Workings of brain protein suggest therapies for inherited intellectual disability, autism

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Researchers now have a much clearer understanding of how mutations in a single gene can produce the complex cognitive deficits characteristic of Fragile X Syndrome, the most common inherited form of intellectual disability. As the majority of patients with Fragile X Syndrome also display autism-like symptoms, the findings offer hope for treating both conditions.

A report in the July 22nd issue of the journal *Cell*, published by Cell Press, defines a set of messenger RNA (mRNA) molecules that the Fragile-X mental retardation protein (FMRP) binds in the brains of mice. Many of these mRNAs encode proteins that function at neurons' connection points. When properly bound, FMRP prevents the translation of these mRNAs into proteins until the time is right.

"By understanding for the first time the direct targets of FMRP and its actions, we open up a whole world of potential avenues for therapies designed to make kids with Fragile X or autism better," said Robert Darnell, a Howard Hughes Medical Institute investigator at The Rockefeller University.

"The power comes from taking two diseases with similar symptoms and looking at what is in common," added Jennifer Darnell, also at The Rockefeller University. Of the almost 850 identified targets of FMRP, she explained, it is likely only a much smaller subset has a real impact on health or disease.

The Darnell team's breakthrough uses a technique they developed a few years ago based on a "biochemical trick". They use ultraviolet light to solidify the bonds between a protein, in this case FMRP, and the mRNAs it binds. Those protein-mRNA complexes could then be isolated and sequenced to reveal a "beautiful map" of the mRNA transcripts and precisely where they are bound to FMRP.

The experiments reveal that FMRP specifically binds to the protein-coding portions of those brain mRNAs. Jennifer Darnell said that distribution is unlike what they've seen before and looked much like the distribution of ribosomes, the cellular components that assemble proteins.

Further experiments suggest that FMRP acts as a "brake," reversibly stalling ribosomes after they bind mRNA. Robert Darnell likened FMRP to the nozzle at the end of a hose. It allows the mRNA transcripts to be loaded with ribosomes in the locations where they will be needed, and when the time is right, bursts of translation (protein synthesis) can occur. That sort of tight control is likely to be critical for the formation and plasticity of neural connections, the cellular foundation for learning and memory.

Their basic scientific discoveries suggest two different overall strategies for treating Fragile X Syndrome: by lowering the activity of particular proteins normally kept under wraps by FMRP or by replacing FMRP's ability to stall ribosomes. Notably, the Darnells say the latter is exactly what antibiotics do to slow the growth of bacteria.

"We may be able to take the edge off of the extra protein synthesis," Jennifer Darnell said.

Ultimately, there will be more to the story, Robert Darnell added. "FMRP is one of many regulatory proteins in the neuron. It doesn't work

all by itself."

Provided by Cell Press