This Week in The Journal

● Cellular/Molecular

Kinesin-6 Knockdown Affects Axons and Dendrites

Shen Lin, Mei Liu, Olga I. Mozgova, Wenqian Yu, and Peter W. Baas

(see pages 14033–14049)

Microtubules are essential for axonal and dendritic growth and for the establishment of neuronal polarity. Short tubulin polymers formed in the soma are transported by motor proteins into neurites, where they elongate by addition of tubulin subunits. Early in morphogenesis, microtubules in all neurites are oriented with their faster-growing "plus" ends distal to the soma, but minus-end-distal microtubules are subsequently transported into dendrites. Suppression of kinesin-6 expression with antisense oligonucleotides prevents dendritic transport of minus-end-distal microtubules and causes dendrites to acquire axonal characteristics. But because antisense oligonucleotides are often nonspecific, Lin et al. re-examined the role of kinesin-6 using knockdown via RNA interference in rat sympathetic neurons. Although dendrites persisted after kinesin-6 knockdown, they had fewer minus-end-out microtubules and became morphologically similar to axons. Axonal expression of kinesin-6 is normally low, but nonetheless, axons grew longer after kinesin-6 knockdown and microtubules entered axons more frequently, suggesting kinesin-6 restricts microtubule entry into axons.

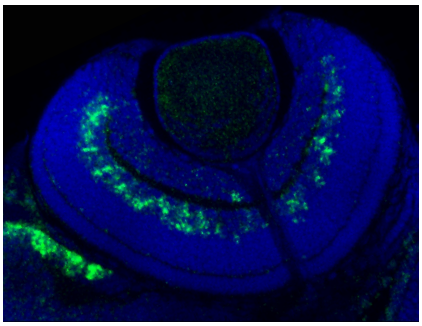
▲ Development/Plasticity/Repair

Bahrl2 Biases Amacrine Subtype Specification

Patricia R. Jusuf, Shahad Albadri, Alessio Paolini, Peter D. Currie, Francesco Argenton, et al.

(see pages 13929–13944)

Neuronal fate is progressively specified as precursors undergo successive cell divisions and changes in gene expression. For example, expression of transcription factor Atoh7 in zebrafish retinal progenitors precedes an asymmetrical division that produces one ganglion cell and one progenitor that divides to produce other cell types. Expression of transcription factor Ptf1a in daughter cells is required to produce an inhibitory phenotype, and Jusuf et al. report that subsequent expression of Bahrl2 biases these cells to become specific subtypes of amacrine cell. Consistent with mounting evidence that cell fate specification is a stochastic rather than deterministic process, Bahrl2 expression was present at different levels in different amacrine cell types: high expression consistently occurred in amacrines expressing serotonin, GABA, and/or calbindin, but low expression sometimes occurred in amacrines expressing neuropeptide Y or choline acetyltransferase. Knocking down Bahrl2 significantly reduced the proportion of the former subtypes and increased the proportion of the latter types.



Bahrl2 (green) is expressed in a subset of cells in zebrafish embryos, biasing them to become specific subtypes of amacrine cells. See the article by Jusuf et al. for details.

■ Behavioral/Systems/Cognitive

Tonic ON and OFF Cell Activity Has Little Effect on Pain

Kevin M. Hellman and Peggy Mason

(see pages 13668–13678)

Nociceptive transmission in the spinal cord can be facilitated or inhibited by descending inputs from the brainstem nucleus raphe magnus (RM). Withdrawal from painful stimuli is associated with increased spiking by RM ON cells and silencing of RM OFF cells. Based on recordings in anesthetized animals, tonic activity in ON cells has been proposed to favor hyperalgesia, which is normally balanced by tonic OFF cell activity that favors analgesia. Contrary to this model's predictions, however, Hellman and Mason found that in unanesthetized mice, tonic OFF cell activity was greater before a noxious stimulus elicited paw withdrawal than when no response occurred, and tonic ON cell activity was not different in responding vs nonresponding trials. Furthermore, morphine, which reduced stimulus-induced withdrawal, inhibited stimulus-induced decreases in OFF cell activity, as well as phasic increases in ON cell activity, without affecting tonic activity. The authors propose that stimulus-induced, phasic changes in ON and OFF cell activity facilitate and synchronize pain reflexes, respectively.

♦ Neurobiology of Disease

GLP-1 Cleavage Product Reverses Cognitive Impairment

Tao Ma, Xueliang Du, Joseph E. Pick, Guangzhi Sui, Michael Brownlee, et al.

(see pages 13701–13708)

Cognitive decline is epidemiologically linked with metabolic disorders such as insulin resistance, prompting researchers to examine roles of metabolic proteins in neural function. One such protein is glucagon-like peptide-1 (GLP-1), which is secreted by intestinal cells, stimulates insulin secretion, and is reduced in type 2 diabetes. GLP-1 receptors are expressed in many brain regions, and mice lacking GLP-1 receptors exhibit learning and memory deficits. Furthermore, treatment with GLP-1 analogs can improve cognitive performance in mouse models of Alzheimer's disease (AD). But Ma et al. suggest that beneficial effects of GLP-1 extend beyond the regulation of glucose metabolism. GLP-1 is rapidly cleaved *in vivo* to form GLP-1 $(9\text{-}36)^{\text{amide}}$, which does not induce insulin secretion. GLP-1 $(9\text{-}36)^{\text{amide}}$ has other physiological functions, however, including reducing mitochondrial production of superoxide. Ma et al. found that GLP-1 $(9\text{-}36)^{\text{amide}}$ rescued synaptic plasticity, learning, and memory in mice harboring AD-linked mutations. Levels of β-amyloid were unaltered, but mitochondrial production of superoxide was reduced.