This Week in The Journal

Cellular/Molecular

AGAP3 Links NMDAR Activation to AMPAR Recruitment

Yuko Oku and Richard L. Huganir

(see pages 12586–12598)

Long-term potentiation (LTP), a fundamental element of learning and memory, requires NMDA-type glutamate receptor (NMDAR) activity and calcium influx, which in turn boosts trafficking of AMPA-type receptors (AMPAR) to synapses—but how? Oku and Huganir reveal a critical link: a protein called AGAP3. They used a yeast-two-hybrid strategy to find the potential culprit; as bait they used the Ras GTPase activating protein (RasGAP) domain of SynGAP, a member of the NMDAR complex previously shown to activate key pathways in LTP. They indicated AGAP3 as interacting with SynGap and specifically with the NMDAR subunit NR2B. Next, the team used small hairpin RNA (shRNA) interference to knock down AGAP3, which disrupted glycine-induced LTP. They used molecular-replacement experiments to examine the differential contributions of AGAP3's GTPase-like, ArfGAP, and plekstrin homology domains to LTP-related signaling. These suggested that the ArfGAP domain bears responsibility for basal AMPAR trafficking, whereas the GTPase domain regulates Ras/ERK signaling and activity-dependent AMPAR trafficking. The work adds AGAP3 to the collection of proteins required for LTP.

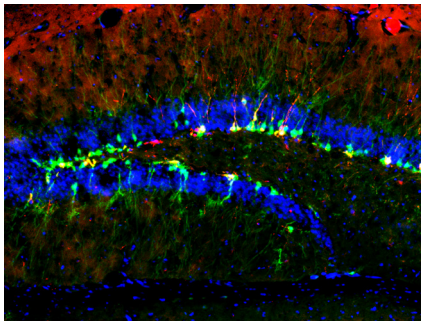
Development/Plasticity/Repair

Progenitor Cell Survival, Neurogenesis Require p63 Protein

Gonzalo I. Cancino, Adelaide P. Yiu, Michael P. Fatt, Chandrasagar B. Dugani, Elsa R. Flores, et al.

(see pages 12569–12585)

Into adulthood, rodent hippocampal granule cells arise from the dentate gyrus subgranular zone (SGZ), and olfactory bulb interneurons spring from the subventricular zone (SVZ) of the lateral ventricles. In order for the brain to birth new neurons, it must maintain its population of neural precursor cells (NPC). To understand NPC survival, Cancino et al. looked to the p53 family of transcription factor proteins. Although the proteins mostly promote apoptosis—functioning as tumor suppressors, for example—a truncated form of p63 (ΔNp63) inhibits proapoptotic transcriptional activity of full-length p53 proteins. Experiments in mice haploinsufficient for the p63 gene showed that ΔNp63 was crucial to NPC survival, but not proliferation. These $p63^{+/-}$ mice lost 30–40% of NPCs to apoptosis and had fewer new neurons than did their wild-type counterparts. Acute, conditional genetic ablation of p63 from adult NPCs also shrunk the NPC and newborn neuron populations. Further, memory processes that require new hippocampal neurons were impaired in mice with reduced p63, indicating cognitive deficit as a consequence of NPC loss.



Confocal fluorescent image of dentate gyrus SGZ in an adult triple-mutant mouse with p63 ablated from NPCs. NPCs and adult-born neurons are labeled with YFP (green) and doublecortin (red); nuclei are labeled with Hoechst (blue). See the article by Cancino et al. for more information.

Behavioral/Cognitive

Wnt Signaling Underlies Hippocampal Memory Consolidation

Ashley M. Fortress, Sarah L. Schram, Jennifer J. Tuscher, and Karyn M. Frick

(see pages 12619–12626)

Wnt proteins are best known for their role in neural development. In adult mice, the signaling pathway underlies certain hippocampal learning processes, according to new work from Fortress et al. Wnt signaling had already been implicated in hippocampal plasticity, but this study marks the first to show a role in memory per se. In the so-called canonical Wnt pathway, binding of Frizzled receptors increases GSK3β phosphorylation and β-catenin accumulation, whereas noncanonical pathways involve calcium and other signaling molecules. Here, the authors trained mice in an object-recognition task, followed immediately by infusion of the dorsal hippocampus with Dickkopf-1 (Dkk-1), an inhibitor of canonical Wnt signaling. Whereas control mice that received vehicle infusion recognized the object the following day, those that received Dkk-1 failed to form a memory. Dkk-1 produced a rapid drop in GSK3β phosphorylation, and 4 h later β-catenin fell. The authors present the work as new evidence for a key role for canonical Wnt signaling in hippocampal memory consolidation.

Neurobiology of Disease

Narcolepsy's Neuronal Loss Traced to Neuropeptide Misfolding

Kanae Obukuro, Mizuki Nobunaga, Moeko Takigawa, Hiroshi Morioka, Akinori Hisatsune, et al.

(see pages 12557–12568)

Narcolepsy, a neurological disorder featuring debilitating sleep-wake cycle disturbances, remains enigmatic one hundred years after it was first described. Lost are hypothalamic neurons that produce the peptide orexin, which contributes to arousal, sleep, and mood. Obukuro et al. paint a detailed picture of how the neurons meet their demise in mice. The team suspected nitric oxide (NO), because NO concomitantly rises with the loss of orexin and has harmful potential. When they experimentally increased NO levels, orexin neurons were lost following orexin aggregation. Orexin contains a pair of intramolecular disulfide bonds, making it subject to misfolding. Protein disulfide isomerase (PDI) normally trims improperly formed disulfide bonds, but with sleep deprivation, PDI was inactivated by NO-induced *S*-nitrosation, making orexin more vulnerable to misfolding and aggregation. The researchers traced the source of NO to nearby NO-producing hypothalamic neurons, which produced excess NO in response to sleep deprivation. The authors present the first evidence of stress-induced neuropeptide misfolding that leads to neurodegeneration.