This Week in The Journal

Cellular/Molecular

T-Cell Receptor Reduces Cholinergic Currents in Cortex

Pragya Komal, Geoff Gudavicius, Christopher J. Nelson, and Raad Nashmi

(see pages 22–35)

Adaptive immune responses are initiated when receptors on T cells (TCRs) bind to specific ligands on antigen-presenting cells, which triggers downstream signaling via tyrosine kinases. The TCR ß subunit (TCRß) is also expressed in cortical neurons, where—as Komal et al. demonstrate—it influences neuronal excitability by regulating nicotinic acetylcholine receptors containing the $\alpha 7$ subunit ($\alpha 7$nAChRs). In mouse brain slices, the TCR agonist ConA reduced the single-channel conductance of $\alpha 7$nAChRs in layer 1 cortical interneurons and reduced current evoked by an $\alpha 7$nAChR agonist. As a result, neuronal excitability was reduced. Furthermore, $\alpha 7$nAChR currents and excitability were greater in TCRß-null neurons than in wild-type, suggesting endogenous activation of TCRß exerts baseline suppression of $\alpha 7$nAChRs. In clonal T lymphocytes transfected with $\alpha 7$nAChRs, ConA increased tyrosine phosphorylation of $\alpha 7$nAChRs and not only decreased single-channel conductance, but also reduced surface expression of the receptors. These effects did not occur if tyrosine 442 of $\alpha 7$nAChRs was mutated, suggesting phosphorylation of this residue mediated the effects.

Development/Plasticity/Repair

Adipose-Derived Stem Cells Reduce Neuronal Injury

Naoki Tajiri, Sandra A. Acosta, Md Shahaduzzaman, Hiroto Ishikawa, Kazutaka Shinozuka, et al.

(see pages 313–326)

Much effort has been devoted to developing stem cell therapies for brain damage. Besides differentiating into neurons, stem cells can protect neurons by secreting growth factors, anti-inflammatory molecules, and transcription-regulating long noncoding RNAs (lncRNAs). Although transplanting stem cells into the brain can be beneficial, peripheral administration can also improve outcomes after brain injury—even if few cells enter the brain. Tajiri et al. found that peripherally injected human adipose-derived stem cells (hADSCs) or hADSC-conditioned medium (CM) reduced cortical and hippocampal damage and loss of motor and cognitive function in adult rats that had been subjected to traumatic brain injury, although only ~1% of cells survived in the brain. The beneficial effects were reduced by knocking down either of two secreted lncRNAs, which reduced levels of two growth factors in CM. hADSCs did not improve motor function or reduce hippocampal damage in old rats, however. The authors attributed this to the fact that fewer hADSCs reached the spleen in these animals.

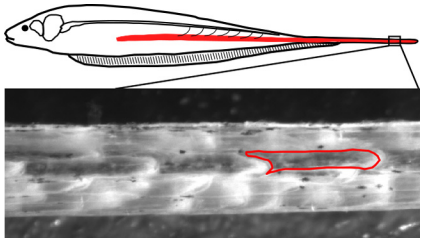
Systems/Circuits

Cost per Spike Increases with Spike Frequency in Electrocytes

John E. Lewis, Kathleen M. Gilmour, Mayron J. Moorhead, Steve F. Perry, and Michael R. Markham

(see pages 197–201)

Action potential propagation involves massive influx of Na^+, which must be pumped out by the Na^+/K^+ ATPase. This consumes large amounts of energy: 10^7 molecules of ATP per spike, depending on how much Na^+ enters the cell. Consequently, action potentials use a significant proportion of an animal's energy budget, and the need to minimize energy consumption is thought to constrain spike amplitude and frequency and to have driven the evolution of more efficient ion channels. Lewis et al. found that action potentials are costlier in the electric fish *Eigenmannia virescens* than estimated in mammals. The total Na^+ current measured during single spikes of electric organ electrocytes suggested that each spike required $\sim 2 \times 10^{10}$ ATP molecules. Because electric organ discharges require synchronous, high-frequency spiking, changes in discharge frequency produced measurable changes in oxygen consumption by the fish. These measures showed that metabolic cost per spike increased with spike frequency, probably in part because greater Na^+ influx is required to maintain spike amplitude at higher frequencies.



Top: Schematic representation of the electric organ (red) in the electric fish *Eigenmannia virescens*. Bottom: A 5-mm-long section of electric organ, with a single electric organ cell (electrocyte) outlined in red. Each electric organ contains 1000–2000 electrocytes that fire synchronous, high-frequency action potentials to generate electric pulses that the fish uses for electrolocation and communication. The metabolic cost of each action potential is high and increases with spike frequency. See the article by Lewis et al. for details.

Neurobiology of Disease

α-Synuclein Normally Resides Near, But Not in, Mitochondria

Cristina Guardia-Laguarta, Estela Area-Gomez, Cornelia Rüb, Yuhui Liu, Jordi Magrané, et al.

(see pages 249–259)

In Parkinson's disease (PD) and several other neurodegenerative diseases, the protein α-synuclein forms insoluble aggregates that accumulate in neurons. In healthy neurons, α-synuclein is localized in synaptic terminals, where it associates with synaptic vesicles. α-synuclein also appears to associate with mitochondria, but as Guardia-Laguarta et al. show, α-synuclein is not normally present in mitochondria themselves. Instead, it is present in a specialized region of endoplasmic reticulum (ER) that is tethered to a portion of the outer mitochondrial membrane—the mitochondria-associated ER membrane (MAM). MAM has roles in phospholipid and cholesterol synthesis, apoptosis, and regulating mitochondrial Ca^{2+} levels, which in turn regulate mitochondrial ATP production. Importantly, PD-causing mutations in α-synuclein reduced appositions between ER and mitochondria and caused the protein to shift from MAM-containing to pure mitochondrial cell fractions. Furthermore, MAM-dependent phospholipid synthesis was reduced and mitochondrial fragmentation was elevated in cells expressing mutant α-synuclein. Interestingly, overexpressing wild-type α-synuclein also caused mitochondrial fragmentation, but expressing wild-type α-synuclein together with the mutated form reduced fragmentation.