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Research adds to evidence that autism is a brain 'connectivity' disorder

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Studying a rare disorder known as tuberous sclerosis complex (TSC), researchers at Children's Hospital Boston add to a growing body of evidence suggesting that autism spectrum disorders, which affect 25 to 50 percent of TSC patients, result from a miswiring of connections in the developing brain, leading to improper information flow. The finding may also help explain why many people with TSC have seizures and intellectual disabilities. Findings were published online in *Nature Neuroscience* on January 10.

TSC causes benign tumors throughout the body, including the brain. But patients with TSC may have autism, epilepsy or intellectual disabilities even in the absence of these growths. Now, researchers led by Mustafa Sahin, MD, PhD, of Children's Department of Neurology, provide evidence that mutations in one of the TSC's causative genes, known as TSC2, prevent growing nerve fibers (axons) from finding their proper destinations in the developing brain.

Studying a well-characterized axon route - between the eye's retina and the visual area of the brain - Sahin and colleagues showed that when mouse neurons were deficient in TSC2, their axons failed to land in the right places. Further investigation showed that the axons' tips, known as "growth cones," did not respond to navigation cues from a group of molecules called ephrins. "Normally ephrins cause growth cones to collapse in neurons, but in tuberous sclerosis the axons don't heed these repulsive cues, so keep growing," says Sahin, the study's senior investigator.

Additional experiments indicated that the loss of responsiveness to ephrin signals resulted from activation of a molecular pathway called mTOR, whose activity increased when neurons were deficient in TSC2. Axon tracing in the mice showed that many axons originating in the retina were not mapping to the expected part of the brain.

Although the study looked only at retinal connections to the brain, the researchers believe their findings may have general relevance for the organization of the developing brain. Scientists speculate that in autism, wiring may be abnormal in the areas of the brain involved in social cognition.

"People have started to look at autism as a developmental disconnection syndrome - there are either too many connections or too few connections between different parts of the brain," says Sahin. "In the mouse models, we're seeing an exuberance of connections, consistent with the idea that autism may involve a sensory overload, and/or a lack of filtering of information."

Sahin hopes that the brain's miswiring can be corrected by drugs targeting the molecular pathways that cause it. The mTOR pathway is emerging as central to various kinds of axon abnormalities, and drugs inhibiting mTOR has already been approved by the FDA. For example, one mTOR inhibitor, rapamycin, is currently used mainly to prevent organ rejection in transplant patients, and Sahin plans to launch a clinical trial of a rapamycin-like drug in approximately 50 patients with TSC later this year, to see if the drug improves neurocognition, autism and seizures.

In 2008, Sahin and colleagues published related research in Genes & Development showing that when TSC1 and TSC2 are inactivated, brain cells grow more than one axon - an abnormal configuration that exacerbates abnormal brain connectivity. The mTOR pathway was,

again, shown to be involved, and when it was inhibited with rapamycin, neurons grew normally, sprouting just one axon.

Supporting the mouse data, a study by Sahin and his colleague Simon Warfield, PhD, in the Computational Radiology Laboratory at Children's, examined the brains of 10 patients with TSC, 7 of whom also had autism or developmental delay, and 6 unaffected controls. Using an advanced kind of MRI imaging called diffusion tensor imaging, they documented disorganized and structurally abnormal tracts of axons in the TSC group, particularly in the visual and social cognition areas of the brain (see image). The axons also were poorly myelinated - their fatty coating, which helps axons conduct electrical signals, was compromised. (In other studies, done in collaboration with David Kwiatkowski at Brigham and Women's Hospital, giving rapamycin normalized myelination in mice.)

Sahin has also been studying additional genes previously found to be deleted or duplicated in patients with autism, and finding that deletion of some of them causes neurons to produce multiple axons - an abnormality that, again, appears to be reversed with rapamycin.

"Many of the genes implicated in autism may possibly converge on a few common pathways controlling the wiring of nerve cells," says Sahin. "Rare genetic disorders like TSC are providing us with vital clues about brain mechanisms leading to autism spectrum disorders. Understanding the neurobiology of these disorders is likely to lead to new treatment options not only for TSC patients, but also for patients with other neurodevelopmental diseases caused by defective myelination and connectivity, such as autism, epilepsy and intellectual disability."

More information: "Tsc2-Rheb signaling regulates EphA-mediated axon guidance," *Nature Neuroscience*, January 10.

Provided by Children's Hospital Boston