This Week in The Journal

● Cellular/Molecular

Lysosomal Proteolysis and Autophagy Do Not Require Presenilins

Xulun Zhang, Krassimira Garbett, Karthikeyan Veeraraghavalu, Brian Wilburn, Reid Gilmore, et al.

(see pages 8633–8648)

Mutations in genes for presenilins (PS1 and PS2) lead to early-onset familial Alzheimer's disease (FAD). It was recently shown that PS1 is required for macroautophagy in mouse blastocysts, and lysosomal proteolysis was proposed as a potential therapeutic target in FAD. Zhang et al. have meticulously tested that hypothesis and found it flawed. The previous work asserted that in cells lacking PS1 (PS1ko-ES), the proton-translocating V0a1 subunit of the vacuolar (H+)-ATPase failed to mature and transport to the lysosome; that lysosomes failed to acidify; and that macroautophagy was impaired compared to normal cells. In contrast, Zhang et al. report that vesicular pH and V0a1 maturation and processing were indistinguishable in wild-type and PS1-null cells and brains, and that autophagic processes were robustly intact. Transcriptome analysis, however, showed that gene expression in the Coordinated Lysosomal Expression and Regulation (CLEAR) network was affected by PS1, hinting at a role for PS1 in lysosome biogenesis.

▲ Development/Plasticity/Repair

Transcription Factors Drive Distinct Neural Circuit Proteins

Zhen Guo, Congling Zhao, Menggui Huang, Tianwen Huang, Mingran Fan, et al.

(see pages 8509–8520)

Neurons of the dorsal spinal cord are critical gatekeepers in somatosensory processing, particularly for pain and itch. In addition to receiving both central and peripheral inputs, these neurons are subject to intraspinal modulation by cross talk. Communication within neuronal circuits depends on the expression of transmitters and peptides and their receptors in complementary sets of neurons. Guo et al. have made gains toward understanding these spinal circuits by cataloging the expression patterns of 78 signal and receptor genes by *in situ* hybridization. The transcription factors *Tlx1/3* and *Ptf1a* fall into a class called "selector genes," which promote expression of one set of genes while suppressing another, thereby driving cell fate. Whereas *Tlx1/3* directs excitatory glutamatergic neuron differentiation, *Pft1a* drives the development of GABAergic cells. In addition, the authors now show, these transcription factors direct the expression of a host of modulatory receptor subunits in their respective cell sets by distinct mechanisms.

■ Behavioral/Systems/Cognitive

Scan Reveals Genes of White Matter Integrity and Intelligence

Ming-Chang Chiang, Marina Barysheva, Katie L. McMahon, Greig I. de Zubicaray, Kori Johnson, et al.

(see pages 8732–8745)

The search for genes that affect human intelligence—or even behavior—has been stymied by the sheer magnitude of the task. Chiang et al. have developed a novel approach using diffusion tensor imaging (DTI) and genome-wide scanning in 472 twins and their non-twin siblings. By taking this global approach, they identified genes that clustered into coexpression networks to influence brain connectivity. DTI provides a measure of fractional anisotropy (FA), an estimate of white matter integrity. Through their genome scanning, the authors identified pairs of single nucleotide polymorphisms (SNPs)—and ultimately a SNP network—that influenced FA throughout the brain. Genes at the "hubs" of this network critically influenced brain function in very basic ways, like mediating neuronal development and excitability. Perhaps most intriguing, these same genes also influenced human intelligence quotient. The network approach allowed identification of these genes that individually have only very small effects on intelligence.

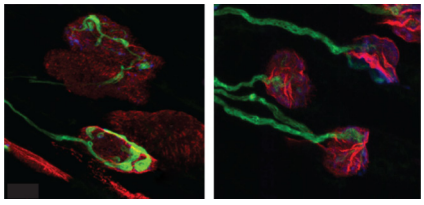
♦ Neurobiology of Disease

Smn *Has Important Roles in Both Muscle and Motor Neurons*

Tara L. Martinez, Lingling Kong, Xueyong Wang, Melissa A. Osborne, Melissa E. Crowder, et al.

(see pages 8703–8715)

Spinal muscular atrophy (SMA) is characterized by profound muscle weakness, culminating in death. It arises from a homozygous mutation in the gene "survival motor neuron" (*Smn*), which, despite its name, encodes a ubiquitously expressed RNA-processing protein. A mouse model of SMA expresses very low levels of full-length SMN. To address the various roles of SMN, Martinez et al. used mice in which a Cre-inducible *Smn* allele was expressed under the control of promoters specific to either motor neurons or muscle cells. Synaptic integrity and function at both peripheral and central synapses hinged on SMN expression in motor neurons alone, but the protein appeared to have distinct roles at either end of the cell. Interestingly, SMN expression in muscle increased fiber size and survival independent of synaptic function at the neuromuscular junction. The report makes strides toward identifying therapeutic targets in motor neurons, but it also indicates that muscle targets should not be excluded.



In mice lacking *Smn* (left), neurofilament (green) accumulates in presynaptic terminals (blue) at neuromuscular junctions (red), which are partially denervated. Restoring *Smn* expression exclusively in motor neurons (right) rescues this phenotype. See the article by Martinez et al. for details.