# This Week in The Journal

## αII Spectrin Provides Myelinated Neurons Life Support

Claire Yu-Mei Huang, Chuansheng Zhang, Daniel R. Zollinger, Christophe Leterrier, and Matthew N. Rasband

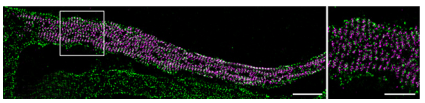
(see pages 11323–11334)

Claire Yu-Mei Huang, Chuansheng Zhang, Tammy Szu-Yu Ho, Juan Oses-Prieto, Alma L. Burlingame, et al.

(see pages 11311–11322)

Neuronal axons travel great distances and encounter tremendous mechanical forces before meeting their targets. Recent evidence points to highly organized structural support molecules called spectrins as key players in withstanding these pressures. This week, Huang et al. show in a pair of papers that αII spectrin is a lynchpin of axonal support in mammalian neurons, and is crucial for organizing the axon initial segment (AIS) and nodes of Ranvier, the spaces between myelin where action potentials are propagated. Because deletion of all αII spectrin is embryonic lethal, the authors generated transgenic mice that were deficient for αII spectrin only throughout the central nervous system (*Nestin-cre;Sptan1$^{f/f}$*). The mice displayed seizures, disrupted cortical architecture, and widespread neurodegeneration, and died by 1 month of age. In wild-type rat hippocampal neurons, αII spectrin was abundant at the AIS. Using stochastic optical reconstruction microscopy (STORM), the authors detected a highly organized cytoskeleton of αII spectrin together with βIV spectrin at the AIS and at peripheral neuron nodes of Ranvier. STORM imaging of neurons from mice lacking αII spectrin showed fewer AIS and disrupted spectrin organization. In addition, the cortex was highly disorganized and cerebellar Purkinje neurons were reduced in number. When the researchers electroporated individual wild-type neurons with a small hairpin RNA directed at αII spectrin, migration was arrested, indicating that αII spectrin is required for normal brain development. Remarkably, β-APP, a marker of axonal degeneration, was found throughout the brain of *Nestin-cre;Sptan1$^{f/f}$* mice, indicative of widespread neurodegeneration.

In a second paper, the authors went on to examine the function of αII spectrin in sensory neurons. Mechanically sensitive DRG neurons are myelinated and contain nodes of Ranvier, whereas pain-sensing neurons are not. *Avil-cre;Sptan1$^{f/f}$* mice that lacked αII spectrin only in peripheral neurons demonstrated behavioral deficits indicative of impaired mechanosensation, whereas pain sensation was intact. Staining the axons showed that large, myelinated sensory neurons degenerated as soon as 1 week after birth, and these neurons were preferentially positive for ATF3+, a marker of axonal injury, compared with small unmyelinated neurons, which were intact. The result indicates that, whereas αII spectrin is crucial for survival and function of myelinated neurons, unmyelinated axons can live without it.



αII spectrin (green) forms a periodic cytoskeleton with βIV spectrin (magenta) at the axon initial segment of rat hippocampal neurons in culture. Scale bars: left, 2 μm; right, 1 μm.

## Fragile X Delays Development of Fast-Spiking Interneurons

Toshihiro Nomura, Timothy F. Musial, John J. Marshall, Yiwen Zhu, Christine L. Remmers, et al.

(see pages 11298–11310)

Fragile X syndrome (FXS), a neurodegenerative disorder that causes sensory hypersensitivity and behavioral and cognitive impairment, arises from silencing of *FMR1*, a gene that encodes a negative translational regulatory protein. FXS has been linked to disruption of the cortical critical period, a time in which neurons are highly plastic and actively forming synapses and circuits. Nomura et al. now show delayed maturation of fast-spiking inhibitory interneurons in the sensory cortex in a mouse model of FXS stemming from a deficit in brain-derived neurotrophic factor (BDNF) signaling. The authors crossed mice lacking the *Fmr1* gene with another mouse line that expresses green fluorescent protein (GFP) specifically in large, parvalbumin-positive basket neurons—including the fast-spiking (FS) GABAergic interneurons of the somatosensory cortex. GFP-positive neurons were filled with the fluorescent dye AlexaFluor 568 and examined with two-photon microscopy, which revealed that FS neurons from mice lacking *Fmr1* had shorter, fewer, and less-complex dendrites than wild-type neurons during the critical period beginning at postnatal day (P)5; their functional maturation was delayed as well. Interestingly, these differences normalized by the end of the critical period at P10. Importantly, while firing bursts of action potentials, mature FS neurons do not adapt—a property the authors quantified using the spike adaptation ratio (SAR), a measure that increases as neurons mature. Neurons from both mouse genotypes showed increasing SAR over the critical period, but in *Fmr1* knock-out mice SAR was significantly lower than wild-type throughout this period. BDNF signaling at its receptor TrkB is required for FS interneuron maturation, and previous research has suggested that BDNF signaling is compromised in adult *Fmr1* knock-out mice. Immunostaining indicated that BDNF was reduced in *Fmr1* knock-out mice during the critical period, which was accompanied by upregulation of TrkB. Daily systemic delivery of the TrkB agonist LM22A-4 normalized the developmental delay in the FS neurons' spiking patterns and rescued the reduction in functional synaptic inputs onto FS neurons seen in *Fmr1* knock-out mice. Although the neurons appeared normal following the critical period, the authors suggest that the transient disruption in FS neurons key to cortical organization could have long-lasting effects that contribute to the disease phenotype.

*This Week in The Journal was written by Stephani Sutherland, Ph.D.*