This Week in The Journal

● Cellular/Molecular

ERK, mTOR, and LTP

Panayiotis Tsokas, Tao Ma, Ravi Iyengar, Emmanuel M. Landau, and Robert D. Blitzer

(see pages 5885–5894)

The stable, late form of long-term potentiation (L-LTP) requires *de novo* protein synthesis. In this week's *Journal*, Tsokas et al. dissected the signaling pathways that coordinate translation at the CA3–CA1 synapse. Like LTP itself, translation required the coincident activation of two pathways. The kinase mammalian target of rapamycin (mTOR) enables translation of terminal oligopyrimidine messenger RNAs, which in turn encode translational machinery proteins such as elongation factor 1A. Expression of these proteins increased in an mTOR-dependent manner minutes after the authors induced L-LTP with high-frequency stimulation (HFS). Inhibitors of the extracellularly regulated kinase (ERK) pathway reduced expression. Conversely, inhibitors of phosphatidylinositide 3-kinase (PI3K), an upstream component of the mTOR pathway, reduced HFS-induced phosphorylation of ERK, suggesting a reciprocal regulation of the ERK and PI3K–mTOR pathways in LTP. The interaction between the two pathways converged at PDK-1 (phosphoinositide-dependent kinase 1).

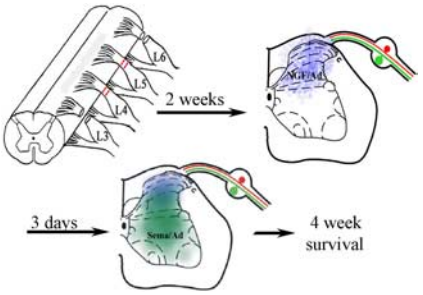
▲ Development/Plasticity/Repair

Targeting Regeneration

Xiao-Qing Tang, Paula Heron, Charles Mashburn, and George M. Smith

(see pages 6068 – 6078)

Getting injured axons to regenerate is only half the battle it seems, as they also have to get to the right target. In the case of sensory axons in the spinal cord, this means getting to, and staying within, the right laminae. Nociceptors that express calcitonin gene-related peptide (CGRP) and Substance P (SP) are normally restricted to laminae I and II. To target axons after a dorsal rhizotomy, Tang et al. used adenovirus to overexpress NGF in the dorsal spinal cord of rats. Three days later, they used more ventral injections to express the repellant guidance molecule semaphorin 3A (Sema3A). NGF-guided axons made it over the barrier of the dorsal root entry zone, but they grew throughout the six dorsal laminae. However, the combination of NGF and Sema3A restricted SP-positive fibers to laminae I and II, similar to the normal pattern. Both groups recovered nociceptive function.



After a crush injury of the right L4/L5 dorsal roots, adenovirus-mediated expression of NGF and Sema3A were used to target regeneration of CGRP(+) sensory axons to specific lamina. See the article by Tang et al. for details.

■ Behavioral/Systems/Cognitive

Mapping the Unpredictable in Mice and Humans

Cyril Herry, Dominik R. Bach, Fabrizio Esposito, Francesco Di Salle, Walter J. Perrig, Klaus Scheffler, Andreas Lüthi, and Erich Seifritz

(see pages 5958 –5966)

The element of surprise is crucial to a good horror movie. Now Herry et al. show that unpredictability increases activity in the amygdala, the brain's fright center, regardless of the stimulus. Mice presented with unpredictably timed neutral sound pulses showed greater c-Fos expression in the basolateral amygdala (BLA) compared with those that received predictable stimuli. In unit recordings, BLA neurons also increased their firing to unpredictable stimuli, whereas cell firing habituated to predictable stimuli. Unpredictable stimuli also provoked anxiety-like behavior in the mice. Humans were not so dissimilar. Subjects' functional magnetic resonance imaging displayed larger blood oxygen level-dependent amygdalar responses to unpredictably timed sound pulses compared with predictable ones. When these subjects were presented with threatening stimuli, in the form of images of angry faces, they rated unpredictable sounds as more unpleasant than predictable sounds. Thus, surprise and fear share some common elements and pathways in mouse and humans.

♦ Neurobiology of Disease

The Limits of Neuronal Grafts in Parkinsonian Rats

Nathalie Breysse, Thomas Carlsson, Christian Winkler, Anders Björklund, and Deniz Kirik

(see pages 5849 –5856)

Transplantation of embryonic dopaminergic (DA) neurons has provided at least the makings of a success story as a cell-based therapy for Parkinson's disease (PD). But outcomes have varied widely. In this week's *Journal*, Breysse et al. used 6-hyrdoxydopamine (6-OHDA)-lesioned rats to assess the limits of the grafting technique. Animals received a unilateral intrastriatal 6-OHDA lesion that targeted dorsal striatum. The authors studied those animals that displayed motor deficits as revealed by amphetamine-induced rotation, cylinder, and stepping tests. Half of the rats received fetal ventral mesencephalon cell transplants, after which motor performance improved markedly. Next, half of the grafted and nongrafted rats had second lesions to DA projections originating outside the substantia nigra pars compacta. The second lesion obliterated improvements gained from grafting. The authors propose that patients who fail to benefit from striatal grafts may have damage to ventral striatum or extrastriatal projections.