NEWS

Non-starring cells may be key in fragile X syndrome

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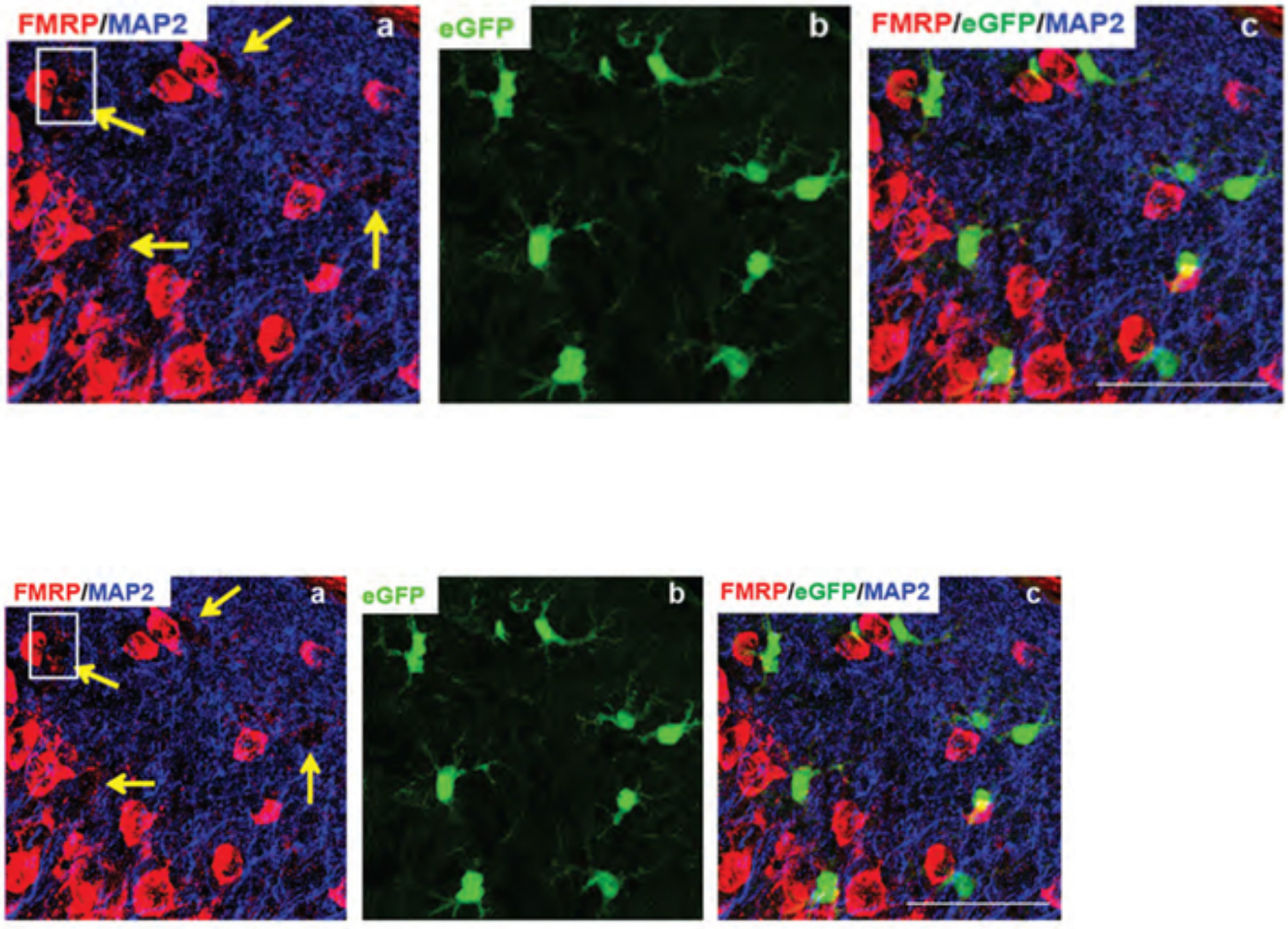

Astrocytes awry: The fragile X syndrome gene FMR1 is expressed in both neurons (shown in red) and astrocytes (shown in green).

Mice missing the **FMR1** gene only in star-shaped support cells called astrocytes recapitulate key features of **fragile X syndrome**. Researchers presented the unpublished results today at the 2014 Society for Neuroscience annual meeting in Washington, D.C.

Fragile X syndrome — a developmental disorder caused by mutations in FMR1 — is a leading cause of autism. Mice missing both copies of the gene show **cognitive and behavioral deficits** reminiscent of those seen in people with the disorder. They also have seizures. But it's unclear whether these features stem from defects in neurons or in glia, support cells in the brain that include immune cells called **microglia** and astrocytes.

In the new study, researchers created mice missing FMR1 only in astrocytes. These stellar cells with long projections support neurons and play a crucial role in synapses — the junctions through which neurons communicate with each other. Mounting evidence suggests that astrocytes and synapses are both altered in autism.

The mutant mice show decreased expression of GLT1 — a transporter that normally helps astrocytes soak up the chemical messenger glutamate from the synapse. With low levels of GLT1, glutamate instead accumulates at the synapse. And the excess glutamate then causes neurons in the mice to fire more frequently than normal.

Ceftriaxone, an antibiotic that activates GLT1, normalizes this excitatory signaling.

"I think GLT1 would be a great candidate for new therapeutics for fragile X syndrome, because it restores the proper extracellular glutamate environment," says **Yongjie Yang**, assistant professor of neuroscience at Tufts University in Boston, who presented the work.

The researchers also homed in on the mechanism by which FMR1 affects GLT1. They found that mutations in FMR1 lower the expression of mGluR5 — a glutamate receptor implicated in fragile X syndrome — in astroglia. They suspect that low levels of mGluR5 in turn dampen the expression of GLT1, leading to a pool of excess glutamate at the synapse.

Mice missing FMR1 in astrocytes also have seizures in response to high-frequency sounds. These 'audiogenic' seizures also occur in mice that lack FMR1 in all cell types, further supporting a role for astrocytes in fragile X syndrome.

"I think astrocytes are playing a very significant role in the fragile X syndrome phenotype," says Yang.

He and his team are assessing social and cognitive function in the mice using various behavioral tests, including the water maze, which measures learning and memory.

*For more reports from the 2014 Society for Neuroscience annual meeting, please **click here**.*