This Week in The Journal

● Cellular/Molecular

Transcriptional Regulation of Acetylcholinesterase

Shelley Camp, Antonella De Jaco, Limin Zhang, Michael Marquez, Brian De La Torre, and Palmer Taylor

(see pages 2459–2470)

Acetylcholinesterase (AChE) expression increases dramatically as myoblasts and neuroblasts differentiate respectively into myotubes and neurons, but the molecular regulators responsible for this switch have not been identified. By expressing the entire *AChE* gene (with successive deletions) in a myoblast cell line, Camp et al. have now identified a region necessary for upregulation of AChE in muscle cells. Remarkably, the regulatory region is not necessary for expression of AChE in neurons. Upregulation of AChE in muscles required the endogenous promoter as well as this regulatory region—which includes consensus binding sites for the muscle regulatory factors MyoD and MEF2—suggesting that the region constitutes an enhancesome. When the regulatory region was removed by homologous recombination in transgenic mice, AChE expression was normal in neurons but almost completely absent from muscles and neuromuscular junctions. This provides the first strong evidence that AChE at neuromuscular junctions is produced in the muscle rather than motor neurons.

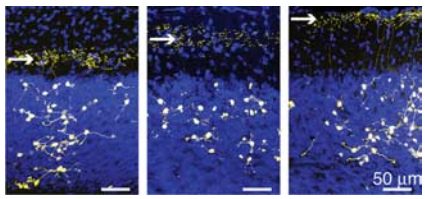
▲ Development/Plasticity/Repair

Mosaic Analysis of Cerebellar Development

J. Sebastian Espinosa and Liqun Luo

(see pages 2301–2312)

Mosaic analysis with double markers is a recently developed technique that can be used to label the progeny of single precursor cells. Espinosa and Luo used this technique to examine the proliferation and differentiation of cerebellar granule cells. Initial work revealed that all the daughters of a single granule cell precursor extend axons in a single sublayer of the molecular layer. The authors now show that although proliferation of precursors generally slows during development, individual precursors and their progeny begin dividing rapidly (and symmetrically) just before differentiation. These neurons form a clonally related group that exits the cell cycle together. As these cells differentiate, their axons extend along the surface of the developing molecular layer, creating a cluster of axons in one sublayer. This is significant because axons in different sublayers synapse onto different interneurons and different regions of Purkinje cells, and therefore clonally related cells may also be functionally related.



Clonally related cells (yellow) extend axons in single sublayers of the molecular layer (arrows).

■ Behavioral/Systems/Cognitive

Cannabinoid Effects on Threat Perception

K. Luan Phan, Mike Angstadt, Jamie Golden, Ikechukwu Onyewuenyi, Ana Popovska, and Harriet de Wit

(see pages 2313–2319)

Cannabinoid receptors are expressed at high levels in the amygdala, where they are thought to play a role in reducing anxiety and extinguishing fear. Although many experimenters report anxiolytic effects of Δ^9-tetrahydrocannabinol (THC), the neural basis for these subjective effects has not been demonstrated in humans. To begin to address this question, Phan et al. used functional magnetic resonance imaging to examine activity in the amygdala when subjects viewed threatening (angry or fearful) or nonthreatening (happy) faces—a probe of reactivity to social threat. As expected, control subjects had more activity in the amygdala when viewing threatening faces than when viewing nonthreatening faces. The difference between threatening and nonthreatening faces was smaller in subjects who had taken THC. This effect depended mostly on decreased responses to threatening faces, but a small increase in responses to nonthreatening faces was also detected.

◆ Neurobiology of Disease

Conditional Model of Parkinson's Disease

Silke Nuber, Elisabeth Petrasch-Parwez, Beate Winner, Jürgen Winkler, Stephan von Hörsten, Thorsten Schmidt, Jana Boy, Melanie Kuhn, Huu P. Nguyen, Peter Teismann, Jörg B. Schulz, Manuela Neumann, Bernd J. Pichler, Gerald Reischl, Carsten Holzmann, Ina Schmitt, Antje Bornemann, Wilfried Kuhn, Frank Zimmermann, Antonio Servadio, and Olaf Riess

(see pages 2471–2480)

The pathological mediators of neurodegeneration in Parkinson's disease (PD) are unknown. One hypothesis postulates that neurodegeneration results from proteolytic stress due to accumulation and aggregation of misfolded or overexpressed proteins. In support of this, mutations and duplications of the *α-synuclein* gene are found in some PD families, and aggregates of α-synuclein in cytoplasmic inclusions (Lewy bodies) are a hallmark of PD. This week, Nuber et al. report the development of transgenic mice that conditionally overexpress α-synuclein. The mice showed progressive loss of motor and cognitive function and some degeneration of hippocampal neurons and of dopaminergic neurons in the substantia nigra. Although cell death occurred in the substantia nigra, levels were below statistical significance, and most was not apoptotic as is seen in PD. α-Synuclein aggregated but did not form Lewy bodies. Interestingly, turning off α-synuclein overexpression slowed the progression of motor dysfunction but did not alter cellular pathology.