This Week in The Journal

Sodium Channel Localization in *Drosophila*

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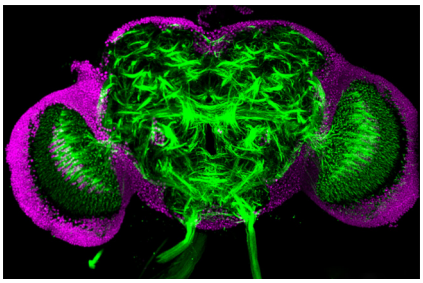
(see pages 7999–8024)

The iconic neuron is multipolar, with several dendrites and a single axon emerging from the cell body. Near the base of the axon, a region called the axon initial segment (AIS) is distinguished by its cytoskeletal structure, the presence of ankyrin G, and a high concentration of voltage-sensitive sodium channels. The AIS is the site of action potential generation, and it serves as a molecular barrier that limits protein diffusion between axonal and somatodendritic domains.

Not all neurons have this stereotypical morphology, however. Many neurons in invertebrates are unipolar, with a single primary neurite bearing both presynaptic and postsynaptic elements. Nevertheless, some of these neurons have distinct dendritic and axonal compartments. In *Drosophila*, for example, some dendritic proteins may be restricted to the proximal branches of the primary neurite, while some axonal proteins are restricted to the distal portion. Intriguingly, a stretch of neurite between these regions can be enriched in Ankyrin1 and have a unique cytoskeletal structure reminiscent of an AIS (Trunova et al., 2011, J Neurosci 31:10451). Whether this structure is the site of action potential generation has been unclear, however, because markers for voltage-sensitive sodium channels in *Drosophila* have been limited. Ravenscroft et al. addressed this question by genetically tagging *para*, the sole voltage-sensitive sodium channel type in *Drosophila*.

The authors first examined *para* expression in third instar larvae. Surprisingly, it was present in less than one-quarter of neurons. Single-cell sequencing of the larval CNS suggested that this sparse expression pattern occurs because most larval neurons are immature, and *para* is restricted to mature, active neurons. Consistent with this, nearly all neurons in adult flies expressed *para*.

Examination of a subset of neurons revealed that *para* is enriched in a region of the primary neurite between dendritic and axonal domains, similar to the AIS-like region described previously. Given the distance from the soma, the authors dubbed the region the distal axonal segment (DAS). Notably, depolarization steps delivered to the soma evoked tetrodotoxin-sensitive sodium currents only after a relatively long delay, suggesting that the spike-initiating zone is far from the soma. These data support the hypothesis that the DAS is functionally equivalent to the AIS and harbors the spike-initiating zone.



Para (green) is enriched in distal axonal segments in neurons of adult *Drosophila*. Magenta marks neuronal somata. See Ravenscroft et al. for details.

A Role for Lysosome Trafficking in Axon Branching

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(see pages 8103–8118)

Axons are supported by central bundles of microtubules and a meshwork of actin filaments beneath the cell membrane. When axons reach their intended target, these structures must be focally dismantled so actin filaments and microtubules can protrude from the axon shaft to form branches. This process is thought to be triggered by extracellular cues and downstream signaling cascades that inactivate actin- and microtubule-stabilizing proteins. The molecular mechanisms underlying site-specific branching remain incompletely understood, however.

Because synaptic components sometimes cluster at sites where axonal branches later emerge, Adnan et al. asked whether Arl8B, a small GTPase involved in transport of these components, plays a role in branch formation. Consistent with such a role, Arl8B overexpression increased, whereas knockdown decreased, axon branching in cultures of chick retinal ganglion cells (RGCs). Notably, however, these effects were not uniform along the axon: Arl8B overexpression reduced branching in the proximal axon, whereas knockdown increased proximal branching. Furthermore, Arl8B expression only partially overlapped with that of synaptic vesicle proteins, and manipulating Arl8B levels had limited effects on the distribution of these proteins, suggesting that the effect on branching did not stem from effects on the trafficking of synaptic components.

Because Arl8B is also required for axonal transport of lysosomes—a participant in autophagy—the authors asked whether local autophagy promotes axon branching. Consistent with this possibility, Arl8B was highly colocalized with a lysosomal marker in RGC axons. Moreover, Arl8B overexpression greatly increased markers of autophagy in distal RGC axons and decreased autophagy markers in the proximal axon, paralleling its effects on branch formation. Furthermore, reducing autophagy reduced axonal branching and blocked the effects of Arl8B overexpression, whereas stimulating autophagy increased branching and occluded the effects of Arl8B overexpression. Finally, knocking out a protein essential for autophagy reduced RGC axon branching in the superior colliculus of mice.

These results identify a role for autophagy in axon branching and suggest that Arl8B influences branching in part by facilitating the transport of lysosomes to distal axons to support local autophagy. Future work should examine whether lysosomes and autophagosomes accumulate selectively at future branch sites and determine which cellular components are broken down to enable branch formation.

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