This Week in The Journal

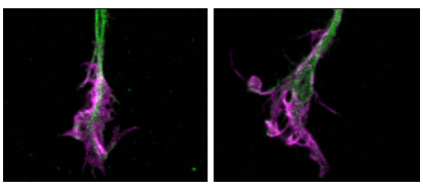
● Cellular/Molecular

Internalization Determines Cortical Neurons' Responses to Cues

Ioana Carcea, Avi Ma'ayan, Roxana Mesias, Bryan Sepulveda, Stephen R. Salton, et al.

(see pages 15317–15329)

Growing axons are guided to appropriate targets by environmental cues. Whether a growing axon responds to a given cue is determined by the spatiotemporal pattern of the cue and by which receptors the axonal growth cone expresses. Axons of cortical pyramidal neurons that project to the contralateral cortex develop in the same environment as those growing toward subcortical targets, suggesting that the different trajectories are determined by different responses to cues. Differential responsiveness likely results from differential expression of transcription factors, such as Satb2, which is expressed preferentially in callosal neurons. Indeed, Carcea et al. show that in cultures, Satb2-expressing neurons were less responsive to the chemorepellant semaphorin 3A (Sema3A) than neurons lacking Satb2. This differential responsiveness cannot be mediated by differential expression of sema3A receptors, however, because these are expressed at similar levels in the two neuronal populations. Instead, differential internalization of Sema3A via raft-mediated endocytosis appeared to underlie the different responses.



Sema3A receptors, including L1CAM (green), are expressed at similar levels in growth cones of cortical axons that are inhibited by Sema3A (left) and those that are not (right). F-actin labeling (purple) reveals the growth cone. See the article by Carcea et al. for details.

▲ Development/Plasticity/Repair

Polarity Develops in Defined Sequence in Cortical Interneurons

Emi Yamasaki, Daisuke H. Tanaka, Yuchio Yanagawa, and Fujio Murakami

(see pages 15221–15227)

A neuron's axon and dendrites differ in structure, molecular composition, and function. How this polarization develops from a spherical neuroblast has long been studied in cultures of dissociated neurons from embryonic rats. In these cultures, cells first develop several apparently undifferentiated neurites, which extend and retract for several hours before one begins growing rapidly and acquires axonal characteristics. Evidence suggests that any one of the initial neurites can become an axon, with the selection influenced by extracellular cues. Whether development proceeds similarly *in vivo* has been questioned, however. In the natural environment, a neurite might be specified as an axon as soon as it emerges, its position determined by the plane of the final mitotic division or by the cell's direction of migration. But Yamasaki et al. report that cortical interneurons nearing the end of their migration in organotypic brain hemisections have apparently undifferentiated neurites like those in cultures, and polarity develops in a similar manner.

■ Behavioral/Systems/Cognitive

TrkB Activation Is Associated with Enlarged Synapses after Learning

Lulu Y. Chen, Christopher S. Rex, Danielle T. Pham, Gary Lynch, and Christine M. Gall

(see pages 15097–15101)

Brain-derived neurotrophic factor (BDNF) is present in vesicles at presynaptic and postsynaptic sites, and calcium influx during synaptic activity stimulates its release. Extracellular BDNF binds to TrkB receptors, causing their phosphorylation and activation of several downstream signaling pathways. TrkB activation produces many cellular effects, including potentiation of glutamate release and increased synthesis and insertion of AMPA receptors. Chen et al. recently reported that after exploration of a novel environment, during which rats learn spatial relationships, TrkB was activated in a subset of hippocampal synapses. The effect was blocked by an NMDA receptor antagonist. They now extend these findings, showing that TrkB activation varied across hippocampal regions: activation was greatest in CA3a of rostral hippocampus, less pronounced in rostral dentate gyrus, and undetected in CA1a and all caudal regions. In addition, they found that synapses containing activated TrkB were significantly larger than nearby synapses in which activated TrkB was not detected.

♦ Neurobiology of Disease

Caspase-6 Is Activated in Early Stages of Huntington's Disease

Rona K. Graham, Yu Deng, Jeffery Carroll, Kuljeet Vaid, Catherine Cowan, et al.

(see pages 15019 –15029)

Huntington's disease (HD) is caused by expansion of a trinucleotide (CAG) repeat in *huntingtin*. Cleavage of mutant huntingtin generates fragments containing a glutamine expansion, and aggregation of these fragments is associated with degeneration of striatal neurons. Graham et al. found that caspase-6 was activated in striatum in patients in early-stage HD, and was further activated at later stages. Moreover, levels of activated caspase-6 were correlated with the number of CAG repeats in *huntingtin*—which was previously shown to be correlated with the age of onset and rate of progression of HD. Mice expressing mutant huntingtin also had elevated caspase-6 activity in striatal neurons, but caspase-6 activation was comparable to that of wild-type in mice expressing a caspase-6-resistant form of huntingtin. This suggests that huntingtin fragments produced by caspase-6 cleavage further activates caspase-6. Caspase-6 inhibitors prevented NMDA-induced death in cultured striatal neurons, suggesting that caspase-6 activation is an important early step in HD-associated neuropathology.