This Week in The Journal

Foxp1 Deletion Impairs Social and Cognitive Behaviors

Daniel J. Araujo, Kazuya Toriumi, Christine O. Escamilla, Ashwinikumar Kulkarni, Ashley G. Anderson, et al.

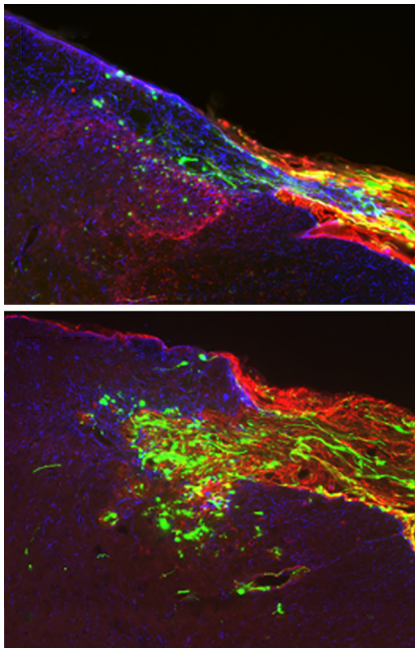
(see pages 10917–10931)

Transcription factors of the FOXP family regulate cell fate specification and development throughout the body. FOXP2 gained prominence when mutations in the protein were linked to impairments in language comprehension and production. Because FOXP1 forms heterodimers with FOXP2 in some tissues, researchers asked whether FOXP1 mutations also contribute to speech impairment. FOXP1 variations were, in fact, found in people with speech delays or impairments, but these impairments appeared to be secondary to severe intellectual disability, sometimes coupled with autism. Thus, FOXP1 is thought to be involved in multiple cognitive functions (Bacon & Rappold 2012 Hum Genet 131:1687).

Consistent with a role for Foxp1 in multiple brain functions, knocking out *Foxp1* in neural tissue caused hyperactivity, impaired short-term object memory, and reduced nest building in mice (Bacon et al. 2015 Mol Psychiatry 20:632). These effects were accompanied by pronounced reduction in the size of the striatum, where Foxp1 is highly expressed. But Foxp1 is also expressed in pyramidal neurons in the cerebral cortex and hippocampal area CA1, and its loss in these areas likely contributes to behavioral phenotypes in *Foxp1*-deficient animals. To address its role in these areas, Araujo et al. knocked out *Foxp1* selectively in cortical and hippocampal pyramidal neurons.

Mutant mice exhibited many of the same behavioral phenotypes as whole-brain *Foxp1*-deficient mice. They were hyperactive and exhibited minimal nest-building behavior. In addition, mutant mice avoided unfamiliar mice in a social interaction test, and in the presence of female mice, mutant males produced fewer and simpler vocalizations than wild-type. Moreover, mutant mice showed no indication of learning in spatial navigation tests. These effects were attributed in part to a decrease in brain size, particularly in the hippocampus, and a reduction in the duration of hippocampal long-term potentiation. These, in turn, stemmed from abnormal regulation of numerous genes, including several genes previously linked to autism and intellectual disability.

These results suggest that reduced Foxp1 function in the hippocampus and cortex might contribute to intellectual disability and autism in people with mutations in this protein. Future work should examine the roles of Foxp1 target genes to determine whether any have more selective effects on behavioral phenotypes. Identifying targets that selectively disrupt social interaction and communication might be especially helpful: they might provide additional clues about the neural bases of autism.



Few regenerating peripheral axons penetrate the spinal cord after dorsal nerve crush, even when GDNF is overexpressed in the dorsal horn (top). Expressing caErbB2 in Schwann cells (bottom) greatly increased spinal cord entry by these cells (red), as well as by axons (green). Blue shows astrocytes. See Han et al. for details.

Activating ErbB2 in Schwann Cells Improves Axon Growth

Seung Baek Han, Hyukmin Kim, Hyunkyoung Lee, Matthew Grove, George M. Smith, et al.

(see pages 10955–10970)

The ability of peripheral nerves to regenerate after injury depends largely on the actions of Schwann cells. After injury, Schwann cells undergo dramatic changes in gene expression, downregulating proteins involved in myelin production and upregulating proteins that allow the cells to clear myelin debris, attract immune cells, and promote axon growth. This so-called repair phenotype persists for a few weeks, but the expression of repair genes eventually declines. The reversal of the repair phenotype typically occurs before long axons have reached their targets, resulting in regeneration failure (Jessen & Mirsky 2016 J Physiol 594:3521). This is a common problem in human patients. Extending the duration of repair Schwann cell activity might therefore improve recovery.

ErbB2 is a receptor tyrosine kinase that is thought to help induce the repair phenotype in Schwann cells. Because ErbB2 expression declines in parallel with the loss of this phenotype, Han et al. asked whether expressing a constitutively active form of the receptor (caErbB2) would prolong the ability of Schwann cells to promote repair. To test this, they used transgenic mice in which caErbB2 expression could be induced selectively in Schwann cells. Induction of caErbB2 was initiated after dorsal roots were crushed, and nerves were examined 2 weeks later, when Schwann cells normally begin to transition from the repair to the myelinating phenotype. Expressing caErbB2 increased Schwann cell proliferation and the total number of Schwann cells in the crushed nerve. Furthermore, expression of caErbB2 increased growth of sensory axons beyond the crush site. Remarkably, when glial-cell-line-derived neurotrophic factor (GDNF) was overexpressed in the spinal cord, induction of caErbB2 in Schwann cells enabled these cells, as well as dorsal root axons to penetrate the spinal cord. Importantly, however, myelination and Schwann cell numbers were unchanged in the contralateral, intact nerves of injured animals, and no axon sprouting was evident in these nerves.

These results indicate that activating ErbB2 in Schwann cells can promote peripheral nerve regeneration after injury without affecting uninjured nerves. Thus, targeting this pathway might be a fruitful strategy for improving functional recovery.

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