Research Brief

A SUMMARY OF A PUBLISHED ARTICLE

Lighting up the search for a therapy for fragile X syndrome

Published Article: Establishment of Reporter Lines for Detecting FMR1 Gene Reactivation in Human Neural Cells

By: Meng Li, Huashan Zhao, Gene E. Ananiev, Michael T. Musser, Kathryn H. Ness, Diane N. Maglaque, Krishanu Saha, Anita Bhattacharyya and Xinyu Zhao

WAISMAN CENTER

UNIVERSITY OF WISCONSIN-MADISON

Researchers at the Waisman Center are looking to make stem cells glow.

That glow will tell them that they have successfully turned on a gene that is usually turned off in individuals with fragile X syndrome (FXS). Turning on this gene – called *FMR1* – could be an important way to treat this syndrome.

Fragile X syndrome is the most common cause of inherited intellectual disability and a major genetic factor in autism spectrum disorder. In individuals with FXS, a specific gene - *FMR1* – is silenced or turned off, i.e., cells can no longer make protein using that gene as a blueprint. The FMR protein is thought to be important for normal cognitive development.

What's unusual about FXS is that the mutation that causes the syndrome doesn't delete or disrupt the gene – it just turns it off. “So there is a fully functional *FMR1* gene in individuals with FXS; it just needs to be turned on, and we could have a potential therapy,” says Anita Bhattacharyya, a Waisman Center investigator and study co-author.

However, turning on this particular gene, or any gene, in individuals is easier said than done. Usually, researchers need to search through large numbers – up to millions – of drugs to find ones that can be used for therapy safely and effectively.

Another challenge researchers face is being able to tell quickly when a particular gene is turned on in cells. It would take far too long to apply individual drugs, collect the cells being tested and use traditional methods to check whether a specific gene is turned on or off in those cells.

Bhattacharyya and study co-author Xinyu Zhao, also a Waisman Center investigator, want to be quicker. “We want to be able to assay thousands of different compounds – including those that we already know to be safe – and not just try a few like we usually would in the lab,” says Zhao. “To do that we need a way to easily measure whether the gene is turned on or off.”

"Glowing reporter cells tell researchers that they have successfully turned on the FMR1 gene, which could be a first step to developing a therapy for FXS."

Creating the reporter cell line

Meng Li, a postdoctoral fellow supervised by Zhao and Bhattacharyya, used a technique called CRISPR-Cas9 to precisely position a reporter in the genomes of stem cells derived from individuals with FXS.

"You can put a drug on these reporter cells and if the gene is turned on by that drug then you will get a bright signal," says Bhattacharyya. "It's that simple."

Also, by measuring the intensity of the signal, researchers can estimate how much protein is being made in the cells.

Scanning large numbers of potential drugs quickly

The biggest advantage of reporter cell lines is they can be used in automated systems to check – over relatively short periods of time – whether any of hundreds of thousands of drugs can turn on the gene of interest without harming the cell.

"Comparing to published reporter cells, the cells we have generated are much more sensitive and quantitative, which makes it more amenable for large drug screens," says Zhao.

Future research

With support from the Merck Foundation and the UW-Madison Institute for Clinical and Translational Research, Bhattacharyya and Zhao are now testing hundreds of thousands of compounds to see which ones make the reporter cells glow, but the journey from lab to clinic can be a lengthy one.

"Once we identify potential compounds, we will take it step by step to test, through clinical trials, whether those compounds can be used therapeutically," says Zhao.

Acknowledgements

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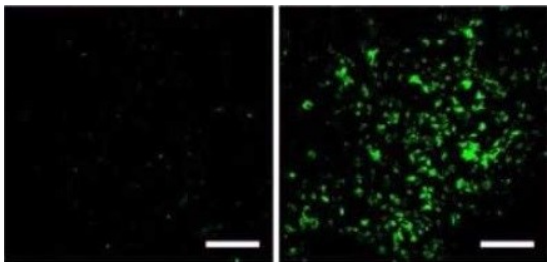

Waisman Center researchers Anita Bhattacharyya and Xinyu Zhao are developing a system where the presence of FMRP in cells will cause them to glow (contrast cells with no FMRP on the LEFT side of the image to cells with FMRP on the RIGHT side).

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