This Week in The Journal

FoxP2 Overexpression Impedes Song Learning

Jonathan B. Heston and Stephanie A. White

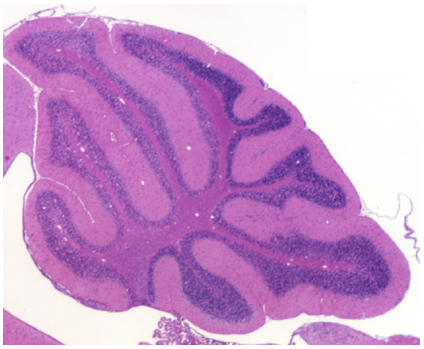
(see pages 2885–2894)

Speech is a complex motor skill in which muscles controlling the tongue, lips, and larynx must be coordinated to make rapid transitions between phonemes. The ability to string syllables together in the proper sequence is impaired in people who have mutations in FoxP2, a transcription factor expressed in projection neurons of cortex, thalamus, cerebellum, and basal ganglia. Because zebra finches, like humans, produce complex vocalizations composed of stereotyped sequences of syllables that juveniles learn by imitating adults, these birds are a useful model system for exploring how FoxP2 expression influences complex motor behavior.

FoxP2 is expressed in Area X, a song-dedicated nucleus of zebra finch basal ganglia, and it is upregulated during the juvenile song-learning period. However, FoxP2 levels are acutely downregulated after juveniles practice singing by themselves. FoxP2 expression also decreases when adult birds sing by themselves, but interestingly, not when the birds sing to females. Notably, songs are more variable during undirected singing than during female-directed singing, suggesting FoxP2 expression is associated with song stability. Indeed, when FoxP2 is knocked down in Area X in juvenile finches, the birds fail to accurately reproduce a tutor's song and they sing more variable songs as adults.

To further investigate the role of FoxP2 in song learning and variability, Heston and White overexpressed the protein in Area X. Like FoxP2 knockdown, overexpression prevented juvenile birds from accurately reproducing their tutor's song. FoxP2-overexpressing birds skipped more syllables than controls, and the syllables that were present were poorer imitations. FoxP2 overexpression did not produce the predicted decrease in song variability, however. In fact, the songs of juvenile FoxP2-overexpressing birds were more variable than controls'. Unlike in FoxP2-deficient finches, however, songs became more stereotyped over time in FoxP2-overexpressing birds, and their adult songs, although different than the tutor's, were no more variable than those of controls.

These results clearly indicate that dynamic regulation of FoxP2 levels is required for songbirds to accurately reproduce a tutor song. But they also suggest that the relationship between FoxP2 levels and song variability is not as simple as previously hypothesized. Moreover, how FoxP2 promotes motor sequencing remains a mystery.



A mutation that reduces expression of an ER chloride channel causes loss of granule cells in the rostral cerebellum of 11-month-old mice. See the article by Jia et al. for details.

Loss of ER Chloride Channel Causes Neurodegeneration

Yichang Jia, Thomas J. Jucius, Susan A. Cook, and Susan L. Ackerman

(see pages 3001–3009)

Many neurodegenerative diseases involve accumulation of misfolded proteins. How this accumulation causes neurons to die is largely unknown, but prolonged activation of the unfolded protein response (UPR) in the endoplasmic reticulum (ER) may be a common contributor. All transmembrane and secreted proteins are processed in the ER, where chaperone proteins help ensure proper folding. Abnormally folded proteins are targeted for degradation, and if they begin to accumulate, the UPR is activated. The UPR involves increased synthesis of proteins involved in protein folding and degradation along with decreased synthesis of most other proteins. If the UPR fails to relieve ER stress, apoptosis is triggered.

Any factor that interferes with protein processing in the ER can activate the UPR. This includes mutations that prevent transmembrane proteins from folding properly, mutations in resident ER proteins, exogenous toxins, and other cellular stressors. These factors can combine to cause prolonged activation of the UPR, leading to cell death. This week, Jia et al. report that mutations in *Clcc1*, a gene that encodes a largely ignored ER chloride channel, contribute to UPR induction and neurodegeneration in mice.

Jia et al. examined inbred mice in which a spontaneous mutation produced ataxia along with progressive degeneration of cerebellar granule cells and peripheral motor axons. This phenotype was linked to the insertion of a transposable element into the *Clcc1* gene, which reduced CLCC1 protein levels in cerebellum and spinal cord. Importantly, signs of elevated UPR activity were present in cerebellar granule cells of *Clcc1*-deficient mice before significant neurodegeneration had occurred, suggesting that UPR activation contributed to degeneration. Interestingly, *Clcc1* expression was reduced in several brain areas, including the hippocampus and cerebral cortex, but neither ER stress nor degeneration were detected in these areas, indicating a cell-type specific effect. Reintroducing wild-type *Clcc1* via a bacterial artificial chromosome rescued granule cell loss and motor nerve degeneration.

These results exemplify a common theme in neurodegenerative diseases: a widely expressed protein of unknown function is linked to degeneration of a specific neuronal type. Given that prolonged activation of the UPR often precedes degeneration, relieving ER stress might be an expedient strategy to treat many diseases.

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