This Week in The Journal

Tao Kinase Inhibits Dendritic Growth in *Drosophila*

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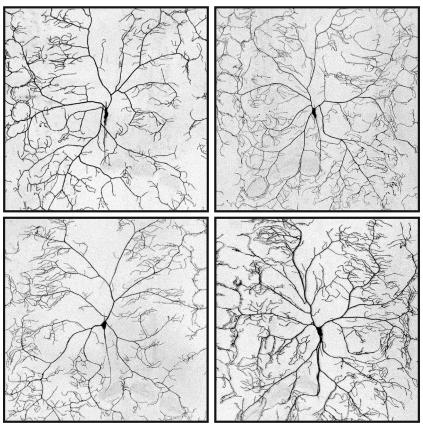
(see pages 1819–1833)

Many genes linked to autism spectrum disorders (ASDs) influence dendritic development. One such gene, *TAOK2*, encodes Tao kinase 2, a protein that phosphorylates proteins that regulate actin and microtubule dynamics. *Taok2* knockout reduces branching of basal dendrites in prefrontal cortical pyramidal cells and reduces social interactions in mice. And recently two *TAOK2* mutations—one that eliminates and one that increases Tao kinase activity—were discovered in people with autism. Furthermore, introduction of typical human *TAOK2* rescued dendritic branching in *Taok2*-deficient mice, whereas expression of the mutant form lacking kinase activity did not, and expression of the overactive form led to excessive branching (Richter et al., 2019, Mol Psychiatry 24:1329). Whether expression of human *TAOK2* isoforms rescues behavioral alterations was not determined, however.

Hu et al. extended these findings by examining the effects of Tao kinase (Tao) on cytoskeletal proteins, dendritic arborization, and behavior in *Drosophila*. In contrast to its effects in mice, loss of Tao increased dendritic branching in *Drosophila* somatosensory neurons, and expressing a hyperactive form of Tao reduced branching. *Tao* knockdown also increased microtubule dynamics, F-actin levels, and expression of a protein that stabilizes microtubules. Notably, knocking down *Tao* in mature neurons also increased branching, suggesting *Tao* acts throughout life to restrain dendritic growth. Moreover, knocking down *Tao* in sensory neurons of adult flies reduced geotaxis and social interactions. Importantly, the effects of *Tao* knockdown on dendritic branching, microtubule dynamics, and behavior were reversed by expressing typical human TAOK2—but not the ASD-linked form lacking kinase activity—selectively in sensory neurons.

These results indicate that although Tao kinase has opposite effects on dendritic growth in *Drosophila* and mice, the human homolog can rescue dendritic branching in both species. This suggests that targets of Tao kinase have opposite roles in cytoskeletal dynamics in *Drosophila* and mammals. The results also show that loss of Tao in sensory neurons is sufficient to disrupt social behaviors in flies, supporting the hypothesis that disruption in sensory processing underlies some autism-related phenotypes. Finally, the results suggest that Tao kinase actively suppresses dendritic growth in mature neurons, suggesting that replacing mutant Tao kinase after the developmental period may reverse behavioral effects.



Knocking down *Tao* (top right) increases dendritic branching in sensory neurons. Branching is restored to near control levels (top left) by expressing functional human *TAOK2* (bottom left), but not by expressing human *TAOK2* lacking kinase activity (bottom right). See Hu et al. for details.

Stress Reduces Input to Deep Layers of Parietal Cortex

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(see pages 1849–1861)

Glucocorticoids released during stressful experiences reshape neural circuits, promoting dendritic growth and synapse formation in some brain areas and synapse elimination and dendritic retraction in others. Although such changes can be beneficial, chronic or severe stress leads to maladaptive plasticity, resulting in mood disorders and cognitive impairment (McEwen and Akil, 2020, J Neurosci 40:12). Because the hippocampus, amygdala, and prefrontal cortex are strongly implicated in emotional processing and cognition, most studies on the negative effects of stress have focused on these areas. But other brain areas, including the posterior parietal cortex (PPC), also contribute to cognitive processes affected by stress. Therefore Libovner et al. examined the effects of repeated exposure to multimodal stress on PPC function.

Mice were subjected to concurrent restraint, rocking, bright light, and unpredictable noise for 1 h/d for 10 d. After this, mice showed reduced spontaneous alternation in a Y maze, suggesting spatial working memory—a function mediated partly by the PPC–was impaired. Stress also caused persistent increases in neuronal activation in PPC, particularly in layers 2/3 and 5. The increased activation may have resulted from an increase in intrinsic excitability of PPC pyramidal neurons: depolarizing current steps evoked more, higher-frequency action potentials in stressed mice than in controls. At the same time, however, the density of postsynaptic sites was reduced in PPC. This synaptic loss was restricted to the lower cortical layers and was attributable to loss of input from primary auditory, visual, and retrosplenial cortex. Notably, however, input to PPC from the contralateral PPC, anterior cingulate cortex, and primary somatosensory cortex was not significantly affected by stress. Finally, although selectively killing visual cortical neurons that project to PPC decreased spontaneous alternation in the Y maze, exposure to restraint stress or bright light alone did not.

By reducing particular synaptic inputs to the lower layers of PPC while increasing the excitability of PPC neurons, repeated exposure to multiple concurrent stressors is likely to increase the influence of inputs to the upper layers on PPC output. Impaired working spatial memory is apparently one consequence of this shift, as revealed in the Y maze. What other functions of PPC are affected should be investigated in future work.

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