This Week in The Journal

Microglia Interact with Axon Initial Segments

Kelli Baalman, Miguel A. Marin, Tammy Szu-Yu Ho, Marlesa Godoy, Leela Cherian, et al.

(see pages 2283–2292)

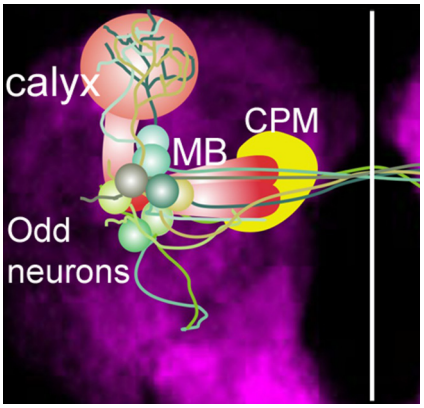
Microglia are known as the resident immune cells of the CNS. Under normal conditions, they repeatedly extend and retract processes, sampling the environment for signs of injury. When injury is detected, microglia migrate toward the injury and release pro- or anti-inflammatory cytokines, depending on the type of insult. They also phagocytose invading bacteria and cellular debris.

Microglial function is not limited to immune responses, however: microglia also influence neuronal activity, connectivity, and plasticity in the healthy brain. Microglia express several types of neurotransmitter receptors that allow them to respond to neuronal activity. In zebrafish, microglial processes detect highly active neurons, and after microglial contact, the neurons' activity declines. During development, microglia help shape neural circuits by pruning inactive and hyperactive synapses. Microglia also influence synaptic plasticity in adults, by releasing glycine and TNF-α, which modulate NMDA receptor activity and AMPA receptor expression, and by releasing brain-derived neurotrophic factor (reviewed in Salter and Beggs, 2014, Cell 158:15).

New work by Baalman et al. suggests that microglia can also influence neuronal activity through specific interactions with the axon initial segment (AIS), where action potentials are generated. In mice, ~8% of cortical microglia extended a process along an AIS, and ~4% of cortical pyramidal neurons had AIS-associated microglia. AIS-associated microglia were less frequent among GABAergic cortical neurons and in subcortical brain regions. But given the high motility of microglial processes, all these measurements may be underestimates.

Because the AIS is dismantled after traumatic brain injury and microglia phagocytose cellular debris, Baalman et al. predicted that such injury would increase the number of AIS-associated microglia. Contrary to expectations, however, fewer microglia were associated with AISs in the injured hemisphere than in the control. Dismantling the AIS by knocking out Ankyrin G, which helps organize the complex protein structure of the AIS, also reduced the number of AIS-associated microglia, suggesting that microglia are only attracted to an intact AIS.

Together, the data suggest that microglia routinely monitor intact AISs, particularly those of excitatory cortical neurons, in the healthy brain. The function of AIS-associated microglia and whether they constitute a unique glial subpopulation remain unknown, however.



Reconstruction of all eight larval Odd neurons in a standard larval brain. Three of these neurons extend dendrites into the calyx of the mushroom body (MB, red) and extend axons into the centroposterior medial compartment (CPM, yellow) and two of these three project across the midline (white vertical line). Odd neurons appear to regulate odor sensitivity. See the article by Slater et al. for details.

"Odd" Neurons Increase Odor Sensitivity in *Drosophila*

Gemma Slater, Peter Levy, K. L. Andrew Chan, and Camilla Larsen

(see pages 1831–1848)

Most animals use olfaction to locate food, recognize conspecifics, and detect poisons and predators. As with other sensory systems, gain control is required to maintain odor sensitivity over a wide range of intensities. This is especially true when olfaction is the primary means by which an animal finds its way to a food source or mate. In *Drosophila*, food odors are detected by olfactory receptor neurons (ORNs) that project to the antennal lobe, where they synapse with projection neurons (PNs), which project to the mushroom body and lateral horn. ORNs and PNs also synapse with local neurons (LNs) in the antennal lobe. As odor concentration increases, more ORNs are activated, resulting in increased activation of inhibitory LNs. These LNs inhibit ORN terminals, thus reducing odor sensitivity and preventing response saturation.

Slater et al. have discovered another group of neurons that influence odor sensitivity in *Drosophila* larvae. The neurons, called Odd neurons because they express the transcription factor Odd-skipped, extend dendrites into the mushroom body calyx, where they form synapses with PNs. Ultrasensitive calcium sensors indicated that Odd neurons respond to attractive odors but not to aversive odors.

Several experiments suggested that manipulating Odd-neuron activity affected odor sensitivity. Silencing Odd neurons reduced, whereas increasing Odd-neuron excitability increased, the number of larvae that reached an attractive odor source. This difference likely stemmed not from differences in locomotor speed, which was similar across genotypes, but from differences in odor-sampling behavior. Compared to controls, Odd-silenced larvae exhibited more lateral head swings (used to determine the orientation of an odor gradient) and took more convoluted paths to the odor source. Conversely, Odd-excited larvae made fewer lateral head swings and took more direct paths to the odor.

These results suggest that Odd neurons increase odor sensitivity. Indeed, whereas normal larvae could discriminate between low-to-moderate odor concentrations that differed sixfold, Odd-silenced larvae required a tenfold difference while Odd-excited larvae could detect a fourfold difference. But Odd-excited larvae strayed farther from strong odor sources than Odd-silenced larvae, suggesting Odd-neuron activity reduced discrimination at higher concentrations. Odd neurons thus appear to boost olfactory sensitivity primarily when odor concentrations are low.

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