# This Week in The Journal

## Cellular/Molecular

### *Learning-Induced Increase in Persistent Firing Requires Arc*

Ming Ren, Vania Cao, Yizhou Ye, Husseini K. Manji, and Kuan Hong Wang

(see pages 6583–6595)

Persistent firing occurs in many neurons, and it is thought to underlie diverse functions, from maintaining gaze to holding items in working memory. To investigate how experience affects persistent firing of frontal cortical neurons, Ren et al. used the promoter of the activity-regulated cytoskeletal protein (Arc) to drive GFP expression, thus labeling neurons that were activated when mice learned a skill. Learning to walk on a rotating rod increased the number of GFP-expressing neurons, and these neurons were more likely to exhibit persistent firing than neurons that had low GFP levels in the same or in untrained mice. Increases in persistent firing may have stemmed from increased numbers of NMDA-receptor-containing synapses, because the frequency of NMDA-dependent miniature EPSCs and the amplitude of evoked EPSCs were increased in GFP-expressing frontal cortical neurons. Interestingly, Arc knockout prevented motor-learning-induced enhancement of persistent firing and NMDA responses while impairing retention of the new motor behavior, suggesting that learning-induced increases in Arc trigger increases in persistent firing.

## Systems/Circuits

### *Hippocampal Replay Reflects Complex Topologies*

Xiaojing Wu and David J. Foster

(see pages 6459–6469)

As rats move through an environment, different hippocampal place cells become active in sequence. The same firing sequence is replayed during sharp-wave ripples that occur in subsequent sleep; this replay appears to be important for memory consolidation. Replay also occurs while rats are exploring the environment: after a rat receives a reward, the place-cell sequence leading to the reward site is replayed in reverse, and replay of place-cell sequences before movement often foreshadow the path taken. These observations suggest that replay is involved in spatial mapping and navigation. Wu and Foster found further support for this hypothesis when recording multiple neurons as rats explored an unfamiliar Y maze. Replay of ensemble activity began to occur after the rats had explored each arm just two or three times, and the duration of the replay was correlated with the length of the trajectory taken. Furthermore, activity patterns during replay suggested that arms were encoded as discrete units that were joined together to represent two-arm trajectories.

## Behavioral/Cognitive

### *Command-Like Neurons in* Aplysia *Have Complementary Roles*

Jin-Sheng Wu, Nan Wang, Michael J. Siniscalchi, Matthew H. Perkins, Yu-Tong Zheng, et al.

(see pages 6510–6521)

Early studies of the neural bases of behavior aimed to identify command neurons that are necessary and sufficient to drive specific behaviors. By this narrow definition, however, few command neurons exist. Instead, most command-like neurons are multifunctional—able to activate different programs under different conditions—or do not reliably initiate behaviors. In *Aplysia*, for example, the command-like cerebral-buccal interneuron CBI-2 can trigger either ingestive or egestive motor patterns, whereas CBI-11, a neuron electrically coupled to CBI-2, initiates only ingestive patterns, but unreliably. Wu et al. show how these neurons work together to produce ingestive patterns. CBI-11 produced small, monosynaptic EPSPs in radula protraction motoneuron B61, but these EPSPs were insufficient to drive spiking in the absence of CP2—a neuropeptide released by CBI-2—which increased B61 excitability. Through synaptic effects on other neurons, CBI-11 also promoted radula closing during retraction, a defining characteristic of ingestive patterns. Thus, CBI-2 may be a general activator of feeding patterns, while CBI-11 influences which pattern is selected.

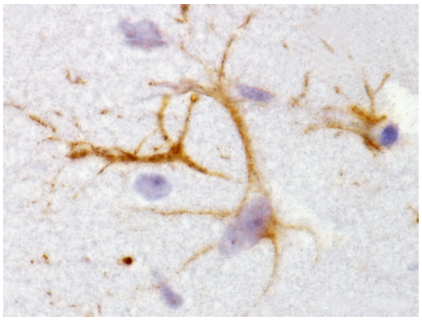
## Neurobiology of Disease

### *TDP-43 Mislocalizes in Astrocytes in Alexander Disease*

Adam K. Walker, Christine M. LaPash Daniels, James E. Goldman, John Q. Trojanowski, Virginia M.-Y. Lee, et al.

(see pages 6448–6458)

TDP-43 is an RNA-binding protein that can potentially bind to ~30% of mRNAs in human brain. Although it normally shuttles between the nucleus and cytoplasm, TDP-43 is predominantly found in the nucleus of healthy cells. In amyotrophic lateral sclerosis and some frontotemporal dementias, however, cytoplasmic levels of TDP-43 increase, and it is a major component of ubiquitinated protein aggregates that characterize these diseases. Similar TDP-43-containing aggregates are also found in neurons in some cases of Alzheimer's, Parkinson's, and other neurodegenerative disease. Walker et al. now report that in Alexander disease (AxD)—which is caused by mutations in glial fibrillary acidic protein (GFAP) and thus primarily affects astrocytes—cytoplasmic mislocalization of TDP-43 occurs in astrocytes. In patient tissue, TDP-43 colocalized with GFAP in the Rosenthal fibers that characterize AxD. TDP-43 also accumulated in cytoplasm in mouse models of AxD. Whether this accumulation underlies predominant manifestations of AxD or is a consequence of primary pathologies remains to be seen, however.



Phosphorylated TDP-43 is found in the cytoplasm of cells at the pial surface of the cortex in a mouse model of Alexander disease. See the article by Walker et al. for details.