

NEWS

Cell skeleton breakdown may spur autism symptoms in mice

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Skeleton crew: Mice with a defective copy of SHANK3 have abnormally few actin filaments (dimmer stain, right), which make up the cell skeleton.

An autism-linked mutation in the **SHANK3** gene alters the protein skeleton of neurons in mice, according to a study published 9 June in *Cell Reports*¹. Repairing the scaffold eases the animals' social deficits.

The findings suggest both that problems with the cell skeleton contribute to autism and that drugs may be able to alleviate them.

The cytoskeleton is a dynamic structure that undergoes continuous remodeling as cells grow and move. Sequencing studies have uncovered autism-linked mutations in genes that **influence cytoskeletal dynamics**, but the link between these mutations and autism symptoms has been unclear.

The new study provides clues about which cytoskeletal regulatory pathways are impaired in autism. "Our study identifies the molecular mechanisms that specifically cause the autism-like behavior deficits," says lead researcher **Zhen Yan**, professor of physiology and biophysics at the State University of New York at Buffalo.

About 1 in 200 people with autism have mutations in SHANK3². The gene encodes a protein found

at **synapses**, or the junctions between neurons. It acts as a molecular bridge between the cytoskeleton and other proteins in the synapse.

For instance, SHANK3 helps to anchor the receptors for **neurotransmitters**, the chemical messengers that transmit signals between neurons, in the synaptic membrane³. It also binds to actin filaments — a principal component of the cytoskeleton.

The new study suggests that SHANK3 mutations that disrupt its binding to actin contribute to autism by triggering a breakdown of the cytoskeleton at the synapse.

“It’s starting to give us a fuller picture of the types of changes in neural function that could contribute to autism-like symptoms,” says **Christopher Cowan**, associate professor of psychiatry at Harvard Medical School, who was not involved in the study.

The findings also raise the intriguing possibility that drugs that stabilize actin filaments could ease symptoms in some people with autism. However, Cowan cautions that this approach may produce side effects, because actin is an integral part of every cell in the body.

Actin up:

Yan and her colleagues looked at mice engineered so that one copy of SHANK3 has a mutation borne by some people with autism. This makes the protein unable to attach to actin. The mice show repetitive self-grooming and lose the natural preference to interact with another mouse rather than with an object — actions reminiscent of the **repetitive behaviors** and social deficits seen in autism.

The researchers dissected brains from the mice at age 6 to 8 weeks and looked closely at the prefrontal cortex — a region involved in social behavior, planning and memory that has been **implicated in autism**. They found fewer actin filaments in the synapses of these mice. A protein called cofilin that disassembles actin filaments is also abnormally active in the mice.

What’s more, neurons in the prefrontal region show abnormally weak activation of NMDA receptors, which respond to the excitatory neurotransmitter glutamate. Impaired NMDA receptor function has been **linked to autism**.

The animals also show reduced levels of proteins that make up NMDA receptors at synapses, but not elsewhere in the cell. Intriguingly, another group of glutamate receptors, called AMPA receptors, are unaffected. This suggests that the symptoms in the mice stem from impaired NMDA activity in synapses.

Taken together, the findings suggest that the SHANK3 mutation triggers the disassembly of actin filaments, leading to fewer NMDA receptors anchored at the synapse and reducing NMDA receptor activity there. Inhibiting cofilin restores the structure of actin filaments in synapses. It also normalizes NMDA activity and eases the mice's symptoms.

These results jibe with studies showing that integrity of the cytoskeleton is critical for transporting NMDA receptors to the cell membrane^{4,5}.

The researchers also showed that boosting the activity of cofilin in normal mice impairs NMDA receptor activity and triggers autism-like social deficits. This result provides further evidence that the breakdown of actin filaments contributes to autism-like symptoms in mice.

"It's actually quite remarkable," says **Scott Soderling**, associate professor of cell biology and neurobiology at Duke University in Durham, North Carolina, who was not involved in the study. "By manipulating this pathway, they can either mimic or reverse social deficits in mice."

Correction: *This article was modified from the original. It has been corrected to clarify the source of the SHANK3 mice, the type of social behavior they display and where the reduction of the actin filaments occurs.*

References:

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