This Week in The Journal

● Cellular/Molecular

Dystrobrevin Clusters BK Channels

Bojun Chen, Ping Liu, Haiying Zhan, and Zhao-Wen Wang

(see pages 17338–17347)

The dystrophin-associated protein complex (DAPC), which forms at neuromuscular junctions and CNS synapses, stabilizes membranes, acts as a scaffold for signaling molecules, clusters neurotransmitter receptors, and contributes to calcium homeostasis. Mutations in DAPC proteins cause muscle degeneration—often accompanied by mental retardation—in muscular dystrophies. Chen et al. have identified a novel role for one component of the DAPC, dystrobrevin: clustering of the calcium- and voltage-activated potassium channel BK near calcium channels in synaptic terminals and muscles. In *Caenorhabditis elegans*, dystrobrevin colocalized with the BK channel SLO-1 in muscle and motor neuron terminals, and null mutations in dystrobrevin prevented normal clustering of SLO-1. BK channels help repolarize membranes, limiting calcium influx, and null mutations in either SLO-1 or dystrobrevin appeared to impair this function, thus increasing neurotransmitter release and the frequency of muscle calcium transients. Expression of mouse dystrobrevin rescued SLO-1 clustering in neurons, suggesting that dystrobrevin plays a similar role in mammalian neurons.

▲ Development/Plasticity/Repair

Loss of Endolysosome Traffic Regulator Impairs Myelination

Jesse J. Winters, Cole J. Ferguson, Guy M. Lenk, Vessela I. Giger-Mateeva, Peter Shrager, et al.

(see pages 17736–17751)

Lysomes are sites of macromolecule degradation in cells, degrading both endocytosed molecules and components of intracellular organelles. Disruption of this system underlies several neurodegenerative diseases including subtypes of Niemann-Pick and Charcot-Marie-Tooth (CMT) disease. Macromolecules reach lysosomes via vesicles from endosomal compartments, and trafficking through this pathway is regulated in part by phosphatase Fig4, which controls levels of a lysoendosome-specific phosphoinositide. Mutation of human FIG4 causes CMT4J, characterized by distal muscle weakness and sensory loss without apparent CNS impairment. In contrast, loss of Fig4 causes severe tremor and central neurodegeneration in mice. Winters et al. found that myelination was reduced throughout the CNS of Fig4-null mice. This resulted not from oligodendrocyte death or loss of oligodendrocyte precursors, but from failure of oligodendrocytes to mature. Remarkably, hypomyelination and tremor in Fig4-null mice were rescued by neuron-specific expression of wild-type Fig4, indicating that disrupting neuronal endolysosome trafficking disrupts the axon–oligodendrocyte communication that directs myelination.

■ Behavioral/Systems/Cognitive

Prefrontal Cortex Connections Are Reduced in Psychopaths

Julian C. Motzkin, Joseph P. Newman, Kent A. Kiehl, and Michael Koenigs

(see pages 17348–17357)

Psychopathy is a neurodevelopmental disorder characterized by a combination of emotional components (e.g., superficial charm, manipulativeness, callousness, and lack of remorse) and antisocial components (e.g., impulsivity, irresponsibility, and aggression). Structural abnormalities in multiple cortical and limbic regions have been proposed to underlie psychopathy, but the ventromedial prefrontal cortex (vmPFC) appears to be especially important. Damage to this area often causes previously normal people to develop psychopathic traits, as famously demonstrated by the case of Phineas Gage. To further elucidate brain abnormalities in psychopaths, Motzkin et al. performed diffusion tensor imaging and functional magnetic resonance imaging on psychopathic and nonpsychopathic criminals. Psychopathy was associated with decreased integrity of the white matter tract connecting vmPFC to the temporal lobe, and with lower levels of correlated activity (thought to reflect functional connectivity) between vmPFC and the amygdala and precuneus/posterior cingulate cortex. These connections have been linked to emotional regulation and self-reflection, respectively.

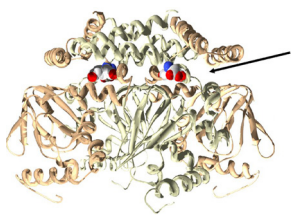
♦ Neurobiology of Disease

Human HCN2 Mutation Is Linked to Epilepsy

Jacopo C. DiFrancesco, Andrea Barbuti, Raffaella Milanesi, Stefania Coco, Annalisa Bucchi, et al.

(see pages 17327–17337)

Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels underlie I_h, a mixed cation current carried by Na^+ and K^+. HCN channels are expressed in many neurons, where they regulate rhythmic firing, dendritic integration, and excitability. Because HCN channels open—leading to current influx—as cells become hyperpolarized and close upon depolarization, they help stabilize resting membrane potentials. Furthermore, because they are partially open at resting membrane potentials—thus reducing membrane resistance—they dampen the effects of other currents, reducing neuronal excitability. Although knock-out of HCN channels causes seizures in mice, no *Hcn* mutations have been definitively linked to human epilepsy until now. DiFrancesco et al. identified a homozygous single-nucleotide mutation in the channel-gating region of *Hcn2* in a single epilepsy patient. Expressing normal and mutated *Hcn2* in cultured rat cortical neurons revealed that the mutation shifted the activation threshold to more negative potentials, making the channel largely nonfunctional at physiological voltages and thus increasing neuronal excitability.



A single-nucleotide mutation, resulting in an acidic-to-basic amino acid substitution within the inner part of the HCN2 channel mouth (arrow), was identified in a patient with epilepsy. See the article by DiFrancesco et al. for details.