This Week in The Journal

Interactions between TrkB and CaSR Signaling in Axon Growth

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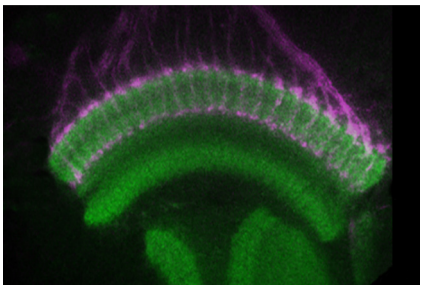
(see pages 5842–5860)

As axons extend toward their targets, they encounter numerous extracellular molecules that can cause them to speed up, pause, turn, or branch. Guidance cues exert these effects by binding to receptors on axonal growth cones, thus initiating intracellular signaling cascades that regulate vesicle trafficking and cytoskeletal dynamics. Much is known about how guidance molecules and their receptors influence axon growth when acting individually, but axons can respond to multiple cues simultaneously. Sometimes the combined effect of these cues equals the sum of individual effects, but sometimes the presence of one cue or receptor alters responses to others. Markworth et al. show that such non-additive interactions occur between the calcium-sensing receptor CaSR and the brain-derived neurotrophic factor (BDNF) receptor TrkB in embryonic chick nodose-ganglion neurons.

Previous work showed that CaSR, which is activated when extracellular calcium levels are high, enhances the neurite-growth-promoting effects of BDNF. Because CaSR begins to be expressed earlier than TrkB in nodose neurons, Markworth et al. examined the TrkB-independent effects of CaSR in young (stage 22) neurons. Exposing these neurons to elevated extracellular calcium or a CaSR agonist increased neurite growth, whereas a CaSR antagonist reduced growth. Stimulation of neurite growth by CaSR involved two downstream kinases, PI3-kinase and Akt.

Activation of CaSR in the absence of BDNF did not affect neurite growth in stage 30 neurons, which express both CaSR and TrkB. Nonetheless, CaSR potentiated the growth-promoting effects of BDNF. Surprisingly, this effect did not involve PI3-kinase or Akt. Instead, activating CaSR in stage 30 neurons led to activation of GSK3α, which then phosphorylated the microtubule-associated protein tau. In addition, CaSR activation altered the effect of BDNF on GSK3 kinases. When CaSR was minimally active, BDNF increased phosphorylation of one site on GSK3α and two sites on GSK3β. But when CaSR was activated, BDNF increased phosphorylation of only one site on GSK3β, likely reducing its activity. Consequently, simultaneous activation of TrkB and CaSR led to cyclical phosphorylation and dephosphorylation of tau.

These results indicate that simultaneous activation of CaSR and TrkB alters the downstream effects of both receptors. The resulting effects on tau phosphorylation may lead to cycling of microtubule stability, thus promoting axon growth and branching.



Axons of R7 and R8 photoreceptors (magenta) project topographically to columns in the multilayered medulla, where N-cadherin (green) is expressed. See Trush, Liu, et al. for details.

Construction of Columns in Drosophila Optic Lobes

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(see pages 5861–5880)

Drosophila eyes have ~800 ommatidia, each of which has eight photoreceptors (R1–R8). Information from each ommatidium is conveyed to a single column in the medulla of the optic lobe, either directly (by R7 and R8) or indirectly, via the lamina. These columns form a topographic map of the retina and are analogous to microcolumns in vertebrate cortex.

To learn how columns form in the medulla during larval development, Trush, Liu, et al. examined the relative timing and pattern of medulla innervation by photoreceptor, lamina, and medulla axons. Column boundaries were identified by their expression of the cell adhesion molecule N-cadherin. Axons of Mi1 neurons—the first medulla neurons to be generated—extended broadly within the medulla before the arrival of photoreceptor axons, but they eventually became restricted to a grid-like pattern outside columns. R8 axons arrived a few hours after Mi1 axons, and their terminals overlapped with N-cadherin in column boundaries. R7 axons arrived next, and they became restricted to the center of columns, where N-cadherin expression was low. Columns were disorganized in mutant flies lacking R7, R8, or Mi1, suggesting that all three of these neurons help direct column formation. In contrast, projections from the lamina and other medulla neurons arrived later in development, and ablating lamina neurons did not alter column formation.

The positions of R7, R8, and Mi1 axons in columns resembled the pattern that emerges when cells of different adhesiveness are mixed and allowed to segregate. In these cultures, cells form clusters with the most adhesive cells in the center and the least adhesive cells in the periphery. N-cadherin levels in R7, R8, and Mi1 axons suggested that differential adhesion contributed to their relative positions: centrally located R7 axons expressed the highest levels of N-cadherin, whereas Mi1 axons expressed the lowest levels. Furthermore, increasing or decreasing N-cadherin levels in individual cell types altered projection patterns in a manner predicted by the differential adhesion hypothesis.

These results suggest that differential adhesion among the first axons to innervate the medulla contribute to column formation. Other factors may participate in the patterning as well, however. Future studies should identify other sources of N-cadherin in column boundaries and how they contribute to medulla patterning.

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