This Week in The Journal

Translational Control of Guidance Receptor Expression

Hanna Hörnberg, Jean-Michel Cioni, William A. Harris, and Christine E. Holt

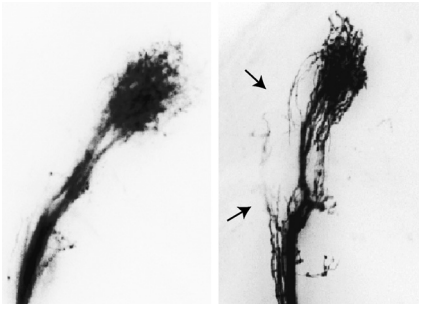
(see pages 12697–12706)

Axons that extend long distances are guided by multiple sets of cues expressed at intermediate targets along their path. To respond appropriately to these cues, axons update the repertoire of guidance-cue receptors expressed in their growth cones as they approach and extend beyond the intermediate targets. For example, as commissural spinal neurons grow toward the ventral midline, they express receptors for attractive midline cues, but after they cross the midline, they express receptors for repulsive midline cues, which drive them laterally and prevent recrossing (Neuhaus-Follini and Bashaw 2015 WIREs Dev Biol 4:377). How the timing of guidance receptor expression is regulated is only beginning to be understood.

Hörnberg et al. present evidence that the RNA-binding protein Hermes helps regulate expression of guidance receptors in retinal ganglion cell (RGC) axons. As zebrafish RGC axons extend in the optic tract, dorsal axons grow in the lateral branch, while ventral axons grow medially. Knocking down Hermes expression disrupted the growth trajectory of dorsal axons, causing many to grow inappropriately in the medial tract. Consequently, the axons had to take a circuitous route to reach their target region in the medial tectum.

Hermes knockdown increased protein synthesis in neurons, suggesting it normally acts as a translational repressor. More specifically, translation of three receptors previously shown to be involved in RGC axon guidance—L1cam, ALCAM, and Neuropilin1—increased when Hermes was knocked down. Notably, knocking down Neuropilin1 together with Hermes reduced the proportion of RGC guidance errors. Neuropilin1 is a receptor for the inhibitory guidance molecule Semaphorin 3A (Sema3A), and consistent with increased Neuropilin1 expression, Hermes-deficient RGCs were sensitive to Sema3A-induced collapse *in vitro* at a stage when wild-type RGCs were insensitive to Sema3A.

These data show that regulation of mRNA translation contributes to axonal pathfinding, likely by regulating the timing of guidance cue expression. This insight should continue to advance our understanding of how axons are guided throughout the CNS, as future work identifies mRNA binding proteins involved in regulating expression of other guidance molecules at other choice points and determines what signals regulate the binding of these proteins to specific mRNAs to turn translation on and off.



Axons from dorsal RGC axons normally grow in the lateral optic tract (left). Knocking down Hermes causes some dorsal axons to grow in the medial tract (arrows, right). See Hörnberg et al. for details.

Multisensory Integration in Rodents

Jacob M. Cloke, Robin Nguyen, Beryl Y.T. Chung, David I. Wasserman, Stephanie De Lisio, et al.

(see pages 12570–12585)

Integrating information from multiple sensory modalities enhances our ability to recognize and discriminate objects and to interpret events. Studies in humans, monkeys, and cats have identified multisensory responses in many cortical and subcortical areas, and animal studies have shown that some neurons in these regions respond more strongly to multimodal than to unimodal stimuli. Still, how information from different sources is integrated at the cellular level, and how multimodal information is combined into unified percepts of objects, remain poorly understood.

Winters and colleagues have been investigating the neural mechanisms of multimodal sensory integration in rodents. They previously reported that lesions of the prefrontal cortex or treatment with the NMDA receptor antagonist ketamine impaired rats' ability to visually recognize objects that had previously been explored by touch, and that this effect was prevented by administrating an α4ß2 nicotinic acetylcholine receptor (nAChR) agonist, which enhanced GABAergic signaling. Because the task used in those studies required rats to remember objects over a delay period, however, definitively attributing the effects to disruption of multimodal integration was impossible. Cloke et al. have therefore developed a new protocol in which several objects are presented simultaneously, allowing multimodal integration to be assessed independently of memory.

Consistent with previous results, ketamine treatment impaired performance on tactile-visual and olfactory-visual integration tasks, but not on unimodal discrimination tasks. Furthermore, the impairment was reversed by infusing an α4ß2 nAChR agonist into the orbitofrontal cortex (OFC) and the effect of the agonist was blocked by a $GABA_A$ receptor antagonist. In addition, parvalbumin expression was reduced in the OFC of ketamine-treated animals, and silencing parvalbumin-expressing neurons in the absence of ketamine impaired performance on the tactile-visual task, but not on unimodal discrimination tasks.

All together, these results suggest that inhibitory neurotransmission in OFC is required for multisensory integration in an object-recognition task. Blocking NMDA receptors reduces GABAergic inhibition, whereas activation of α4ß2 nAChR restores GABAergic function and reverses behavioral deficits. Because ketamine treatment produces cognitive phenotypes similar to those observed in schizophrenia, these experiments emphasize the need for more extensive investigation of multisensory integration deficits in that disease.

This Week in The Journal was written by Teresa Esch, Ph.D.