This Week in The Journal

● Cellular/Molecular

Setting the Clock on OPC Differentiation

Jason C. Dugas, Adiljan Ibrahim, and Ben A. Barres

(see pages 6185–6196)

Oligodendrocyte precursor cells (OPCs) divide a set number of times, about eight, before daughter cells finally heed external cues and differentiate into oligodendrocytes. This week, Dugas et al. tracked down the molecule that makes up this mitogen-dependent intracellular timer. The cyclin-dependent kinase inhibitor $p57^{Kip2}$ was transiently upregulated right after oligodendrocytes differentiated. In a population of cells derived from a single proliferating OPC, $p57^{Kip2}$ expression rose uniformly in successive generations. Overexpression of $p57^{Kip2}$ slowed the proliferation rate of OPCs *in vitro* to various degrees, depending on the availability of mitogen and of external differentiation cues. Buildup of $p57^{Kip2}$ also triggered expression of early gene markers of myelination. When the authors knocked down expression of $p57^{Kip2}$ using RNA silencing, OPC proliferation increased markedly, and differentiation ceased. Thus, $p57^{Kip2}$ fulfills the criteria for the primary component of this cellular clock, informing the cells when to abandon the cell cycle and become full-fledged oligodendrocytes.

▲ Development/Plasticity/Repair

B-Type Plexins in Neural Development

Suhua Deng, Alexandra Hirschberg, Thomas Worzfeld, Junia Y. Penachioni, Alexander Korostylev, Jakub M. Swiercz, Peter Vodrazka, Olivier Mauti, Esther T. Stoeckli, Luca Tamagnone, Stefan Offermanns, and Rohini Kuner

(see pages 6333–6347)

Signaling between plexin receptor molecules and their semaphorin ligands guides many developmental processes. This week, Deng et al. looked beyond the well mapped Plexin-A molecules to track the influence of neuronal Plexin-B proteins. Granule cell precursors (GCPs) of the cerebellum, the dentate gyrus, and the olfactory bulb strongly expressed Plexin-B2 mRNA within their migratory streams, but not once the cells reached their targets. Mice lacking Plexin-B1 ($Plxnb1^{-/-}$) developed normally, whereas mice deficient in Plexin-B2 ($Plxnb2^{-/-}$) displayed severe brain abnormalities, including failure of neural tubes to close (exencephaly). These defects arose from retarded GPC proliferation and migration. Hypertrophied ventricular zones of all $Plxnb2^{-/-}$ mice, even the small proportion without exencephaly, indicated reduced neuroblast proliferation. Although there was some overlap in the distribution of semaphorin 4D (Sema4D) with Plexin-B2 *in vivo*, the high-affinity interaction with Sema4C suggested that it is the more likely effector for the neurodevelopmental effects of Plexin-B2.

■ Behavioral/Systems/Cognitive

A Wake-Up Call in Temporal Auditory Coding

Maria Ter-Mikaelian, Dan H. Sanes, and Malcolm N. Semple

(see pages 6091–6102)

Within the temporal features of their firing, neurons of the inferior colliculus (IC) and primary auditory cortex (AI) encode timing and location features of auditory stimuli. The latency to fire after a stimulus is thought to be particularly important, based on studies in anesthetized animals in which the precise spike timing is preserved or even improved between the IC and AI. But Ter-Mikaelian et al. report rather different results in awake compared with anesthetized gerbils. The authors made single-unit recordings from IC and AI neurons responding to auditory tones. In awake animals, first-spike timing variability increased in AI compared with IC neurons, indicating a reduction in temporal precision of firing. AI temporal precision improved during anesthesia, but many trials evoked no firing whatsoever. IC firing was not significantly influenced by anesthesia. The authors propose that AI responses in the awake animal, although apparently less precise, more accurately represent auditory stimuli.

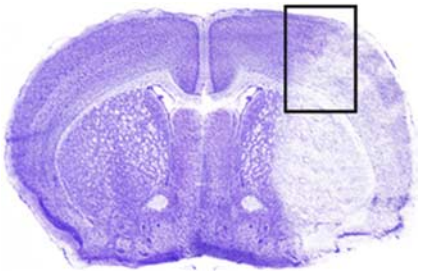
♦ Neurobiology of Disease

HIF-1 and Cerebral Ischemia

Oxana Baranova, Luis F. Miranda, Paola Pichiule, Ioannis Dragatsis, Randall S. Johnson, and Juan C. Chavez

(see pages 6320–6332)

For several days after a stroke, damage continues to evolve in the penumbra surrounding the ischemic core. The extent of the damage depends on many factors, including the balance of expression of destructive and protective molecules. This week, Baranova et al. examined the influence of hypoxia inducible factor (HIF-1), a transcription factor perfectly suited to regulate gene expression after ischemia. Under normoxic conditions, the HIF-1α subunit is hydroxylated, marking it for rapid degradation. But hypoxia prevents hydroxylation, allowing the α subunit to accumulate and form active dimers with HIF-1β. Mutant mice with conditional deletion of HIF-1α in forebrain neurons fared worse than wild-type (WT) mice after focal cerebral ischemia. WT mice that received pharmacological activators of HIF-1 showed further improvements. HIF-1α in neurons is not the whole story of neuroprotection, however, as hypoxic preconditioning was still neuroprotective in HIF-1α-deficient mice.



The image shows a coronal section of mouse brain 6 h after transient middle cerebral artery occlusion. The section is stained with cresyl violet, with the lighter region on the right indicating the area of ischemia. See the article by Baranova et al. for details.