This Week in The Journal

Cellular/Molecular

A Methyl-Binding Protein Helps Shape Cortical Gene Expression

Katsusuke Hata, Hiroaki Mizukami, Osamu Sadakane, Akiya Watakabe, Masanari Ohtsuka, et al.

(see pages 19704–19714)

Functional specialization of cortical areas likely involves area-specific gene expression, possibly resulting from epigenetic modification. Expression of several genes differs between primary visual cortex (V1) and prefrontal cortex (PFC) in macaques; Hata et al. asked whether differential methylation of CpG dinucleotides—an epigenetic modification often associated with transcriptional repression—contributed to patterned expression of these genes. Indeed, the promoters of PFC-associated genes were highly methylated in V1, whereas methylation of V1-associated genes was low. Surprisingly, however, these genes had the same methylation patterns in PFC, indicating that differential expression did not result from methylation alone. Instead, differential expression appeared to depend on expression of a methyl-CpG binding protein, MBD4, which was enriched in PFC. Knockdown of MBD4 in PFC reduced expression of two PFC-associated genes (*PNMA5* and *RBP4*), whereas inducing expression of MBD4 in V1 increased expression of PFC-associated genes in V1. Another PFC-associated gene, *SLIT1*, was not influenced by changes in MBD4 expression, however, indicating other regulatory mechanisms exist.

Development/Plasticity/Repair

Slow Debris Clearance Hinders PNS Regeneration

Hyuno Kang and Jeff W. Lichtman

(see pages 19480–19491)

Unlike CNS axons, peripheral axons regenerate after injury. In old animals, however, recovery is slow and incomplete. Many factors thought to prevent regeneration of CNS axons have been proposed to hinder peripheral axon growth in old animals. These include a reduced intrinsic ability to grow, insufficient levels of growth factors, and the presence of debris that stymies growth. Kang and Lichtman investigated impediments to motor axon regeneration in mice. Both young and old axons extended at variable rates as they regrew, and slow growth was associated with growth cone broadening and axonal swelling or thinning. These morphological changes occurred when growth cones encountered and navigated around debris, and they were more frequent in old than in young mice. Slower debris clearance in old animals led to slower average growth rate, but the peak growth rate and the rate of synapse formation were similar in young and old axons. Therefore, slow debris clearance is probably the primary impediment to PNS regeneration in old animals.

Behavioral/Cognitive

Extinction Differs for Recent and Remote Memory

Kevin A. Corcoran, Katherine Leaderbrand, and Jelena Radulovic

(see pages 19492–19498)

Retrieval of episodic memories initially requires activation of both hippocampal and cortical circuits, but the role of the hippocampus decreases over time as new memories become integrated with older memories in the cortex. During this process, memories become more schematic and less vivid, which may allow emotions (such as fear) aroused by the memories to subside. Corcoran et al. hypothesized that because new and old memories are stored and retrieved differently, different processes must be required to extinguish recently and remotely acquired contextual fear responses. Although neuronal activity in retrosplenial cortex (RSC) was required for extinction of both recent and remote fear, only remote fear extinction required activation of NMDA receptors containing the NR2B subunit (NR2BRs) and caused increased phosphorylation of the transcription factor CREB in RSC. Furthermore, whereas extinction reduced association of NR2BRs with protein kinase A (PKA) in all cases, inhibiting PKA after extinction training accelerated extinction only of remote memories, whereas activating PKA slowed extinction of remote memories.

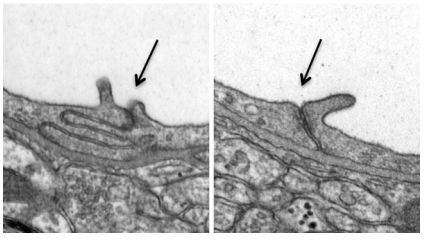
Neurobiology of Disease

Loss of Progranulin Weakens Blood–Brain Barrier

Katherine Jackman, Timo Kahles, Diane Lane, Lidia Garcia-Bonilla, Takato Abe, et al.

(see pages 19579–19589)

Frontotemporal dementia (FTD) is characterized by degeneration of the frontal and temporal lobes, resulting in behavioral and/or language deficits without substantial memory loss. Different forms of FTD are caused by mutations in different genes, including the gene encoding progranulin, a multifunctional growth factor that is expressed throughout the body. In the brain, progranulin has neuroprotective and anti-inflammatory functions, and it is also expressed in the developing vasculature. How loss-of-function mutations in progranulin lead to FTD is unclear, but Jackman et al. suggest that weakening of the blood–brain barrier (BBB) might be a factor. Artery occlusion produced more extensive ischemic damage in progranulin-deficient mice than in wild-type. These changes were not caused by differences in microvasculature density, cerebral blood flow, or inflammatory mediators produced during ischemia, but instead were associated with greater BBB breakdown. The BBB was probably more susceptible to ischemic injury in progranulin-deficient mice because the tight junctions between endothelial cells in cerebral microvessels were fewer, shorter, and less complex than normal.



Tight junctions between endothelial cells of cerebral microvessels (arrows) are shorter and less complex in progranulin-deficient (right) than in wild-type mice (left), likely making the BBB more susceptible to damage. See the article by Jackman et al. for details.