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Two Causes of Autism Found to be Cellular Opposites

Fragile X syndrome and tuberous sclerosis both cause autism and intellectual disabilities in a majority of affected patients. And both diseases have been linked to abnormalities in the amount of proteins made by brain cells at their synaptic junctions, suggesting that treatments for one disease may be applicable to the other. But new research reveals that the underlying cellular mechanisms of the two are polar opposites: while the genetic mutations that cause fragile x syndrome lead to an increase in synaptic protein synthesis, tuberous sclerosis is characterized by a dampening of the same pathway.

The study suggests that to function normally, brain cells must produce a level of synaptic proteins that falls within a particular range; deviations in either direction can cause problems.

“These diseases have an overlapping constellation of symptoms,” says Howard Hughes Medical Institute investigator Mark Bear, who led the new study, published online in *Nature* on November 23, 2011. “So our initial guess was that they would share cellular characteristics. But every experiment ended up being a huge surprise.”

Fragile X syndrome is the most common form of inherited intellectual disability and affects an estimated 90,000 people in the U.S. A decade ago, Bear’s lab at the Massachusetts Institute of Technology discovered that *Fmr1*, the gene responsible for fragile X syndrome, normally makes a protein that puts the brakes on a receptor dubbed mGluR5. Mutations in *Fmr1* mean these brakes on mGluR5 are lifted in the cells of patients with fragile X syndrome. The result is that protein synthesis, the process by which a cell produces new proteins, speeds up.

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This increase in protein synthesis in brain cells, Bear has shown, accounts for multiple symptoms in animal models of fragile X. Drugs that block mGluR5 to treat autism and intellectual disability in patients with fragile X are now in clinical trials.

Bear wanted to know whether these same drugs could treat the very similar behavioral symptoms of tuberous sclerosis. Tuberous sclerosis is caused by mutations in one of two genes, *Tsc1* or *Tsc2*, and leads to malformed tissue that can affect the skin, brain, kidneys, heart, and other organs. It also often causes autism and learning delays. Mutations in the *Tsc* genes are known to lead to an increase in activity of a protein called mTOR. Scientists had hypothesized that this increase in mTOR might accelerate protein synthesis, working through the same pathway as mGluR5.

"The hypothesis was that mGluR5 signals through mTOR to stimulate protein synthesis," says Bear. "So if you have a disease caused by changes to mTOR, it might overlap a lot with fragile X and respond to the same treatment."

Bear's team used a mouse model of tuberous sclerosis to study how mutations in *Tsc2* affected protein synthesis. To their surprise, protein synthesis was decreased in neurons with the *Tsc2* mutations. When the scientists treated the mice with a drug that blocks mTOR activity, protein synthesis increased to normal levels. To test whether the effect was mediated by mGluR5, they next treated the *Tsc2* mice with a drug that turns up activity of mGluR5—the opposite action of the drugs in trials to treat fragile X syndrome. The drugs, like the mTOR inhibitors, increased protein synthesis to normal levels.

"We checked off every box to show that in tuberous sclerosis, mutations are having the opposite effect on this pathway than *Fmr1* mutations have," says Bear. "But what's still unanswered is the question of exactly how excess mTOR is suppressing protein synthesis."

"One of the messages that comes from this is that even though patients may exhibit common symptoms, that doesn't mean there is a shared cause and can be shared treatments," says Bear. In fact, the new data suggests that trying to

treat tuberous sclerosis-associated autism with the same drugs being tested for fragile X would in fact worsen the problem.

A drug that blocks mTOR—called rapamycin – is already in clinical trials to treat tuberous sclerosis, and Bear’s new study offers an explanation of how the drug works to reverse some problems caused by the disease. Next, he hopes to more fully understand how the pathway controls protein synthesis.