged macrophages and axons in zebrafish over the course of degeneration and regeneration *in vivo*. The severed ends of axons began to retract immediately after transection, and fragmentation began 2–4 h later. Over the next day, debris was removed, and the proximal portion of axons began to regenerate, reinnervating muscle within 24 h. Unexpectedly, macrophages appeared at the injury site before axonal fragmentation began. Furthermore, macrophage recruitment appeared normal in fish lacking Schwann cells. Therefore, neither axonal debris nor Schwann cell cytokines were required to recruit macrophages to the severed nerve.



Macrophages (green, arrowhead) are recruited to nerve fiber within 1 h of injury (left), when severed axon (red) is still intact. When axonal fragmentation occurs (right), macrophages phagocytose distal axon debris (arrows). See the article by Rosenberg et al. for details.

■ Behavioral/Systems/Cognitive

Dentate Gyrus Has Two Sets of Spatially Selective Neurons

Joshua P. Neunuebel and James J. Knierim

(see pages 3848–3858)

Granule cells (GCs) of the dentate gyrus have been proposed to reinforce unique features of new experiences via their mossy fiber projections to CA3 pyramidal neurons. Mossy fibers also form *en passant* synapses on mossy cells in the dentate hilus, and these cells provide excitatory feedback to GCs. The response properties of GCs and the role of mossy cells in hippocampal information processing are poorly understood, however. Many dentate neurons fire at specific locations within an open arena, but some fire in multiple locations; whether both firing patterns are properties of GCs has been debated. After electrophysiologically analyzing dentate gyrus excitatory neurons, Neunuebel and Knierim concluded that there are, in fact, two distinct populations of spatially selective neurons. Neurons that fired selectively in single locations were rarely active during behavior and were likely to be GCs, whereas neurons with multiple fields were more active during foraging and were probably mossy cells or immature GCs.

♦ Neurobiology of Disease

Restoring SMN1 in Motor Neurons Has Small Effect on Lifespan

Rocky G. Gogliotti, Katharina A. Quinlan, Courtenay B. Barlow, Christopher R. Heier, C.J. Heckman, et al.

(see pages 3818–3829)

Several diseases that primarily affect a single class of neurons are caused by mutations in ubiquitously expressed genes that regulate basic cellular processes. For example, spinal muscular atrophy (SMA), which causes motor neuron degeneration, paralysis, and death, is caused by mutations that reduce expression of "survival of motor neurons" (SMN1), a protein involved in removing introns from pre-mRNA in all cells. Although SMA is characterized primarily by motor neuron loss, whether other cells contribute to this loss is unclear. To resolve this issue, Gogliotti et al. restored normal levels of SMN1 expression in motor neurons of otherwise SMN1-deficient mice. This greatly improved motor performance, restored muscle innervation to normal levels, and prevented loss of excitatory inputs to motor neurons. Nonetheless, lifespan was extended by only 5 days, indicating that SMN deficiency outside motor neurons contributes substantially to lethality in SMA. Notably, autonomic innervation of the heart remained abnormal after SMN1 expression was rescued in motor neurons.