This Week in The Journal

● Cellular/Molecular

Notch1 Signaling and Radial Glia

Brooke A. Patten, S. Pablo Sardi, Samir Koirala, Masato Nakafuku, and Gabriel Corfas

(see pages 3102–3108)

Migrating neurons move along tracks laid by radial glia. In the cerebellum, radial (Bergmann) glia arise from cerebellar astroglia, a process triggered by glial–neuronal contact. This glial differentiation involves activation of Notch1 and binding of its intracellular domain to Suppressor of Hairless [Su(H)] and Deltex1 (DTX1). These canonical and noncanonical pathways lead to expression of brain lipid binding protein (BLBP) and the receptor tyrosine kinase erbB2, respectively. BLBP affects cell–cell adhesion, whereas glial erbB2 interacts with neuregulin I expressed by migrating granule cells. This week, Patten et al. report that overexpression of DTX1 or a dominant-negative form disrupted Su(H)-mediated signaling, but expression of Su(H) had no effect on DTX1-induced events. In contrast, RNAi-mediated knock-down of DTX1 selectively blocked the effects of DTX1, leaving Su(H) signaling intact. The authors propose a hierarchical relationship between the two pathways, in which radial glia differentiation depends on the relative expression of the two molecules.

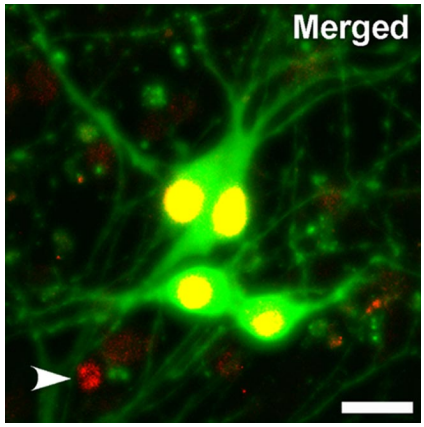
▲ Development/Plasticity/Repair

Motoneuron Differentiation from ES Cells

Prabakaran Soundararajan, Gareth B. Miles, Lee L. Rubin, Robert M. Brownstone, and Victor F. Rafuse

(see pages 3256–3268)

This week, Soundararajan et al. provide additional evidence that embryonic stem (ES) cells can be directed to generate defined classes of motoneurons, an important general issue for successful cell transplantation. The authors treated ES cells with sonic hedgehog (Shh) ligand and retinoic acid (RA) for 5 d in culture and tracked the cells with enhanced green fluorescent protein (eGFP) under control of the Hb9 promoter. Most of the Hb9-expressing motoneurons also expressed Lhx3 *in vitro*, a homeobox gene that distinguishes motoneurons in the medial aspect of the medial motor column (MMC_m). Indicative of their class specificity, cells transplanted into the neural tube lumen of chick embryos were later found in the MMC_m and either selectively projected axons with the dorsal ramus to epaxial muscle targets or, interestingly, misprojected axons to skin targets. Whole-cell recordings showed that cells transplanted *in ovo* had electrical and synaptic properties comparable with endogenous MMC_m cells.



The vast majority of $eGFP^+$ ES cells, as well as a few $eGFP^-$ cells (arrowhead), expressed the transcription factor Lhx3 after treatment with retinoic acid and sonic hedgehog ligand. See the article by Soundararajan et al. for details.

■ Behavioral/Systems/Cognitive

Releasing Dopamine with Cocaine

B. Jill Venton, Andrew T. Seipel, Paul E. M. Phillips, William C. Wetsel, Daniel Gitler, Paul Greengard, George J. Augustine, and R. Mark Wightman

(see pages 3206–3209)

Cocaine works by competitively inhibiting the dopamine transporter, thus slowing uptake of dopamine (DA) and increasing extracellular DA. But this week, Venton et al. provide evidence for a second, long-postulated mode of action for this psychostimulant: release of a reserve pool of DA vesicles. The authors delivered long electrical stimuli to the mouse medial forebrain bundle and measured DA by cyclic voltammetry in the striatum. Cocaine increased DA release by approximately one-half. However, when the readily releasable DA pool was depleted, cocaine still increased DA release, suggesting that cocaine also affects the reserve pool of vesicles. Because synapsins bind to vesicles and segregate them into reserve pools, the authors tested cocaine in a knock-out mouse deficient in all three synapsins. In these mice, cocaine elicited a much smaller increase in DA release. How cocaine triggers this DA release from vesicles sequestered by synapsin remains a question.

♦ Neurobiology of Disease

Oligodendrocyte Cell Therapy in MLD Mice

Maria I. Givogri, Francesca Galbiati, Stefania Fasano, Stefano Amadio, Laura Perani, Daniela Superchi, Pablo Morana, Ubaldo Del Carro, Sergio Marchesini, Riccardo Brambilla, Lawrence Wrabetz, and Ernesto Bongarzone

(see pages 3109–3119)

Metachromatic leukodystrophy (MLD) results from deficiency of the lysosomal enzyme arylsulfatase A (ARSA). The clinical course includes progressive neurodegeneration caused by accumulation of sulfatides, oligodendrocyte dysfunction, and myelin loss. Hematogenous stem cell transplantation in patients and gene therapy in $ARSA^{-/-}$ mice have been tried, but this week, Givogri et al. test a more universal approach. They transplanted migratory oligodendrocyte progenitor cells (OLPs) into young $ARSA^{-/-}$ mice. In culture, OLPs differentiated into mature cells with elaborate processes and expressed oligodendrocyte (OL) markers. The authors grafted ARSA-expressing OLP cells into newborn MLD and wild-type pups. In MLD brains, the cells spread throughout the brain within a few days, survived and proliferated, whereas wild-type or older MLD mice were less receptive to the cells. *In vivo*, the grafted cells differentiated into OLs and became myelinating. Most importantly, transplantation reduced sulfatide deposits by 20–50% and normalized several measures of nerve function and behavior.