This Week in The Journal

● Cellular/Molecular

Pinceau Formation Lacks GABAergic Synapses

Atsushi Iwakura, Motokazu Uchigashima, Taisuke Miyazaki, Miwako Yamasaki, and Masahiko Watanabe

(see pages 9438 –9448)

Axon initial segments (AISs) are structures rich in voltage-gated Na^+ channels, specialized for action potential generation. In several cell types, the AIS is enveloped by axons of GABAergic interneurons. Evidence suggests that GABAergic synapses on the AIS of cortical pyramidal cells modulate spike timing. Pinceau formations made by basket cell (BC) axons on the AIS of cerebellar Purkinje cells (PCs) are assumed to have a similar function, although few synapses are detected in these structures. In fact, Iwakura et al. found that astrocytic processes interdigitated with BC axons in the pinceau formation and enwrapped most of the AIS. Furthermore, whereas GABAergic synaptic proteins were numerous where BC terminals contacted PC somata, labeling for these proteins was weak and diffuse in the pinceau formation. Therefore, BCs are unlikely to regulate PC firing via GABAergic synapses on the AIS. Nevertheless, BCs inhibit PCs via perisomatic GABAergic synapses, and they may regulate spiking via electrical synapses in the pinceau formation.

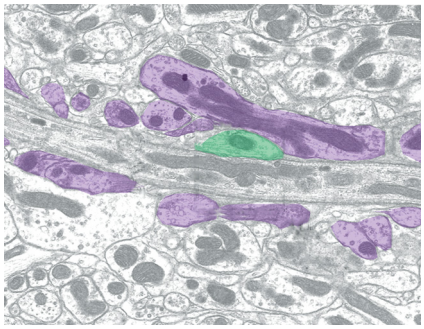
▲ Development/Plasticity/Repair

Blocking Otx2 Binding Reopens Critical Period

Marine Beurdeley, Julien Spatazza, Henry H. C. Lee, Sayaka Sugiyama, Clémence Bernard, et al.

(see pages 9429 –9437)

During development, many CNS regions exhibit critical periods of enhanced plasticity, after which the ability to rewire circuits is limited. For example, monocular deprivation for a short period early in life causes long-lasting reductions in the occluded eye's ability to drive V1 activity. The V1 critical period opens as parvalbumin (PV)-expressing GABAergic basket cells develop, which is driven by uptake of Otx2, a transcription factor synthesized in the retina and transsynaptically transported to V1. Closure of the critical period parallels the development of perineuronal nets—a highly organized form of extracellular matrix constructed around PV somata—which also depends on Otx2. Beurdeley et al. have discovered that Otx2 binds specifically to sugar moieties of perineuronal nets, and this facilitates Otx2 internalization by PV cells. A peptide comprising the Otx2 binding domain reduced Otx2 uptake and reopened the critical period in mice, allowing recovery from earlier monocular deprivation.



The pinceau formation and axon initial segment of a mouse Purkinje cell. Profiles of basket cell axons separated from the AIS with putative astroglial sheets are colored purple and one directly contacting the AIS is green. See the article by Iwakura et al. for details.

■ Behavioral/Systems/Cognitive

$GABA_B$ Antagonist Improves Memory in Down Syndrome Model

Alexander M. Kleschevnikov, Pavel V. Belichenko, Mehrdad Faizi, Lucia F. Jacobs, Khin Htun, et al.

(see pages 9217–9227)

Down syndrome (DS) is caused by trisomy of human chromosome 21 (hsa21), which leads to overexpression of some of the ~300 genes located on that chromosome. This produces multiple phenotypes, including abnormal hippocampal structure and learning and memory deficits. Many hsa21 genes are trisomic in Ts65Dn mice, which also show deficits in hippocampal-dependent learning and long-term potentiation (LTP). These deficits also occur in mice trisomic for a single hsa21 gene—encoding a G-protein-coupled inwardly rectifying K^+ channel, GIRK2—suggesting an important role for this gene in DS. GIRK2 is activated by metabotropic $GABA_B$ receptors ($GABA_B$Rs), and signaling through this pathway is enhanced in Ts65Dn mice. Kleschevnikov et al. now report that a specific antagonist of $GABA_B$Rs ameliorates some learning deficits in Ts65Dn mice, including deficits in short-term place recognition, long-term object recognition, and contextual fear conditioning tasks. The antagonist also rescued hippocampal LTP, partly by enhancing the NMDA receptor-mediated component of tetanus-evoked depolarization.

♦ Neurobiology of Disease

PolyQ Expansions in Ataxin-2 Promote Caspase 3 Activation

Michael P. Hart and Aaron D. Gitler

(see pages 9133–9142)

Several proteins contain stretches of glutamine residues, and expansion of these polyglutamine (polyQ) regions underlies different neurodegenerative diseases. For example, polyQ expansion from <24 to >34 residues in ataxin-2 causes spinocerebellar ataxia 2 (SCA2), characterized by primary loss of Purkinje cells. Interestingly, intermediate expansion of this tract—to 27–32 residues—is a common risk factor for amyotrophic lateral sclerosis (ALS), characterized by primary loss of motor neurons. In most cases of ALS, the RNA-binding protein TDP-43 becomes abnormally phosphorylated, fragmented, and aggregation prone, and it accumulates in cytoplasmic inclusions. This accumulation is promoted by ataxin-2 containing intermediate polyQ expansions. Hart and Gitler provide evidence that this occurs because cells expressing intermediate polyQ ataxin-2 (but, remarkably, not ataxin-2 with longer or shorter polyQ regions) exhibit stress-induced activation of caspase 3. Caspase 3 then cleaves TDP-43, leading to its phosphorylation and accumulation. Inhibiting caspase 3 reduced accumulation of phosphorylated TDP-43 fragments in these cells.