Scientists design molecule that reverses some fragile X syndrome defects

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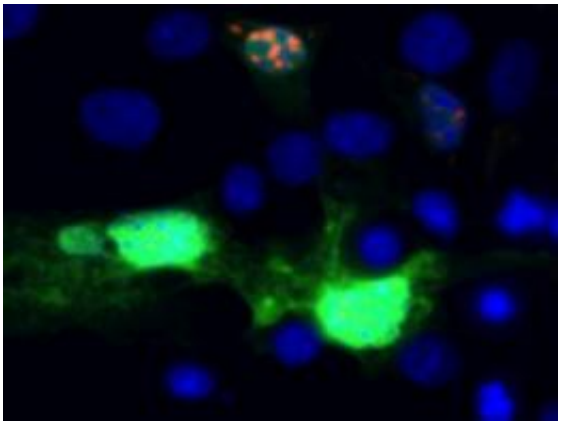

These FXTAS model cells show the defects, in orange, that cause tremor ataxia syndrome. Credit: Disney lab, The Scripps Research Institute

(Phys.org)—Scientists on the Florida campus of The Scripps Research Institute have designed a compound that shows promise as a potential therapy for one of the diseases closely linked to fragile X syndrome, a genetic condition that causes mental retardation, infertility, and memory impairment, and is the only known single-gene cause of autism.

The study, published online ahead of print in the journal *ACS* Chemical Biology September 4, 2012, focuses on tremor ataxia syndrome, which usually affects men over the age of 50 and results in Parkinson's like-symptoms—trembling, balance problems, muscle rigidity, as well as some neurological difficulties, including short-term memory loss and

severe mood swings.

With fragile X syndrome, tremor ataxia syndrome, and related diseases, the root of the problem is a structural motif known as an "expanded triplet repeat"—in which a series of three nucleotides are repeated more times than normal in the genetic code of affected individuals. This defect, located in the fragile X mental retardation 1 (FMR1) gene, causes serious problems with the processing of RNA.

"While there is an abundance of potential RNA drug targets in disease, no one has any idea how to identify or design small molecules to target these RNAs," said Mathew Disney, a Scripps Research associate professor who led the study. "We have designed a compound capable of targeting the right RNA and reversing the defects that cause fragile X-associated tremor ataxia."

Preventing Havoc

In tremor ataxia syndrome, the expanded triplet repeat leads to the expression of aberrant proteins that wreak widespread havoc. The repeats actually force the normal proteins that regulate RNA splicing —necessary for production of the right kind of proteins—into hiding.

The compound designed by Disney and his colleagues not only improves the RNA splicing process, but also minimizes the ability of repeats to wreak havoc on a cell.

"It stops the repeat-associated defects in cell culture," Disney said, "and at fairly high concentrations, it completely reverses the defects. More importantly, the compound is non-toxic to the cells. It looks like a very good candidate for development, but we're still in the early stages of testing."

Overall, this study reinforces Disney's earlier findings showing it is possible to identify and develop small molecules that target these traditionally recalcitrant RNA defects. In March of this year, Disney published a study in the *Journal of the American Chemical Society* that described a small molecule that inhibited defects in myotonic dystrophy type 1 RNA in both cellular and animal models of disease.

"We've gotten very good at targeting RNA with small molecules, something a lot of people said couldn't be done," Disney pointed out. "Our approach is evolving into a general method that can be used to target any disease that is associated with an RNA, including, perhaps, fragile X syndrome itself."

The new compound also works as a probe to better understand how these repeats cause fragile X syndrome and how they contribute to tremor ataxia, Disney added.

More information: "Small Molecule That Targets r(CGG) and Improves Defects in 2 Fragile X-Associated Tremor Ataxia Syndrome," pubs.acs.org/doi/full/10.1021/cb300135h

Provided by Scripps Research Institute

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