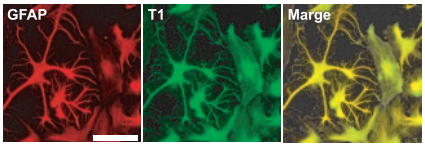
This Week in The Journal

● Cellular/Molecular

TrkB Signaling without the Kinase Domain

Koji Ohira, Haruko Kumanogoh, Yoshinori Sahara, Koichi J. Homma, Hirohisa Hirai, Shun Nakamura, and Motoharu Hayashi
(see pages 1343–1353)

Brain-derived neurotrophic factor (BDNF) exerts its role in neural development through tropo-myosine-related kinase B (TrkB) receptors. The full-length TrkB isoform, TK+, signals through its intracellular tyrosine kinase domain, but two truncated isoforms, T1 and T2, lack the kinase domain. T1 may act as a dominant-negative inhibitor of TK+, but there is also evidence for signaling through T1. This week, Ohira et al. report a pathway by which T1 has a nonkinase action. Using the short cytoplasmic domain of T1 to purify T1-binding proteins, they identified Rho GDP dissociation inhibitor 1 (GDI1), a protein that stabilizes the inactive form of Rho GTPases. In cultured hippocampal astrocytes that express T1, Rho GDI1 dissociated from T1 with BDNF binding. Rho GTPases remodel the cytoskeleton. Consistent with a T1-mediated action on the cytoskeleton, BDNF signaling through GDI1 inhibition of Rho GTPases caused rapid transformation of astrocytes from fibrous to flat shapes.



Astrocytes in culture were immunoreactive for GFAP (red; left) and the T1 isoform of the TrkB receptor (green; middle). Almost all cells were colabeled, as seen in the merged panel (yellow; right). See the article by Ohira et al. for details.

▲ Development/Plasticity/Repair

Axotomy-Induced Motor Neuron Death

Sumiko Kiryu-Seo, Teruhisa Hirayama, Ryuichi Kato, and Hiroshi Kiyama
(see pages 1442–1447)

In a search for molecules that mediate cell death, Kiryu-Seo et al. exploit a striking difference between adult Wistar rats and C57BL/6 mice in the pattern of cell death after axotomy. Two months after hypoglossal nerve transection, adult mice suffered extensive motor neuron loss, whereas motor neurons in adult rats all survived. The authors focused on downstream targets for the tumor suppressor gene p53, frequently activated in damaged neurons. In a survey of genes activated after axotomy, the authors found many common genes, including several p53-transactivated genes. However, the p53 target, Noxa, was an exception. After axotomy, only mice expressed this Bcl-2 homology domain 3-only, proapoptotic protein. Noxa expression was decreased in p53-deficient mice, accompanied by dramatic increase in neuronal survival. However survival was less dramatic in Noxa-deficient mice, suggesting a role for other p53-activated proapoptotic molecules. Although this difference appears to be between species, one wonders about similar differences attributable to genetic background in mice (or men).

■ Behavioral/Systems/Cognitive

Memories of Opiate Withdrawal

François Frenois, Luis Stinus, Francesco Di Blasi, Martine Cador, and Catherine Le Moine
(see pages 1366–1374)

Relapse into compulsive drug seeking is a constant danger for the former addict. Memories of the sights and sounds and smells associated with the withdrawal experience constitute one trigger for relapse. In this view, relapse is motivated in part by the avoidance of withdrawal. To test this idea, Frenois et al. compared the neural pathways recruited during the formation and retrieval of withdrawal memories. Morphine-dependent rats underwent naloxone-induced withdrawal under specific environmental and sensory conditions. Later, they were re-exposed to the same environment to test retrieval of an "emotional aversive state." Withdrawal modified c-*fos* mRNA in a number of structures, only of subset of which were activated on reexposure. The latter consisted of a set of interconnected limbic structures, including the amygdala, hippocampus, and ventral tegmental area. Acute withdrawal evoked different patterns of activation than reexposure in the central and basolateral nuclei of the amygdala. The authors argue that memory retrieval may induce a motivational state leading to compulsive drug seeking.

♦ Neurobiology of Disease

AIF and Caspase-Independent Neuronal Death

Eric C. C. Cheung, Lysanne Melanson-Drapeau, Sean P. Cregan, Jacqueline L. Vanderluit, Kerry L. Ferguson, William C. McIntosh, David S. Park, Steffany A. L. Bennett, and Ruth S. Slack
(see pages 1324–1334)

Both caspase-dependent and caspase-independent cell death pathways involve signals from mitochondria. This week, Cheung et al. investigate the role of the mitochondrial protein apoptosis-inducing factor (AIF) in cell death. It has been suggested that AIF offers protection against oxidative damage, because neurons in Harlequin (*Hq*) mutant mice, which express only 20% of normal AIF levels, are more vulnerable to peroxide-mediated apoptosis. However, once a cell death pathway is activated, AIF can translocate to the nucleus and cause DNA fragmentation and cell death. So is AIF pro-life or pro-death? The authors crossed *Hq* mice with *Apaf1*$^{-/-}$ mice, because the loss of Apaf1 prevents caspase activation. DNA damage and excitotoxic insults were used to trigger cell death. In neurons cultured from the double mutants, apoptosis was reduced and cells retained their mitochondrial membrane potential. The authors conclude that AIF contributes to cell death induced by either camptothecin-mediated DNA damage (BAX dependent) or glutamate-mediated excitotoxicity (BAX independent).