This Week in The Journal

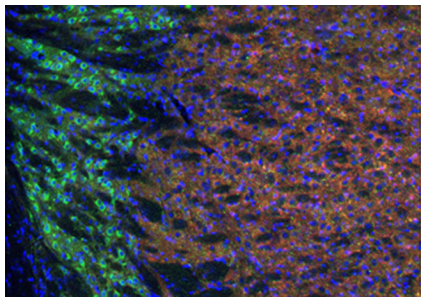
● Cellular/Molecular

GABA Depolarizes Adult Thalamic Reticular Nucleus Neurons

Yan-Gang Sun, Chia-Shan Wu, John J. Renger, Victor N. Uebele, Hui-Chen Lu, et al.

(see pages 7782–7790)

The thalamic reticular nucleus (TRN) is a thin sheet composed primarily of GABAergic neurons that surrounds the dorsal thalamus. TRN neurons receive collateral inputs from corticothalamic and thalamocortical axons, and they project broadly within the thalamus. The TRN has an important role in generating the spindle-type thalamocortical oscillations that occur during non-REM sleep and are thought to facilitate memory consolidation; it is also hypothesized to direct attention to specific sensory inputs. TRN neurons are interconnected by GABAergic synapses, which have been proposed to mediate shunting inhibition. Surprisingly, however, Sun et al. found that because expression of the Cl^--extruding K^+/Cl^- cotransporter (KCC2) is extremely low in the TRN, the Cl^- reversal potential is relatively high and activation of $GABA_A$ receptors depolarizes neurons. Although current through $GABA_A$ receptors is insufficient to trigger spiking, it activates T-type voltage-gated Ca^{2+} channels, thus triggering bursts of spikes that produce long-latency inhibition of neurons in other thalamic nuclei.



Cl^--extruding KCC2 (red) is expressed in GABAergic (green) neurons of the thalamic ventral posteromedial nucleus (right side of image), but not in the adjacent TRN (left). Nuclei are blue. See the article by Sun et al. for details.

▲ Development/Plasticity/Repair

Dimerization Partners Determine Targets of Neurogenin-2

Saiqun Li, Pierre Mattar, Dawn Zinyk, Kulwant Singh, Chandra-Prakash Chaturvedi, et al.

(see pages 7791–7805)

The transcription factor neurogenin-2 is expressed in neocortical progenitors throughout the neurogenic period. Early in mouse cortical development—around embryonic day 12.5 (E12.5)—neurogenin-2 promotes transcription of proneural genes, thus triggering differentiation; it is required for specification of cortical neurons born at this stage. Neurogenin-2 is not required for specification of later-born neurons, however; instead, it regulates genes involved in those neurons' migration and morphological development. Indeed, Li et al. found that neurogenin-2 overexpression lost its ability to stimulate neuronal differentiation between E12.5 and E14.5. During this time, canonical Wnt signaling also decreased. Because Wnt signaling sequesters glycogen synthase kinase 3 (GSK3) in endosomes, the developmental decline in Wnt signaling was paralleled by increases in GSK3 activity. GSK3 phosphorylates neurogenin-2, and this phosphorylation causes neurogenin-2 to heterodimerize with transcriptional cofactor E47 rather than forming homodimers. This switch in dimerization partners appears responsible for the change in transcriptional targets by neurogenin-2.

■ Behavioral/Systems/Cognitive

Marker Genes Can Distinguish MVN Neuron Subtypes

Takashi Kodama, Shiloh Guerrero, Minyoung Shin, Seti Moghadam, Michael Faulstich, et al.

(see pages 7819 –7831)

Studies of neurophysiology and synaptic plasticity often focus on cortex, cerebellum, and hippocampus, not only because these regions have prominent sensory, motor, and cognitive roles, but also because the principal neurons in these structures are organized in relatively easy-to-target layers. Most brainstem nuclei, in contrast, comprise multiple functionally distinct cell types that are intermingled and difficult to distinguish. The identification of genes expressed in specific neuronal subtypes, however, enables cell type-specific expression of exogenous proteins that facilitate physiological studies. Using single-cell expression profiling combined with retrograde tracing, Kodama et al. have now identified markers for six neuronal subtypes in mouse medial vestibular nucleus (MVN), a brainstem nucleus involved in the vestibular ocular reflex. Markers for excitatory neurons included vesicular glutamate transporters, corticotropin releasing hormone (CRH), secreted phosphoprotein 1, and adenylate cyclase-activating polypeptide 1; markers for inhibitory neurons included glutamic acid decarboxylase, a glycine transporter, CRH binding protein, a voltage-dependent sodium channel, and cochlin.

♦ Neurobiology of Disease

NO Synthesis Stimulates Proliferation in Some Glioblastomas

Sidharth V. Puram, Caleb M. Yeung, Arezu Jahani-Asl, Chieyu Lin, Nuria de la Iglesia, et al.

(see pages 7806 –7818)

Glioblastomas (GBMs), the most aggressive and lethal of adult brain tumors, are caused by accumulated mutations in genes that regulate cell proliferation and differentiation. Thirty to 50% of GBMs involve mutations that constitutively activate the epidermal growth factor receptor (EGFR). Expression of one such mutant receptor, EGFRvIII, causes malignant transformation of mouse astrocytes. This transformation is accomplished at least partly by changing the transcriptional targets of the transcription factor STAT3, which normally inhibits tumorigenesis. The identity of pro-oncogenic STAT3 targets was unknown, but Puram et al. report that inducible nitric oxide synthase (iNOS) is among them. STAT3 binds to the iNOS promoter in EGFRvIII-expressing astrocytes, and reducing iNOS activity reduced proliferation of these astrocytes and of EGFRvIII-expressing human glioblastoma cells. Furthermore, reducing iNOS activity greatly impaired the ability of EGFRvIII-expressing astrocytes to form tumors when injected into mice. Therefore, local inhibition of iNOS might slow progression of glioblastomas in which EGFR is hyperactive.