This Week in The Journal

● Cellular/Molecular

Silencing Cell-Cycle Reentry in Postmitotic Neurons

Angeles Almeida, Juan P. Bolaños, and Sergio Moreno
(see pages 8115–8121)

Once neurons differentiate, cell-cycle proteins are downregulated, seemingly locking the cell in G_0 phase. This suggests very tight control of expression of these proteins. However, increasing evidence suggests that cell-cycle proteins can be reactivated and contribute to cell demise. For example, the Cdk1–cyclin B1 complex can be reactivated in Alzheimer's disease. The E3-ubiquitin ligase anaphase-promoting complex (APC) marks mitotic cyclins such as B1 for degradation, and APC is activated by Cdh1 at the end of mitosis. Because Cdh1–APC remains active in postmitotic cells, Almeida et al. tested whether Cdh1 can keep cyclin B1 in check, thus preventing cell-cycle reentry. The answer seems to be yes. The authors silenced Cdh1 using a targeted small hairpin RNA (shRNA). Cdh1 silencing in differentiated neuroblastoma cells or postmitotic cortical neurons promoted cell-cycle reentry and produced apoptosis, whereas a cyclin B1-targeted shRNA increased the survival of these cells. In primary cortical neurons, Cdh1 overexpression also prevented β-amyloid-induced apoptosis.

▲ Development/Plasticity/Repair

REN and Cerebellar Granule Cell Proliferation

Beatrice Argenti, Rita Gallo, Lucia Di Marcotullio, Elisabetta Ferretti, Maddalena Napolitano, Sonia Canterini, Enrico De Smaele, Azzura Greco, Maria Teresa Fiorenza, Marella Maroder, Isabella Screpanti, Edoardo Alesse, and Alberto Gulino
(see pages 8338–8346)

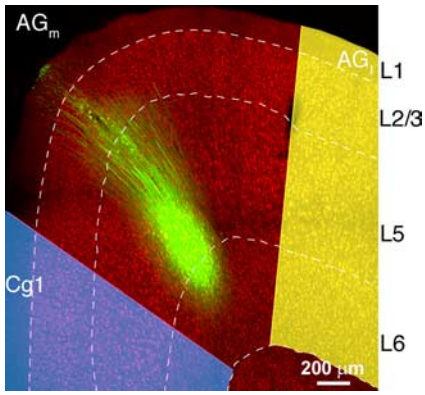
Cerebellar granule cells take a well studied path from their origin in the external granule layer (EGL) through the molecular layer and on to their final home in the internal granule layer (IGL). The mitogenic action of Sonic Hedgehog (Shh) drives granule cell proliferation in the EGL, before they exit the cell cycle and differentiate in the inner EGL. Unchecked activity of the Hedgehog pathway results in the childhood tumor medulloblastoma. REN, a tumor suppressor that is often deleted in human medulloblastoma, is thought to antagonize Shh signaling. Thus Argenti et al. examined whether REN may control granule cell development. REN was expressed in the correct location for such a function: the inner EGL and IGL of developing mouse cerebellum. Overexpression of REN reduced proliferation of granule cell precursors, as did expression of the proliferation-regulating molecule p27/Kip1, and differentiation was enhanced. Loss of REN function, in contrast, enhanced proliferation and Shh signaling.

■ Behavioral/Systems/Cognitive

Monosynaptic Whisker Control in the Rat

Valery Grinevich, Michael Brecht, and Pavel Osten
(see pages 8250–8258)

Primates have fine motor control of their digits and orofacial muscles because of direct connections between the primary motor cortex and spinal motor neurons. Whiskers, the primary somatosensory tool in rodents, move independently during object exploration. This does not seem to be consistent with existing anatomical evidence for purely polysynaptic innervation of motor neurons by vibrissa motor cortex (VMC) neurons. This week, Grinevich et al. reexamined the possibility of direct innervation. After identifying the VMC by electrical microstimulation, the authors labeled pyramidal neurons using injections of lentivirus expressing green fluorescent protein (GFP). Four weeks later, axons of GFP-labeled VMC neurons could be seen in the lateral facial nucleus (FN), the origin of motor neurons that innervate the whiskers. Injection of retrograde tracers into whisker follicles revealed motor neurons within 250 μm of the VMC terminals, a distance well within the dendritic tree of motor neurons. Electron microscopy confirmed a monosynaptic VMC-to-FN pathway, well positioned to precisely control whisker movements.



Confocal image of the lentiviral injection area showing GFP-expressing pyramidal neurons in layer 5 of the agranular medial area (AG_m). Neuronal somata were stained with anti-neuron-specific nuclear protein (red). The neighboring cingulate area 1 (Cg1) and agranular lateral field (AG_l) regions are color-coded. See the article by Grinevich et al. for details.

♦ Neurobiology of Disease

Antidepressant Responsiveness and 5-HT Synthesis

Luigi Cervo, Alessandro Canetta, Eleonora Calcagno, Silvia Burbassi, Giuseppina Sacchetti, Silvio Caccia, Claudia Fracasso, Diego Albani, Gianluigi Forloni, and Roberto W. Invernizzi
(see pages 8165–8172)

Although selective serotonin (5-HT) reuptake inhibitors (SSRIs) benefit many patients, some patients are nonresponders. This week, Cervo et al. explored a possible genetic cause for SSRI responsiveness. The gene for the brain-specific isoform of tryptophan hydroxylase-2 (*TPH-2*), the rate-limiting enzyme in serotonin synthesis, contains a single nucleotide polymorphism (SNP) that is reportedly associated with a poor response to SSRIs in some depressed patients. This *TPH-2* SNP (G1463A) affects serotonin synthesis, as does a nearby SNP in the mouse *TPH-2* gene. DBA/2J and BALB/c mice homozygous for the 1473G allele produce less 5-HT than C57BL/6J and 129/Sv mice homozygous for the 1473C allele. The authors tested the mice in the forced swim test that has been used to screen compounds for antidepressant effects. The SSRI citalopram reduced immobility time in the C57BL/6J and 129/Sv mice but had no effect in the DBA/2J or BALB/c mice, suggesting that genetic differences in serotonin synthesis could contribute to the efficacy of SSRIs.