This Week in The Journal

Selective Role for Robo2 in Motor Axon Regeneration

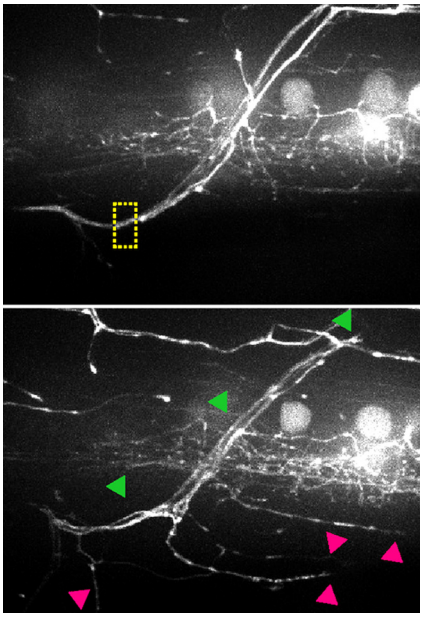
Patricia L. Murphy, Jesse Isaacman-Beck, and Michael Granato

(see pages 762–776)

Unlike CNS axons, peripheral nerves can regenerate and reinnervate their targets after injury. This requires axons to navigate through an environment that has changed substantially since the axons' initial growth. Moreover, because individual axons within a nerve innervate different targets, they must follow different paths. Little is known about how regenerating axons are guided, but work in zebrafish has shown that a small group of Schwann cells provide cues that guide dorsally projecting motor axons. As motor axons leave the spinal cord, dorsally projecting and ventrally projecting axons travel in the same nerve, but they ultimately diverge to innervate different target muscles. After nerve transection, a group of Schwann cells near this branch point transiently increase expression of the collagen protein Col4a5 and the repulsive guidance cue Slit1a, which is anchored to the basement membrane by Col4a5. These molecules steer dorsal axons in the right direction. Murphy et al. report that the Slit receptor Robo2 also contributes to the guidance of dorsal axons at this choice point.

When all Schwann cells were made to express *col4a5*, dorsal axons grew normally during development, but made more errors than normal when regenerating after transection. This suggests that restricted expression of *col4a5* at branch points is necessary for guiding dorsal axons selectively during regeneration. Knocking out Robo2, which is normally expressed in dorsal nerves, also increased the number of dorsal axons that followed errant trajectories during regeneration. Conversely, inducing the expression of Robo2 in ventral axons caused them to follow a dorsal trajectory. The latter effect was absent in Col4a5-deficient fish, however. Finally, time-lapse imaging revealed that Robo2-deficient dorsal axons were no more likely than controls to enter improper nerve tracts. But, unlike control axons, which soon stalled or retracted after making such errors, Robo2-deficient axons continued to extend.

These results suggest that Robo2 expression in dorsally projecting motor axons allows regenerating axons to recognize collagen-bound Slit1a at an essential choice point. If axons initially turn the wrong way, Slit1–Robo2 interactions prevent the axons from extending further. The stalled axons are likely pruned by different signaling molecules. Future work should identify these molecules and determine how stalled dorsal axons reinitiate growth in the proper direction.



After nerve transection (at the site marked by box, top panel), many Robo2-deficient regenerating dorsal axons erroneously grow ventrally or laterally (pink arrowheads) instead of dorsally (green arrowheads). See Murphy et al. for details.

How Learning Alters Neurons and Ensembles in Gustatory Cortex

Elor Arieli, Nadia Younis, and Anan Moran

(see pages 909–921)

In gustatory cortex, tastes are encoded by the spatiotemporal pattern of activity across a large population of broadly tuned neurons. This population activity can be represented as a sequence of distinct network states, with different taste qualities being represented by different sequences. Notably, gustatory cortical activity evoked by a taste initially represents taste identity and then transitions to representing valence. Therefore, patterns elicited by a given taste change if the valence changes, as occurs with conditioned taste aversion (CTA). Like other forms of learning, CTA has acquisition and consolidation phases in which synaptic strength and the spiking of individual neurons changes. How these changes at the single-cell level relate to changes in population dynamics that drive behavior is unclear. To address this, Arieli et al. recorded the responses of multiple gustatory neurons to saccharin over a 48 h period, starting 24 h before LiCl was injected to induce CTA.

Many neurons in CTA animals showed altered responses to saccharin after LiCl injection, but individual neurons' responses changed in different directions (increases and decreases) and at different times. Nevertheless, averaging across the population revealed an overall increase in firing during the acquisition phase of CTA (1–3 h after LiCl injection) and during the consolidation phase (6–18 h after injection), with a return to baseline levels in the intermediate period (3–6 h), Notably, activity changes occurred predominantly in the late portion of the saccharin response, when population activity encodes taste valence. Importantly, when ensemble activity was represented as a vector rather than an average, saccharin responses were distinct from pretraining patterns during the intermediate as well as the consolidation phases of CTA. As expected, the valence of the taste was represented more quickly after CTA than before. But this more rapid valence representation did not appear until the consolidation phase, despite the fact that aversive behavioral responses to saccharin appeared almost immediately.

These results suggest that after CTA training, changes in the activity of individual gustatory neurons do not occur in a predictable, unidirectional way. Instead, the activity of neurons is continuously adjusted in order to alter the ensemble activity, including the rate of progression between states.

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